UDC 547.9, 615.31

DOI: 10.15372/CSD2020239

Modulators of Hematopoiesis Disorders (a Review)

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(Received January 27, 2020; revised May 13, 2020)

Abstract

Disorders of hematopoiesis caused by the action of various factors (hemotoxic substances, drugs, cytotoxic drugs, radiation) lead to a deviation from the norm and the development of the diseases varying in complexity. The restoration of hematopoiesis under extreme conditions is vital, and the search for the drugs stimulating hematopoiesis is an extremely urgent task. The most interesting agents are low molecular weight compounds that can stimulate hematopoiesis in case of its disorders. The presented literature review discusses various factors leading to hematopoietic disorders, and drugs that have shown sufficient effectiveness in eliminating these disorders, in particular with cytostatic therapy and the treatment of hemolytic pathologies. The review can be useful in the search for agents that stimulate hematopoiesis, and is addressed not only to medical and chemical professionals, but also to a wide range of readers.

Keywords: hematopoiesis, bone marrow, cytostatic drug, hemostimulating activity, anemia, leukemia

Contents

INTRODUCTION

Blood is an exclusively reactogenic system which is characterized by various changes of the cell composition and components as a response to the action of pathogenic factors. The blood system includes the following major components: blood and lymph, hematopoietic and immunopoietic organs, as well as blood cells possessing the ability to migrate into paravasal connective tissues. An extremely important role in regulating homeostasis in peripheral blood is allocated to he-

matopoietic organs, especially to bone marrow, in which the dynamic equilibrium between hematopoiesis and cell lysis is maintained under normal conditions.

Reliable data on the nature and mechanisms of hematopoiesis in bone marrow, on the role of cylokines in blood cell histogenesis have been obtained recently. Since birth, the development of human primary pluripotent stem cells and myelopoiesis proceed in bone marrow, while lymphopoiesis takes place in the thymus, the spleen and lymphatic nodes. In adults, myelopoiesis under pathological conditions may be renewed in the spleen and in the liver. Marrow hematopoiesis, the cell composition of peripheral blood, hormonal balance of the organism and cytokine profile of blood under normal conditions and in the case of pathology are characterized by different dynamic shifts providing adaptation or disadaptation under the action of physiological or pathological irritants [1].

SUBSTANCES THAT ARE TOXIC FOR HEMATOPOIETIC SYSTEM

Hematotoxicity is the ability of chemical substances to selectively disturb the functions of blood cells and the cell composition of blood causing a decrease or an increase in the number of blood corpuscles. The major functions of blood cells are hemostasis, oxygen transport, and immunity. Disturbance of the number of blood corpuscles may be a result of the direct destruction of cells in the bloodstream, disorders in the fission and maturation of blood cells in blood-forming organs, and the arrival of mature corpuscles into the blood. The signs of hematotoxicity are usually disturbance of the properties of hemoglobin (carboxyhemoglobinemia and methemoglobinemia), anemia (in particular hemolytic anemia), thrombocytopenia, leucopenia and leucosis. Cell anomalies caused by toxic compounds are usually reversible and disappear after the action of the substance is eliminated. However, persistent forms also occur, which may end in lethal termination in the case of severe injury of bone marrow [2].

Many chemical compounds are known that are toxic for the hematopoietic system, for example, aniline, 4-aminobiphenyl, hydrazine, arsine, phenylhydrazine, benzene, lead-containing compounds, *etc.* Myelotoxicity caused by pesticides entering the human organism with food is observed during recent years. These myelotoxins affect hematopoietic cells in humans and lead to general hematopoietic disorders [3, 4].

The toxicity of benzene is to be mentioned specially. In addition to the application in industrial chemical synthesis, this compound is widely used as a solvent. The major route of benzene entry into the human organism is inhalation. The action of this xenobiotic causes a decrease in the number of lymphocytes, neutrophils and thrombocytes in peripheral blood, which may lead to acute myeloid leucosis or myelodysplastic syndrome [5]. A key enzyme providing the toxic action of benzene on bone marrow may be myeloperoxidase, as its activity is extremely high in the bone marrow. This enzyme catalyzes the transformation of benzene metabolite, hydroquinone, into reactive 1,4-benzoquinone. It was demonstrated experimentally that the simultaneous introduction of benzene and indomethacin **1** (which is an antioxidant and non-steroidal anti-inflammatory drug, Fig. 1) provides a substantial decrease in the myelotoxic effect. It was demonstrated that indomethacin inhibits the activity of not only cyclooxygenase but also myeloperoxidase, thus blocking the oxidation of hydroquinone [2].

Compound **2,** bis-(γ-*L*-glutamyl)-1-cysteinylglycine dilithium salt/*cis*-diaminodichloropalladium/copper (II) chloride (1000 : 1 : 1) was synthesized, and its myelostimulating activity under experimental leucopenia caused by benzene was studied. No animals died in the group receiving compound **2,** and improvement of the general condition of the animals was observed. Hematological examination showed that hemoglobin content and the number of all blood cells were decreased but still almost at the lower boundary of the normal range. This compound also was efficient in the model of lead-caused anemia [6]. Special attention is paid during recent years to poisoning with the compounds of this metal.

It was discovered that zinc mesoporphyrin and protoporphyrin **3**, tin mesoporphyrin and protoporphyrin **4** are powerful inhibitors of the cells of bone marrow and oxygenase of hepatic heme, and tin mesoporphyrin is successfully applied for clinical purposes to decrease the level of bilirubin in plasma in the case of neonatal hyperbilirubinemia and under other clinical conditions. The measurement of the amount of zinc protoporphyrin in erythrocytes is used as a test for lead poisoning or iron deficiency. However, it was stressed that zinc mesoporphyrin and protoporphyrin, unlike tin compounds, are inhibitors of hematopoiesis in the bone marrow of animals and humans and are toxic for hematopoietic cells, so these compounds are to be applied with care. The

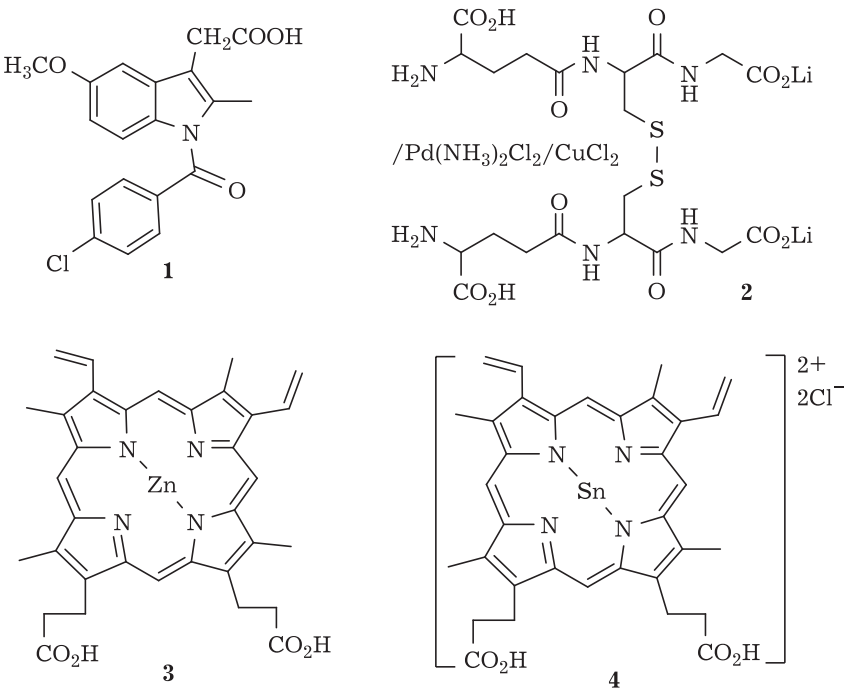

Fig. 1. Structures of indomethacin **1**; complex **2**; zinc protoporphyrin **3** and tin protoporphyrin **4**.

use of chromium porphyrins even caused the death of animals [7, 8].

BONE MARROW TRANSPLANTATION

Transplantation of bone marrow (TBM) is a comparatively new method to treat blood diseases, in use since the 70-es of the XX century, but rapidly developing and increasingly broadly applied. TBM is usually used to treat oncological pathology. However, there are some other cases in which this method is recommended or even is the only method to achieve recovery (for example, in the case of organ transplantation).

Bone marrow transplantation involves the replacement of the cells of the bone marrow of the recipient by the cells from a relative or non-relative donor (in case of allogenic transplantation) or by the own cells of the recipient pre-treated pharmacologically (in case of autologous transplantation). Hematopoietic stem cells (HSC) obtained from the peripheral blood of the donor after stimulation procedure or from puncture and sampling of bone marrow.

In spite of the fact that the TBM procedure is permanently improved, doctors use this method only in extreme cases when the risk of patient death from the disease is much higher than the risk connected with transplantation itself. The most complicated aspect of TBM is patient management during the first weeks after transplantation because of the highest risk of severe complications (infections, side effects of pharmaceutical preparations, disorders of the immune system, the cell composition of blood, etc.) during this period. Patients need permanent medical control in intensive care units. The first 100 days after TBM are considered as the critically important time because engraftment of the transplanted HSC of bone marrow is to be completed during this time [9].

The mode of TBM may differ insignificantly in different clinics but the general features are as follows. Several days before HSC transplantation, the patient is conditioned, or prepared with the help of chemotherapy and radiotherapy to the transfusion of autologous or allogenic HSC. This preparation procedure is carried out in order to achieve tumour eradication, to make a new springboard of hematopoiesis and induction of immunosuppression (in case of allogenic transplantation) to a level sufficient for engraftment of donor HSC [10]. Cytostatic preparations are used for this purpose according to the scheme applied for the treatment of a specific oncohematological disease. Chemotherapy is sometimes combined with whole-body irradiation to exterminate the residual cancer cells. Conditioning is car-

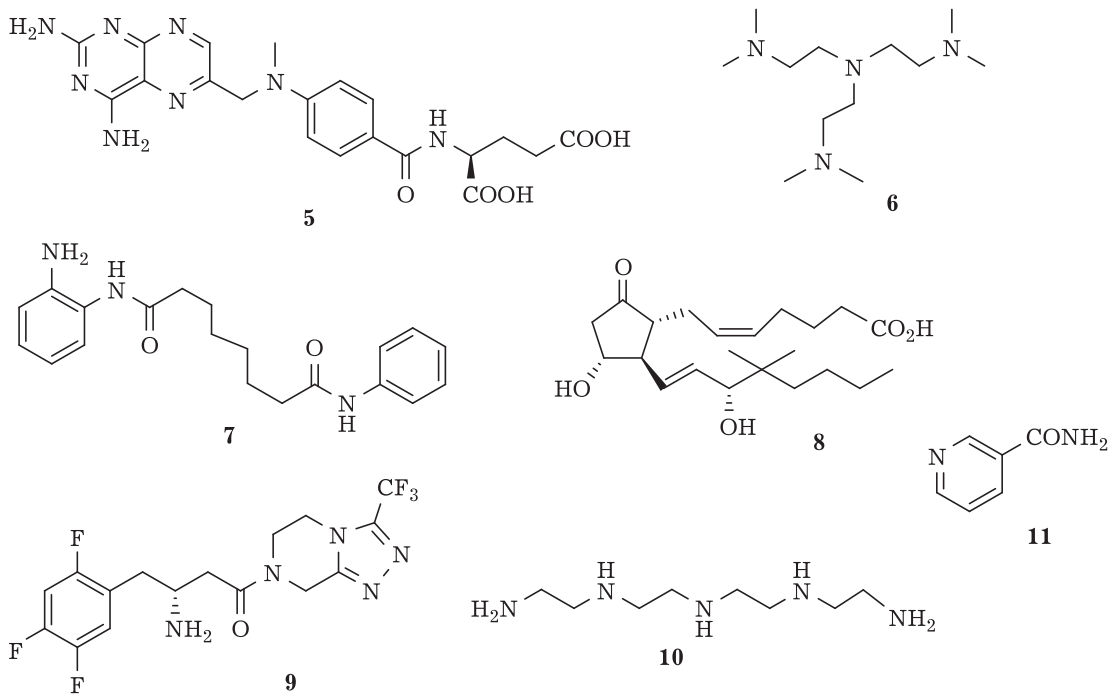

Fig. 2. Structures of methotrexate **5**; tris[2-(dimethylamino)ethyl]amine **6**; CAY10433 **7**; 16,16-dimethylprostaglandin E2 **8**; sitagliptin **9**; tetraethylenepentamine **10** and nicotinamide **11**.

ried out most frequently with cyclophosphamide, cytosar, busulphan, vepesid, *etc*. [9].

One of the most frequent complications of allogenic TBM is graft versus host disease (GvHD). GvHD of a definite degree of severity is observed after 30–50 % of transplantations from a relative donor and after approximately 80 % of transplantations from a non-relative donor. The occurrence of GvHD is connected with the immune conflict between the donor and recipient cells. Donor T-lymphocytes attack the alien cells and tissues of the new host. The targets of this attack are most frequently the skin, mucous membranes, liver and intestines of the recipient. GvHD is treated with the preparations possessing immunosuppressive action. At first, the patients are treated with glucocorticoids, and then, in the case, if the necessary effect is not achieved, other preparations are used, for example, methotrexate **5** (Fig. 2) [11].

The mobilization of hematopoietic stem and progenitor cells from the bone marrow into the bloodstream is widely used for hematopoietic transplantation. For this purpose, the intravenous introduction of the preparations belonging to hematopoiesis stimulators is carried out: granulocytic colony-stimulating factor or plerixafor, or a combination of both. Granulocytic colony-stimulating factor interacts with receptors on the cell surface in the bone marrow, stimulates cell proliferation, differentiation, functional activation and cell escape into blood [12]. Plerixafor (an antagonist of chemokine receptor CXCR4) is able to reversibly disturb the bonds of HSC with the stromal micro-surroundings in the bone marrow and to provide the escape of HSC into peripheral blood [13]. Then HSC is extracted with the help of cytopheresis, concentrated and stored till the moment of transplantation.

However, according to the data of different authors, failures of the attempts to prepare a transplant from the peripheral blood account for 5–40 % [14]. New mobilizing agents are necessary to increase the amount of stem cells in peripheral blood for the efficient recovery of hematopoiesis. For example, tris[2-(dimethylamino) ethyl]amine **6** manifested itself in mobilization in mice even better than the granulocytic colony-stimulating factor [15]; according to the opinion of the authors, it may become a promising mobilizing agent for hematopoietic cells in TBM. In another study, the authors proposed an optimal composition of rather small molecules (the best version was CAY10433, or BML-210, **7**) and cytokines,

which may provide substantial conservation of HSC characteristics through enhancement of cell expansion suppressing their differentiation [16].

Small molecules are clinically useful and powerful tools for the expansion of hematopoietic cells. Some compounds (16,16-dimethylprostaglandin E2 **8**, peroral hypoglycemic preparation sitagliptin **10**, vitamin nicotinamide **11**) were used in a clinical trial [17].

COMPOUNDS WITH HEMATOPOIETIC ACTIVITY

Various chemical compounds affecting hematopoiesis have been discovered. Xanthopterine **12** (Fig. 3), the substance that occurs in butterfly wings, brought relief of anemia in salmons and had a hematopoietic effect on young individuals, which correlated with the dose of this compound [18]. The synthesized compounds palmitoyldeoxyinosine **13** and palmitoylguanosine **14** enhanced hematopoiesis in normal mice. On the tenth day, the spleen mass, total leukocyte and neutrophil content were substantially higher in the mice treated with these compounds, in comparison with the individuals from the reference group [19]. Investigation of the cells of bone marrow revealed the hematopoietic effect of melatonin **15**, which is the major hormone of the pin-

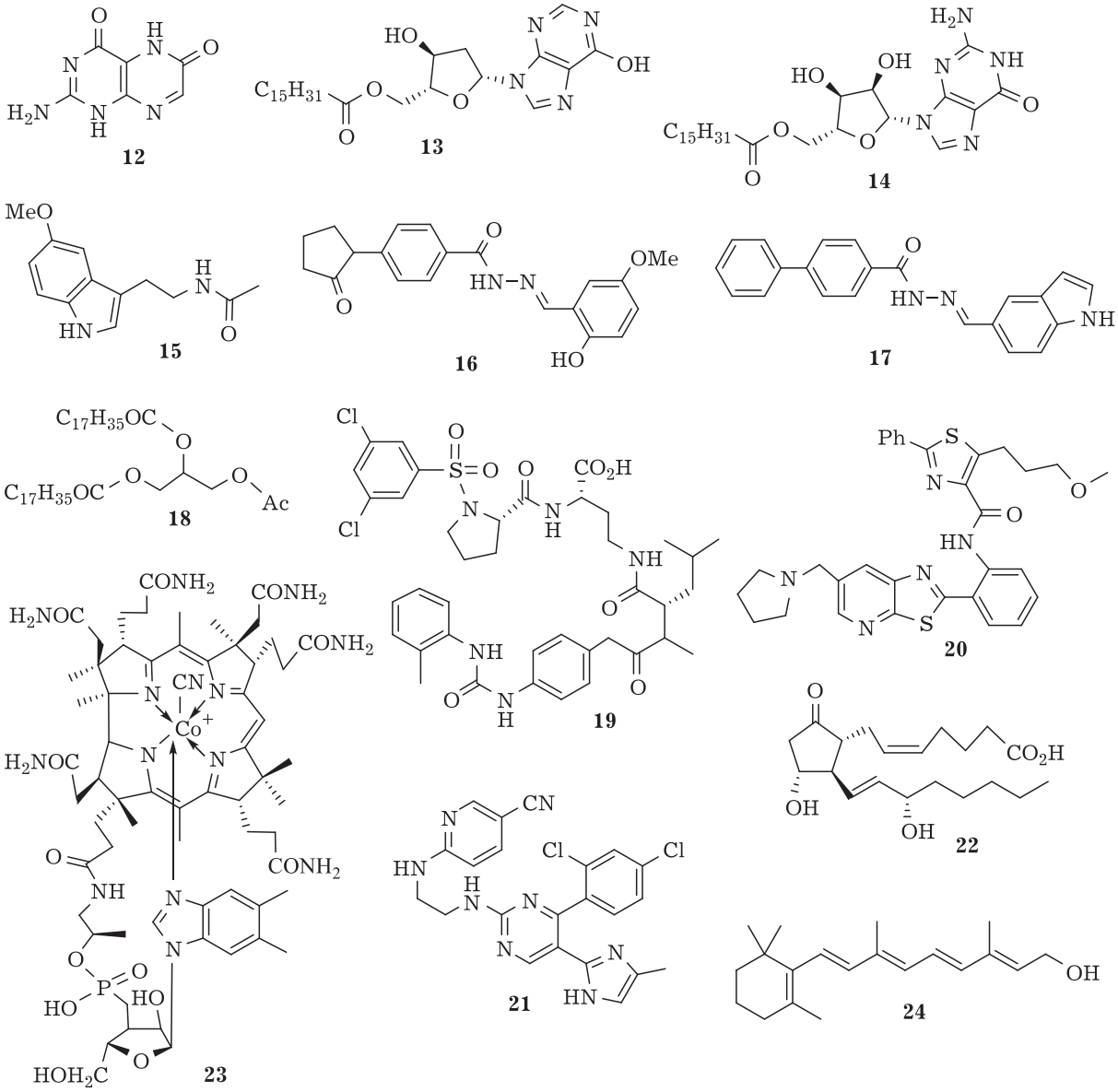

Fig. 3. Structures of xanthopterin **12**; palmitoyldeoxyinosine **13**; palmitoylguanosine **14**; melatonin **15**; compounds **16–18**; BIO5192 **19**; SRT3025 **20**; CHIR99021 **21**; prostaglandin E2 **22**; vitamin B_{12} **23** and vitamin A **24**.

eal gland [20]. The extract of *Angelica sinensis* plant is used in traditional Chinese medicine and exhibits a hematopoietic effect. It was established through fraction separation that this effect is due to water-soluble polysaccharides [21].

Some compounds were synthesized, and preliminary experiments on the effect of these compounds on cells allowed concluding that they may be used separately or in combination with other agents for the modulation of hematopoiesis, erythro-, granulo-, thrombo- and myelopoiesis. In the opinion of the authors, the proposed compounds may be also used separately or in combination with other agents for the treatment and prophylactics of diseases or states caused by the anomalous function of hematopoiesis and myelopoiesis [22]. The formulas of the two most active hydrazides **16** and **17** are shown in Fig. 3.

The extract of deer antlers fermented by *Bacillus subtilis* did not exhibit any direct effect but revealed the stimulating hematopoietic action on the cells of bone marrow in mice [23]. A mixture of monoacetyldiglycerides was isolated for the first time from the extract of *Cervus nippon* antlers. The structure of nine glycerides was established; the major compound in the mixture was glyceride **18**. The synthesized compound **18** exhibited even higher hematopoietic activity than the mixture of glycerides [24]. The compound BIO5192 **19** (an inhibitor of VLA-4) was determined to mobilize hematopoietic cells itself or in combination with the granulocytic colony-stimulating factor [25]. The compound SRT3025 **20** which activates deacetylase SIRT1 improved hematopoiesis in mice with Fanconi anemia, a rare genetic disease [26]. One more compound, CHIR99021 **21**, stimulated hematopoiesis in human stem cells [27].

Prostaglandin E2 **22** is the most widespread and the most biologically active prostaglandin in mammals. Its contribution to many diseases connected with cell proliferation, apoptosis, inflammation and immunity was revealed. It was also demonstrated that it plays a regulating role in hematopoiesis through the inhibition of myelopoiesis with simultaneous stimulation of the formation of erythroid and multilinear colonies [28]. Prostaglandin E2 enhances the survival and proliferation of HSC [29].

Among the substances that regulate hematopoiesis, vitamins are to be mentioned. Thus, nicotinamide **11** (inhibitor of SIRT1) promotes the expansion of hematopoietic cells [30]. The lack of vitamin B_{12} **23** manifests itself in humans in the form of hematopoietic disorders affecting in particular the formation of erythrocytes, neurological/psychical disorders and changes in the epithelium of the mucous membrane in the digestive tract [31]. Vitamin A **24** is important during all periods of life. Its physiologically active metabolite, retinoic acid, acts through its nuclear receptors as a powerful regulator during embryonal development, and also it is necessary for tissue homeostasis in adults. In adults, this acid regulates granulocytes and enhances erythropoiesis. Vitamin A may promote iron absorption and metabolism preventing anemia, and also it plays a key role in immune reactions of the mucous membrane modulating the function of regulatory T-cells. In addition, the defective transfer of the signals of retinoic acid /receptors of retinoic acid manifests itself in the pathogenesis of acute leukemia [32].

RESTORATION OF HEMATOPOIESIS AFTER INTAKE OF MEDICINAL PREPARATIONS

Various disorders of the blood system, for example, hemorrhages and thromboses as the side effects of drug intake, comprise a serious diagnostic and therapeutic problem. In the USA, the Food and Drug Administration (FDA) revealed the major side effects of medicines causing the highest level of anxiety of doctors. These effects include disorders of hematopoiesis and hemostasis. Among the 15 most widespread preparations causing hematological disorders, there are antidepressants (citalopram, duloxetine, escitalopram, paroxetine, fluoxetine, bupropion, sertralin), statins (rosuvastatin, atorvastatin, simvastatin), angiotensin-converting enzyme inhibitor (lisinopril), hypoglycemic agent (metformin), antiviral drug (oseltamivir), potency regulator (sildenafil) and paracetamol.

Depression is the main indication for the use of selective serotonin reuptake inhibitors. For the correction of hemorrhage at the background of drug intoxication participated by selective serotonin reuptake inhibitors, the efficiency of a combination of vitamin K **25** (Fig. 4) and a concentrate of prothrombin complex was demonstrated. In another study, spontaneous aplastic anemia arose in an elderly woman after lisinopril intake for 12 months. The treatment involved high-dose (up to 150 mg/day) therapy with prednisolone **26** and granulocytopoiesis stimulation (filgrasrim, 300 μg/day through hypodermic injections for 25 days) [33].

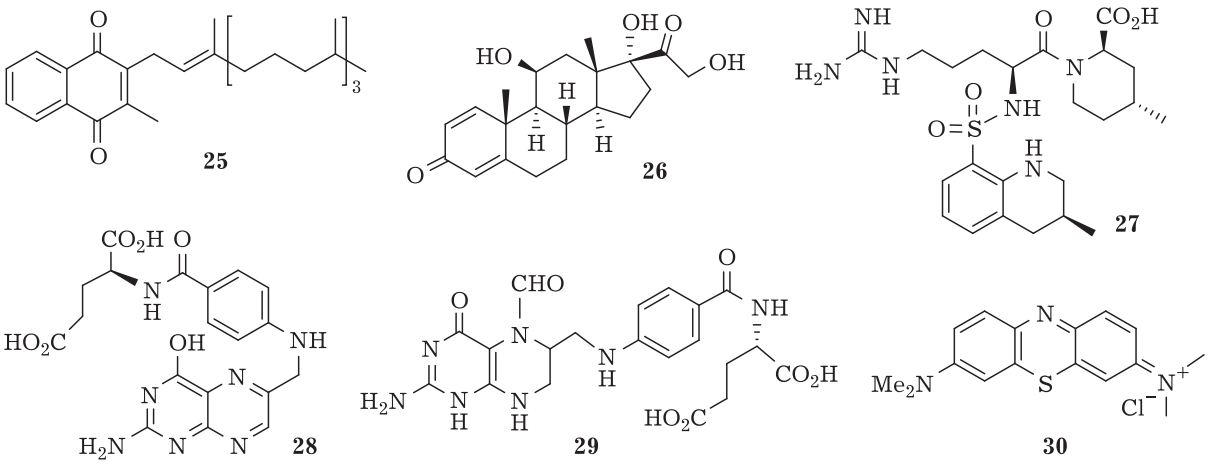

Fig. 4. Structures of vitamin K **25**; prednisolone **26**; argatroban **27**; folic acid **28**; folinic acid **29** and methylene blue **30**.

In rare cases, the application of statins may cause the development of thrombotic thrombocytopenic purpura. The clinical prognosis for patients improves with the immediate start of infusion therapy and plasma filtration [33]. In Great Britain, a usual reason of thrombotic thrombocytopenic purpura is the application of the derivatives of thienopyridine: ticlopidine and clopidogrel, however, the cases of this disease caused by the intake of simvastatin (40 mg) and atorvastatin (20 mg) were observed. The treatment was performed through the intravenous administration of methylprednisolone for three days (0.5–1.0 g), and some patients were treated with the monoclonal antibody rituximab [34].

Heparin-induced thrombocytopenia is a form of thrombocytopenia caused by the intake of heparin, which is widely used in clinical practice for the prophylactics and treatment of thromboses. For patients with heparin-induced thrombocytopenia, instead of heparin, anticoagulants argatroban **27** and some other preparations with more complicated structures were licensed for the prophylactics and treatment of thrombosis [35]. Eptifibatide and tirofiban (inhibitors of ligand mimetics) are often applied after coronary angioplasty to decrease thrombosis by distorting the function of thrombocytes. However, in addition to the desirable thrombocyte disfunction, they may cause severe thrombocytopenia in a low percentage of patients [36].

A combination of antibacterial preparations trimethoprim/sulfamethoxazole is used against a broad range of bacterial infections and is a preferable medicine to treat some kinds of pneumonia. After the administration of a high dose of trimethoprim and sulfamethoxazole (20 and 100 mg/kg of body mass per day, respectively), the signs of acute megaloblastic anemia were detected in the treated patient on the 4th day, which was a consequence of the deficit of folic acid (vitamin B_9) **28**. Antibacterial preparations were withdrawn, and then 15.0 mg of folic acid was administered intravenously in 6 doses, along with 5.0 mg of folinic acid per day perorally (the bioactive form) **29**. Within 48 h, a thin blood film test revealed the signs of recovery with rapid reticulocytosis (8.6 %), large thrombocytes and the left shift in the series of granulocytes; later on blood analysis reverted to the norm [37]. It was detected that the interaction between folic acid and antiepileptic drug phenytoin is bidirectional. The deficit of the vitamin as a result of long-term therapy with phenytoin is a common phenomenon, but the progress of deficit into megaloblastic anemia occurs rarely. However, the data available allow assuming that the arising deficit is harmful to patients. On the other hand, the addition of folinic acid to patients with the deficit of folic acid-treated with phenytoin leads to a decrease in its concentration in blood serum and may cause the loss of control over the convulsive state [38].

The preparations that cause methemoglobinemia either directly oxidize hemoglobin or are activated to form oxidizing substances. Phenazopyridine, which is used to relieve cystitis, may cause oxidative hemolysis. Dapson, which is used to treat leprosy, dermatitis herpetiformis and for the prophylactics of pneumocystic carinii, is metabolized to a hydroxylamine derivative and may cause methemoglobinemia. Isoamylnitrite and isobutylnitrite, used in medicine, also may lead to methemoglobinemia. The treatment of this pathology includes rejection of the preparation, administra-

tion of oxygen inhalations and oral intake of methylene blue **30** [36]. Though the latter compound is itself able to oxidize hemoglobin, due to the interaction with coenzyme it causes a substantial shift of the equilibrium to the formation of hemoglobin from methemoglobin [39].

RESTORATION OF HEMATOPOIESIS AFTER CYTOSTATIC THERAPY

Chronic liver diseases are usually accompanied by mild or moderate anemia. The development of anemia in the case of hepatite or hepatocirrhosis is due to distortions of proliferation in bone marrow with the emergence of immature erythrocytes into the blood, as well as to the toxic effect of viruses, drugs and toxins. A definite role in the development of anemia in the case of hepatocirrhosis is played by the violation of absorption, the deficit of iron, folic acid and vitamin B_{12} [40]. The cytopenic syndrome was revealed by the authors in 97.4 % of the patients of the group under investigation. The most clearly pronounced changes in hematopoiesis were detected in the patients with hepatocirrhosis of viral etiology. In general, the changes in bone marrow hematopoiesis depending on the etiology of liver disease were revealed with a high rate in the patients suffering from hepatocirrhosis [41]. The disorders of this kind are observed in the patients suffering from AIDS, rheumatoid arthritis and some other chronic diseases [42].

The development of a malignant tumour in the organism is accompanied by the local changes connected with the distortion of the morphological structure of tissues in the affected organ, hemorrhage, pain, as well as general changes in the blood system, skin diseases and arthropathy, fever and other disorders. Changes in the blood system are most often manifested as the development of anemia, leucocytosis, thrombocytosis or thrombocytopenia. The major role in the development of anemia in the case of oncological diseases is played not by a decrease in the production of erythropoietin but by the suppression of the response of the cells that are precursors of erythropoiesis. Anemia develops in patients as a consequence of accelerated and increased destruction of erythrocytes. Disregulatory processes in myeloid hematopoiesis in oncological patients are accompanied by neutrophilic leucocytosis, eosinophilia and leucemoid reactions. Radiation therapy and chemotherapy usually bring even more complications into disregulation in the vitally important system, so an improvement of the methods of correction is required [42].

The use of the models of myelosuppressions (the administration of cytostatic preparations possessing different action mechanisms, radiation) showed that the development of hypoplasia of hematopoietic tissue, the dynamics of hematopoiesis recovery and the direct suppressing effect of toxic agents on hematopoietic cells are mainly determined by the nature of disregulation of hematopoiesis, and first of all separate regulatory elements. Reparative processes in the hematopoietic tissue are to a substantial extent performed by the stromal cells of bone marrow due to the resistivity to the action of their precursors – mesenchymal stem cells [43].

The toxic effects of the combination of doxorubicin with docetaxel were studied in breast cancer patients of the III-IV stages with respect to the erythroid and granulocytic hematopoietic lineages, and the processes of their recovery were studied in detail. It was demonstrated that intense maturing of erythroid and granulocytic colony-forming units provides recovery of hematopoiesis even in the case of decreased proliferative activity of these cells [44]. The stimulating effects of filgrastim, a preparation of colony-stimulating factor, with respect to granulocytic hematopoietic lineage were studied. It was demonstrated that the introduction of filgrastim (in the dose of 300 μg, twice) caused activation of bone marrow granulocytopoiesis suppressed by the doxorubicin/docetaxel combination [45]. Neutropenia is fraught with the most substantial danger in the manifestation of myelodepression. The most toxic agents for neutrophils are alkylating substances (cyclophosphamide, nitrosocarbamide, etc.) and preparations hindering the synthesis of nucleic acids (for example anthracycline antibiotics). The degree and duration of neutropenia after chemotherapy are in direct correlation with the rate of infectious complications. Antibiotics are used to treat infection; different approaches are developed against myelotoxicity, for example, the application of filgrastim [46]. The prophylactics of neutropenia during chemotherapy may be performed by myelostimulators of prolonged action, which are prolonged forms of myelocytokines [47].

In some cases, a pronounced side action of cytostatic preparations may require drug treatment, delay or even cessation of chemotherapy. In this connection, it is important to develop new means that would be able to enhance the efficiency of specific treatment and decrease the tox-

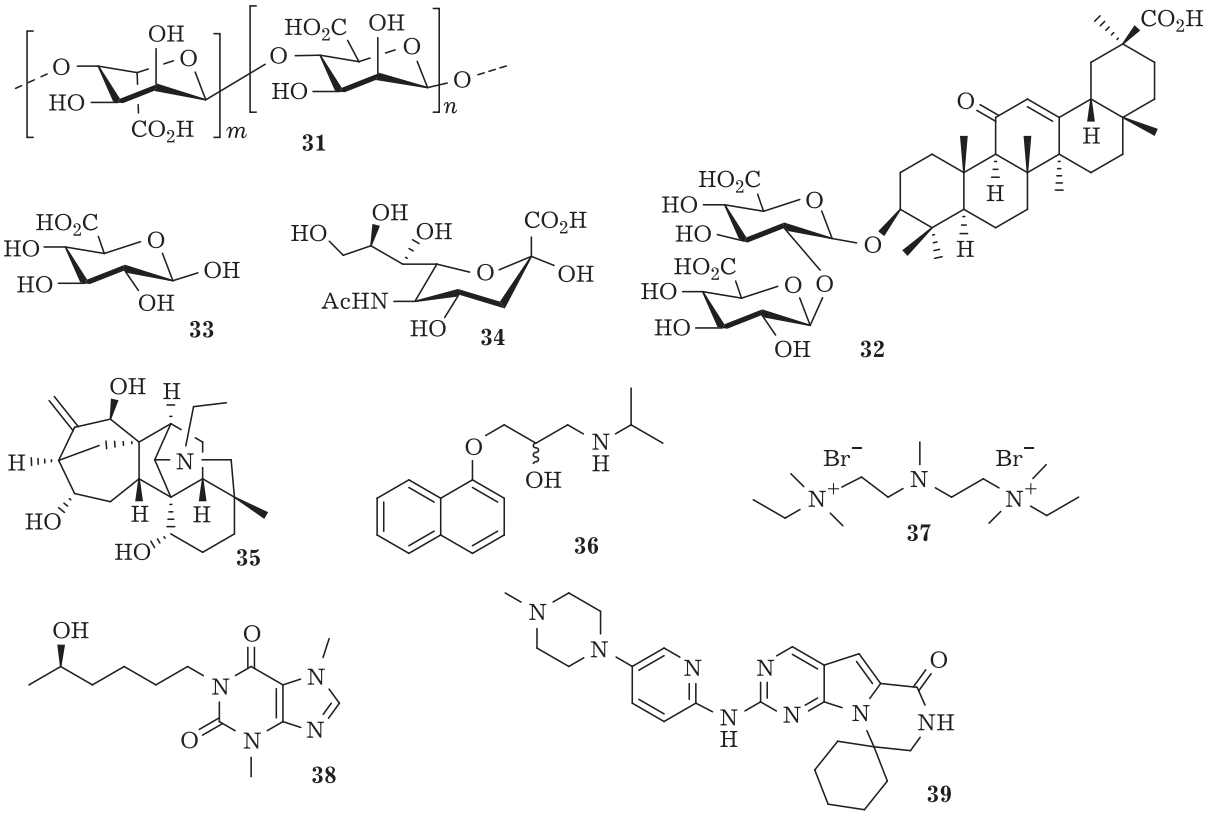

Fig. 5. Structures of alginic acid **31**; glycyrrhizic acid **32**; *D*-glucuronic acid **33**; N-acetylneuraminic acid **34**; napellin **35**; propranolol **36**; azamthonium bromide **37**; lisophylline **38** and trilaciclib **39**.

icity of cytostatic agents. Polysaccharides originating from plants and possessing a broad range of pharmacological action were considered as promising preparations. The possibility to use water-soluble polysaccharides extracted from rhizomes of *Acorus calamus* as the means to enhance chemotherapy of tumours and to decrease the side effect of the cytostatic agent on the blood system and on the liver of animals was demonstrated [48]. The effect of low-molecular sodium alginates (the salt of the polysaccharide of alginic acid **31**, Fig. 5) on the parameters of peripheral blood and bone marrow of mice with lung carcinoma, alone and in combination with the alkylating agent cyclophosphane, was studied. It was demonstrated that the administration of sodium alginate with the molecular mass 1–10 and 20–30 kDa (in the dose of 100 mg/kg for 12–22 days) in animals with carcinoma decelerates the growth of the tumour, normalizes the content of blood corpuscles and prevents leucopenia. This preparation activated regeneration of the granulocytic hematopoietic lineage damaged by the introduction of the cytostatic preparation, due to stimulation of the activity of precursors of granulocytopoiesis [49].

It was demonstrated that the preparation which is a mixture of glucose and pantohematogen stimulates cytostatically suppressed bone marrow granulocytopoiesis at the level of morphologically differentiated elements of bone marrow and peripheral blood [50]. Comparative evaluation of the hemostimulating activity of granulicytopoiesis stimulators was carried out for granulocytic colony-stimulating factor, pantohematogen, glycyram (its active substance is the ammonium salt of glycyrrhizic acid **32**) and the preparation of *D*-glucuronic acid **33** – with respect to the granulocytic hematopoietic lineage suppressed by 5-fluorouracyl or cyclophosphan. The effects of the indicated stimulators at the background of the action of 5-fluorouracil are substantially lower than the effect after the administration of cyclophasphan, which may be connected with deeper destructive changes in the cell elements of hematopoietic micro-surroundings [51].

Glucuronic acid **33** may be used as the medication that decreases the toxic action of cytostatic agent on hematopoiesis through the stimulation of granulocytopoiesis. For example, it was established experimentally in mice that the intro-

duction of glucuronic acid in the dose of 50 mg/kg on the 3rd, 4th, 5th day after the intake of the cytostatic agent in the maximal endurable dose stimulates granulocytopoiesis [52]. In order to decrease the toxic effect of cytostatic agents on hematopoiesis through the stimulation of erythro- and granulomonocytopoiesis, N-acetylneuraminic acid **34** (a compound which is widespread in animal tissues) was proposed as a stimulator of hematopoiesis for hypoplastic states of bone marrow. It was established in the experiments in mice that the introduction of this acid in the dose of 50 mg/kg on the 3rd, 4th, 5th day after the intake of a cytostatic agent in the maximal endurable dose stimulates erythro- and granulomonocytopoiesis [53].

Myelostimulating activity of the synthesized compound bis-(γ-*L*-glutamyl)-1-cysteinyl-glycine dilithium salt /*cis*-diaminodichloropalladium/copper (II) chloride (II) (1000 : 1 : 1) **2** (in the dose of 5–10 mg/kg) was investigated in rats at the background of the preliminary introduction of cyclophosphate in the dose of 100 mg/kg. The introduction of the compound has a noticeable stimulating effect, which was most clearly pronounced for the red hematopoietic lineage. It was noted that erythroid processes displaced leukocytic ones, and expansion of granulocytic lineage was also observed. The appearance of immature forms of leykocytes in blood was the evidence of activated hematopoiesis in bone marrow. An improvement of the general condition and a positive body mass dynamics were observed in animals; death cases were not observed [6].

Alkaloid napellin **35**, extracted from Baikal aconite exhibited clearly pronounced regenerative effects with respect to the granulocytic hematopoietic lineage in the model of cytostatic myelosuppression in mice. The mechanism of the stimulating action of napellin involves the activation of the functions of hematopoietic precursor cells. It is also indicated that the development of not only an agent stimulating hematopoiesis, but also a drug for regenerative medicine in general is promising on the basis of an alkaloid [54].

Guanosine, guanine improved the recovery of hematopoiesis in mice after the introduction of cyclophosphamide, and the synthesized compounds palmitoyldesoyinosine **13** and palmitoylguanosine **14** caused an increase in the number of colony-forming units in the bone marrow, recovered hematopoiesis after the introduction of cyclophosphamide and 5-fluorouracyl [19]. A medication that stimulates erythropoiesis and granulocytopoiesis under the toxic action of cytostatic preparations is the extract of *Scutellaria baicalensis* containing flavonoids, coumarins, saponins, steroids [55]. Results showed that melatonin **15** protects bone marrow and lymphoid tissues from the destructive action of cytotoxic preparations and stimulates depressed bone marrow [56].

It was established that a beta-adrenoreceptor blocking drug obsidian or propranolol **36** (in the dose of 5 mg/kg two times) has a substantial stimulating effect on the rate of eth recovery of bone marrow hematopoiesis after the intake of 5-fluorouracil. In particular, on the 8th day of the experiment, the content of erythrocaryocytes of different maturity in the bone marrow of mice after receiving propranolol at the 3rd day after the introduction of the cytostatic agent was reliably higher than that not only in the reference group (by a factor of more than 6) but also in the intact animals (more than 2 times). As a result, the introduction of propranolol was accompanied by an increase in the absolute number of erythrocartocytes by a factor of more than 9 and 4.5 times in comparison with the reference and initial level, respectively [57].

The introduction of ganglionic blocker pentamine **37** (azamethonium bromide) in mice receiving 5-fluorouracil was accompanied by the clearly pronounced stimulating effect with respect to the speed of recovery of bone marrow hematopoiesis. For instance, the total amount of myelocaryocytes in the bone marrow of mice having received pentamine at the 3rd day after the introduction of the cytostatic agent was reliably 1.5–2 times higher than in reference animals after the introduction of 5-uracil alone. It was demonstrated that an increase in the total amount of myelocaryocytes at the 9th day is due first of all to a substantial (more than 5 times) increase in the content of erythrocaryocytes in the bone marrow. In addition, pentamine **37** stimulated also granulocytopoiesis suppressed by the cytostatic agent. On the 7th and 9th day, the amount of immature neutrophilic granulocytes reached the initial level and statistically significantly (by a factor of 4) exceeded the corresponding reference values. Accelerated recovery of the content of mature forms of neutrophilic granulocytes in the bone marrow was also detected [58].

Ginsan is a polysaccharide from the extract of *Panax ginseng*. The effect of ginsan (up to 250 mg/kg) on hematopoiesis and immunological functions was evaluated in mice after the administration of a sublethal dose of cyclophosphamide. It was discovered that ginsan caused a substantial improvement of the survival (by a factor

of 5.3) in comparison with the survival in mice treated with cyclophosphamide alone, in 24 h after the treatment with the cytostatic agent. It was assumed that subsequent intake of ginsan may decrease immunohematopoietic suppression and allow using a higher dose of cytotoxic preparations to treat cancer [59]. It was established in another investigation that the treatment of mice with chemotherapeutic preparations triggers the inhibitors of hematopoiesis but the induction of these inhibitors may be eliminated by applying an anti-inflammatory agent lisofylline **38** (100 mg/kg). Due to this, lisofylline may accelerate the recovery of hematopoiesis after cytotoxic therapy [60]. It was shown that the simultaneous introduction of trilaciclib **39**, which is a low-molecular inhibitor of ciclin-dependent kinases 4 and 6 (CDK4/6), with cytotoxic chemotherapy protects hematopoietic stem cells in mice from depletion caused by chemotherapy with 5-fluorouracil [61].

RESTORATION OF HEMATOPOIESIS AFTER THE ACTION OF RADIATION

Irradiation doses affect mainly rapidly fissioning cells of the organism and cause various affections. Because of this, hematopoietic organs and the organs of the immune system suffer from radiation to the highest extent. It was established that after the oral administration of the polysaccharide of yellow melilot - pectin **40** (Fig. 6) in the dose of 0.5 g/kg hematopoiesis processes were

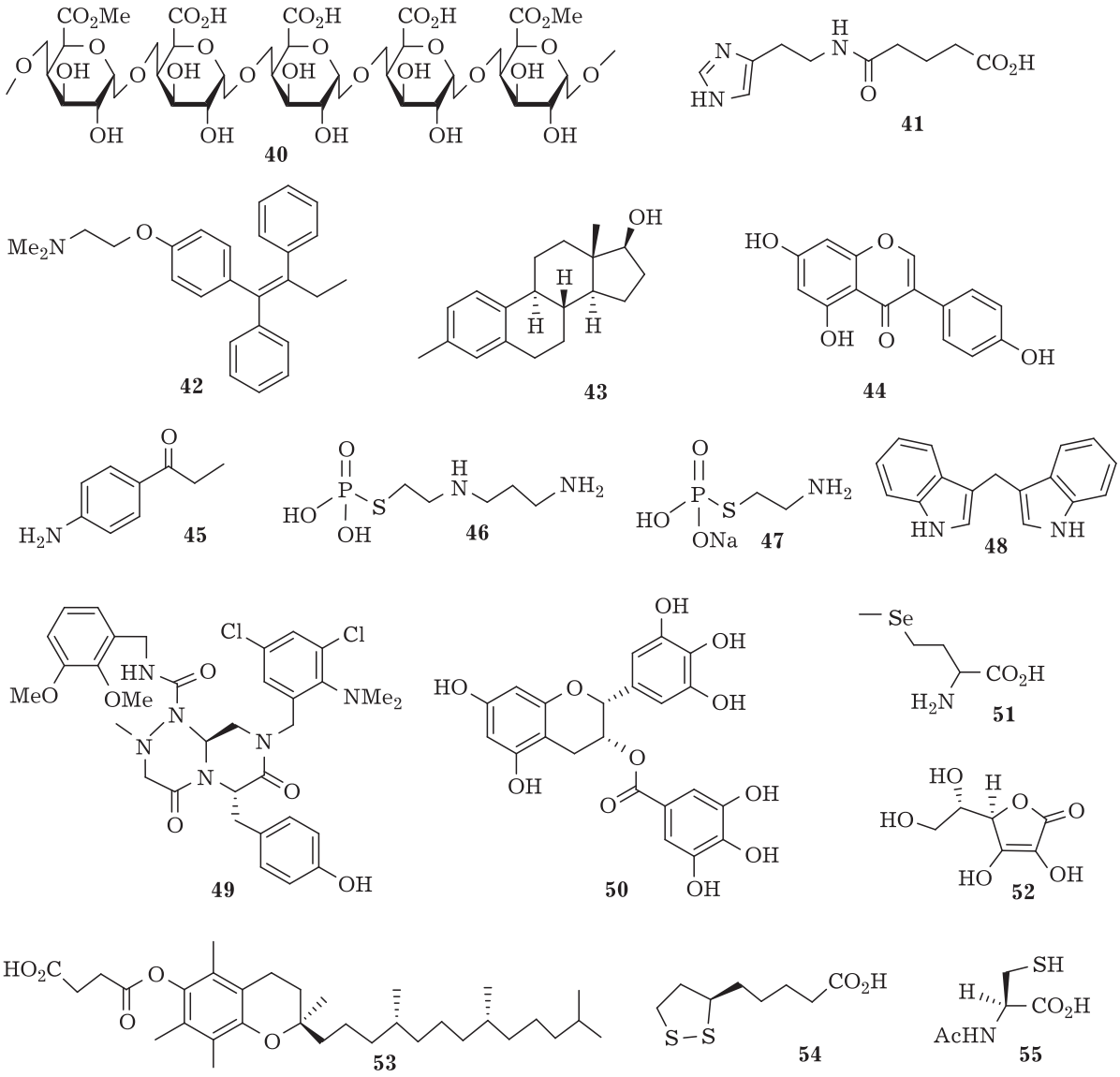

Fig. 6. Structure of pectin **40**; imidazolylethanamide of pentanedionic acid **41**; tamoxifen **42**; β-estradiol**43**; genistein **44**; 4′-aminopropiophenon **45**; amifostine **46**; WR-638 **47**; 3,3′-diindolylmethane **48**; YH250 **49**; (−)-epigallocatechine-3-gallate **50**; *L*-selenomethionine **51**; vitamin C **52**; vitamin E succinate **53**; α-lipoic acid **54** and N-acetylcysteine **55**.

restored in rats irradiated totally or partially with medium doses of γ-rays. The polysaccharide was most efficiently restoring erythropoiesis and lymphopoiesis in rodents with the preserved hematopoietic territory [62].

In another investigation, the effect of dicarbamine (imidazolylethaneamide of pentanedioic acid) **41** on the dynamics of the leucocytic pattern of peripheral blood of mice after single action of ionizing radiation in the mode of therapeutic oral administration in the doses of 0.5–50.0 mg/kg was studied. It was demonstrated that the compound in the dose of 5.0, 15.0, 50.0 mg/kg revealed statistically significant radioprotective effect, thus decreasing the extent of a drop in the number of leukocytes due to segmented neutrophils, lymphocytes, and accelerating the restoration of the number of leukocyte cells to the initial level [63].

It was established in the 40-es of the XX century that steroid hormones, in particular estrogens, also exhibit radioprotective activity. Radioprotective agent indometafen was discovered (no formula is given in the literature for this preparation), which is a synthetic nonsteroidal antiestrogen from the group of tamoxifen **42**, pharmaceutical substance and antagonist of estrogen. It was demonstrated that this drug exhibits high radioprotective and therapeutic efficiency in case of chronic radiation injuries caused by external irradiation with different dose rates. Indometafen is able to prevent myelopoietic disorders and accelerate the recovery of cells in peripheral blood in the case of a substantial total irradiation dose. The efficiency of indometafen in the prophylactics of hematopoietic disorders under the action of X-rays was established [64]. To reveal possible mechanisms of the radioprotective action of the agents (indometafen, β-estradiol **43**, isoflavon genistein **44**) on bone marrow, the number of leukocytes in the peripheral blood of rats was studied within different time intervals after irradiation. After the oral introduction of indometafen in the dose of 30 μg/kg, 5 days before irradiation, the survival of mice subjected to radiation increased by 20–40 % on average. After the intramuscular introduction in the dose of 40 mg/kg 5 days before radiation action, β-estradiol promoted an increase in the survival of irradiated mice by 8–58 %. Genistein exhibited radioprotective properties when applied in the dose of 200 mg/kg, 24 h before irradiation [65].

The efficiency of compound **2**, dilithium salt of bis-(γ-*L*-glutamyl)-1-cysteinyl-glycine/*cis*-diaminodichloropalladium/copper (II) chloride (1000 : 1 : 1) was investigated in the model of radiation-caused pancytopenia (the dose of γ-radiation absorbed per one rat was 3.5 Gy for dose rate 1.4 Gy/min). The compound stimulated hematopoiesis and promoted correction of post-radiation myelosuppression. It should be stressed especially that as early as on the 3rd day after irradiation of experimental animals at the background of the introduction of this compound the number of leukocytes in the peripheral blood increased approximately by a factor of 3 in comparison with irradiated reference [6].

Irradiation with a dose of 3–8 Gy leads to death within ~30 days due to the development of neutropenia and thrombocytopenia, higher doses cause death earlier due to the injury of the gastrointestinal system and the central nervous system. In 1969, the protective capacity of several radioprotective agents was tested in mice against three kinds of death after irradiation. Almost all these agents provided better protection from hematopoietic disorders and lower protection from the injury of the gastrointestinal tract. Among these agents, only 4′-aminopropiophenon **45** (40 mg/kg), which is itself able to cause hematopoietic disorders, exhibited efficiency in weakening the injury of the central nervous system. Among other compounds, the lowest toxicity was exhibited by the presently well-known cytoprotector amifostine **46** and WR-638 salt **47** in the doses of 500 mg/kg [66]. The clinical trial showed that amifostine introduced in the dose of ≤200 mg/m^2 3 times a week was well tolerable and exhibited hematological activity in patients with the myelodysplastic syndrome [67]. A case was described when an 11 years old boy with multiple recurrencesthe of lymphoblastic leucosis became dependent on hemotransfusion with myelodysplasia and chromosome disorders after 5 years of aggressive therapy. Intravenous introduction of amifostine in the dose of 200 mg/m^2 3 times a week resulted within 1 month in normalization of the amounts of leukocytes and neutrophils, as well as the level of hemoglobin. The number of thrombocytes increased, so finally, the need for hemotransfusion was eliminated. The boy returned to school and to normal life. So, amifostine may improve hematopoiesis in the case of secondary myelodysplastic syndromes [68]. Amifostine was recognized as the most efficient chemical radioprotective agent among the compounds synthesized and tested during the years 1959–1973. It was stressed that amifostine provides highly selective differential radioprotection of normal tissues (hematopoietic

tissue, gastrointestinal system, and skin) in comparison with a tumour [69].

It was demonstrated that octadecenyl thiophosphate $(H_{35}C_{18}O)_3PS$ exhibited radioprotective activity in mice after oral or intraperitoneal introduction 30 minutes before the whole-body irradiation with a dose of 9 Gy. Acute disturbance of hematopoiesis and gastrointestinal tract was moderated under the action of octadecenyl thiophosphate. In general, the data obtained indicate that this agent is a powerful radioprotector and weakens the injury of tissues in case of acute hematopoietic and acute gastrointestinal radiation syndrome [70]. In the dose up to 75 mg/kg, 3,3′-diindolylmethane **48**, which is present in broccoli, Brussels sprouts and cabbage, improved the survival of rodents within a broad range of doses (5–13 Gy). This allows assuming that this agent may moderate both gastrointestinal and bone marrow injuries [71].

At present, there is no therapeutic agent approved by the FDA to treat acute radiation syndrome after irradiation. It was discovered that a small molecule YH250 **49** (specific antagonist of p300/catenin interaction) stimulates hematopoiesis in mice irradiated lethally or sub-lethally. A single introduction of YH250 24 h after irradiation may cause a substantial stimulation of the proliferation of hematopoietic stem cells, improve survival and accelerate the restoration of the parameters of peripheral blood [72].

In addition to amifostine, which is accepted by the FDA as a radioprotector, the search for other possible agents is ongoing permanently. It was established in experiments with mice that prostaglandin E2 **22** increased the survival of hematopoietic stem cells and accelerated the recovery of hematopoiesis after radiation injury [73]. It was discovered that ginsan (polysaccharide from the extract of *Panax ginseng*) causes a substantial increase in the number of bone marrow cells, spleen cells, granulocytic colony-forming cells, and circulating neutrophils, lymphocytes and thrombocytes in irradiated mice. These data point that ginsan may be a useful agent to decrease the time necessary for the recovery of hematopoietic cells after irradiation [74]. Another study demonstrated that the doses of hydrogenated castor oil Cremophor within the range of 25–50 μl/kg, introduced intravenously in mice 1 day before sublethal irradiation, protected the regenerative ability of bone marrow, which resulted in hematopoietic radioprotection and long-term survival of irradiated mice [75].

The introduction of the extract of black tea provided a substantial increase in the survival of mice after whole-body irradiation with a dose of 7.0 and 7.5 Gy. The obtained data showed that the extract of black tea may prevent radiation-induced hematopoietic syndromes and may be useful as protection of radiation-caused injury [76]. The goal of another investigation was to study the radioprotective effects of tea polyphenols against radiative injury in mice. The radioprotective action on the hematopoietic system, serum cytokines and endogenous antioxidant enzymes was studied. A mixture containing approximately 50 % (−)-epigalllocatechine-3-gallate **50** in addition to other catechines exhibited the highest radioprotective effect against radiation-caused changes in hematological parameters (the number of erythrocytes, leukocytes and hemoglobin) and sustained the parameters of the spleen and thymus [77]. The radioprotective potential of (−)-epigallocatechine-3-gallate was studied in mice. The treatment with this compound (0.183 mg/kg) 1.5 h after whole-body irradiation of mice with the lethal dose provided the survival of 45 % of individuals for 30 days and helped to recover the body mass of the animals. Earlier recovery of various hematological parameters was observed in the animals receiving (−)-epigallocatechnie-3-gallate, in comparison with the group of irradiated animals without treatment. Substantial recovery of the number of colony-forming units of bone marrow was observed in the irradiated animals treated with this phenol [78]. Other results allow assuming that (−)-epigallocatechine-3-gallate provides better protection for erythropoiesis than granulopoiesis from radiation-caused injury [79].

The problem was set to determine whether the nutrition additive containing *L*-selenomethionine **51**, vitamin C **52**, succinate of vitamin E **53**, α-lipoic acid **54** and N-acetylcysteine **55** can improve the survival of mice after whole-body irradiation. Antioxidants introduced before or after irradiation caused a substantial increase in 30 days survival of mice after the action of a potentially lethal dose of X-rays. Preliminary treatment of the animals with antioxidants caused a substantial increase in the total amount of leukocytes and neutrophils in peripheral blood after 4 and 24 h from irradiation with the dose of 1 and 8 Gy. The antioxidants were effective in the prophylactics of peripheral lymphopenia but only in the case of irradiation with a low dose. The consumption of antioxidants also caused an increase in the number of bone marrow cells after irradia-

tion. The antioxidant diet provided more efficient restoration of bone marrow after sub-lethal or potentially lethal irradiation. So, the consumption of antioxidants is likely to be an efficient approach to radioprotection of hematopoietic cells and improvement of the survival of animals, while modulation of apoptosis is the mechanism of the protection of the hematopoietic system by antioxidants [80].

TREATMENT OF HEMATOPOIETIC PATHOLOGY

Hematopoiesis leads to the formation of different blood cells. Distortions in this development programme cause blood cell diseases including leucosis. Hematopoietic cytokines, such as granulocytic colony-stimulating factor, are used at present in medicine to correct the defects of hematopoiesis including the restoration of normal hematopoiesis in oncological patients suppressed by chemotherapy, stimulation of the development of normal granulocytes in patients with congenital agranulocytosis, and mobilization of hematopoietic precursors during transplantation of blood cells [81].

Fanconi anemia is a rare congenital disease arising in the case if a defect is present in the cluster of proteins responsible for DNA reparation. As a result, the neoplastic process (most frequently acute myeloblastic leucosis) and aplastic anemia develop in patients by the age of 40 on average. Investigations showed that the application of antioxidants tempol **56** and resveratrol **57** (Fig. 7), respectively, held back the development of the tumour and caused a decrease in hematological defects in the mouse models of Fanconi anemia [82]. Defects of hematopoiesis in these mice may be partially corrected by the application of resveratrol [83]. It was also established that metformin **58** improves hematopoietic defect and delays the formation of tumours in the mice with Fanconi anemia [84].

True polycythemia is a benign tumour process in the blood system connected with excessive myeloproliferation (hyperplasia of the cell elements of the bone marrow). As a result, thrombosis and embolism arise in arterial and venous vessels of different sizes. The first-line therapy for the treatment of true polycythemia is still the cytostatic preparation hydroxycarbamide **59** or interferon. The latter is most frequently used for young patients [85]. The efficiency in weakening the symptoms of true polycythemia and primary myelofibrosis (a tumour disease) was demonstrated for ruxolitinib **60**, an inhibitor of JAK-kinase 1 and 2. The recent clinical investigation demonstrated its efficiency in weakening the symptoms and the course of true polycythemia [86]. Ruxolitinib caused a rapid improvement of multiple manifestations of myelofibrosis, a less essential increase in the size of the spleen, an improvement of the quality of life and potentially longer survival. However, similar to other chemotherapeutic agents, intake of ruxolitinib is connected with some side effects, such as anemia and thrombocytopenia [87]. It is assumed that a combination of an inhibitor of JAK2-kinase (for example ruxolitinib) and an inhibitor of tyrosine kinase CEP-701 (lestaurtinib) **61** may provide optimal results against similar myeloproliferative diseases [88]. CEP-701 passed clinical trials for the treatment of different kinds of cancer, polycythemia with V617F mutation in the JAK2 gene and essential thrombocytosis. Substantial efforts were aimed at the development of CEP-701 for the treatment of acute myelogenous leucosis.

Ataxia telangiectasia (Louis-Barr syndrome) belongs to rare neurodegenerative diseases accompanied by a high risk of lymphomas and leucosis. This syndrome is due to the defect in the ATM gene, with its protein coordinating timely reparation of double-stranded DNA splits. Antioxidant N-acetylcysteine **55** decreases morbidity and risk of lymphoma in laboratory mice in which the defect of the ATM gene was modelled [89].

Non-Hodgkin's lymphoma is a general term for a group of various malignant tumours including all lymphomas except Hodgkin's. For patients with low-activity lymphomas, a new combination of two cytostatic preparations was developed: fludarabin **62** (in the dose of 20–30 mg/m^2 of body surface area), mitoxantrone **63** (in the dose of 10–14 mg/m^2) and synthetic glucocorticosteroid dexamethasone **64**, which is well tolerable and very efficient. The second phase of the investigation of the efficiency of this combination involving 51 patients revealed 47 % complete remission cases [90].

Pernicious anemia or megaloblast anemia (obsolete term: malignant anemia) is the disease caused by hematopoietic disorder as a consequence of the lack of vitamin B_{12} **23** in the organism. The therapeutic effect from the parenteral administration of vitamin B_{12} was observed in eight patients with pernicious anemia. Vitamin B_{12} in initial doses 50 or 25 μg caused an increase in the number of reticulocytes and brought the

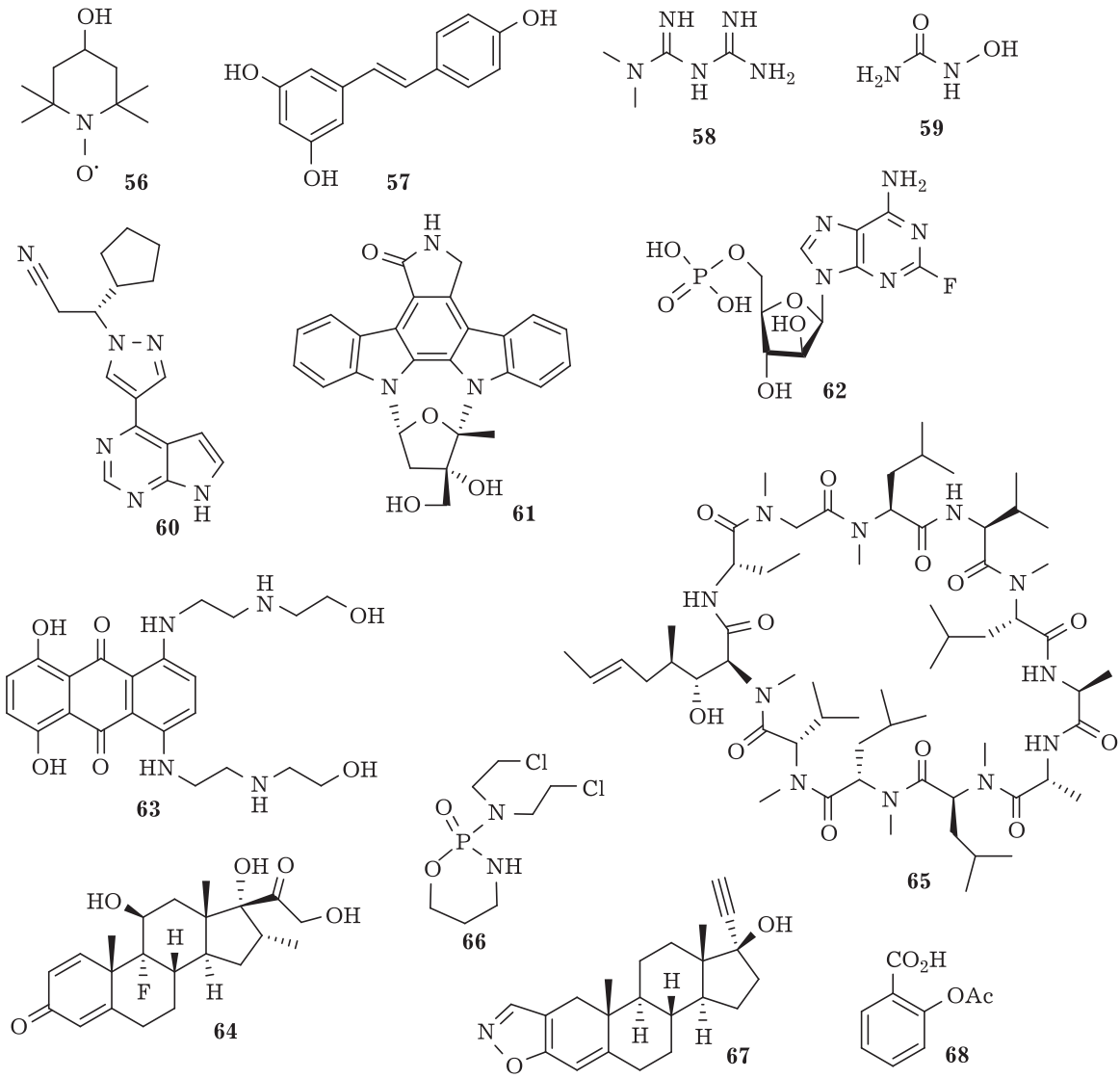

Fig. 7. Structures of tempol **56**; resveratrol **57**; metformin **58**; hydroxycarbamide **59**; ruxolitinib **60;** CEP-701 **61**; fludarabin **62**; mitoxantrone **63**; dexamethasonum **64**; cyclosporine A **65**; cyclophosphamide **66**; danasol **67** and acetylsalicylic acid **68**.

number of erythrocytes back to the normal range within 60 days [91].

Aplastic anemia is considered to be a disease of bone marrow characterized by bone marrow aplasia and pancytopenia of peripheral blood. The majority of patients may be cured successfully with the help of transplantation of hematopoietic stem cells or by means of immunosuppressive therapy, which provides long-term survival. Patients with aplastic anemia are treated with immunosuppressive therapy with the application of antithymocyte globulin, prednisolone **26** and cyclosporine A **65** [92]. In another clinical study, a combination of equine immunoglobulin against human thymocytes and cyclosporine A was the best combination to treat patients with active aplastic anemia providing a 5-year survival advantage [93].

During the differential diagnostics of hemolytic anemias, especially in the case if a patient suffers from accompanying lymphoproliferative disorder, autoimmune disease, viral or bacterial infection, it is necessary to consider autoimmune hemolytic anemia. The choice of treatment depends on the severity of hemolysis, but the intake of folic acid **28** is recommended for all patients. Among different versions of treatment (hemotransfusion, rituximab, *etc.*), the application of im-

mune suppression with the help of glucocorticoids should be mentioned, and in the case of the absence of any effect, cytostatic preparations are necessary (cyclosporine A **65,** cyclophosphamide **66**). For some patients, synthetic androgen danazol **67** turned out to be effective [94]. However, it was also demonstrated that acetylsalicylic acid **68** and other preparations inhibiting the functions of thrombocytes may be useful in some cases in the treatment of microangiopathic hemolytic anemia [95].

Myelodysplastic syndrome is a group of heterogeneous clonal diseases characterized by the presence of cytopenia in peripheral blood, displasia in bone marrow, and the risk of transformation into acute leucosis. Myelodysplastic syndrome with myelofibrosis is a hematopoietic disorder with unfavourable prognosis. It was demonstrated that antitumour preparation azacytidine **69** (Fig. 8) prolongates the survival of patients with high risk. The effect of the agent itself on this disease has not been revealed yet. Azacytidine was administered to elderly men with myelodysplastic syndrome every day in the dose of 75 mg/m^2 subcutaneously for 7 days every 28 days. Hematological improvements were observed after 8 treatment cycles [96]. Structurally close preparation decitabine (5-aza-2′-deoxycytidine) **70** demonstrated substantially worse results for patient revival [97]. So, azacytidine may be used in the future as a bridge to allogenic transplantation of stem cells, and as the medicine to treat recurrences after transplantation or in combination with other new pharmaceuticals for further improvement of the results in patients with myelodysplastic syndrome [98].

Lenalidomide **71** is an antitumour immunomodulator causing immunomodulating and antiangiogenic effects; it is used to treat multiple myeloma. Lenalidomide was approved for the therapy of transfusion-dependent anemia in the case of myelodysplastic syndromes of low or medium risk [99]. Immune anemia (autoimmune hemolytic anemia and pure red cell aplasia) are complications of chronic lympholeucosis. Anemias of this kind were treated with a combination of fludarabine **62**, cyclophosphamide **66** and monoclonal antibody rituximab [100].

The anticancer activity of vitamin K_2 **72** was studied in several clinical studies. Multicentre pilot trial of the treatment of myelodysplastic syndrome and acute myeloid leucosis with the help of vitamin K_2 showed it may cause a substantial decrease in the number of blast cells in the bone marrow and/or in peripheral blood and enhance hematopoiesis, especially in patients with acute myeloid leucosis developing at the background of myelodysplastic syndrome [101].

Intravenous introduction of vitamin C (*L*-ascorbic acid) **52** caused an increase in the number of blood cells and the quality of life for patients with recurrent acute myeloid leucosis [102]. It was established experimentally that the high concentrations of *L*-ascorbic acid provide specific inhibition of the growth of human leucemic cells

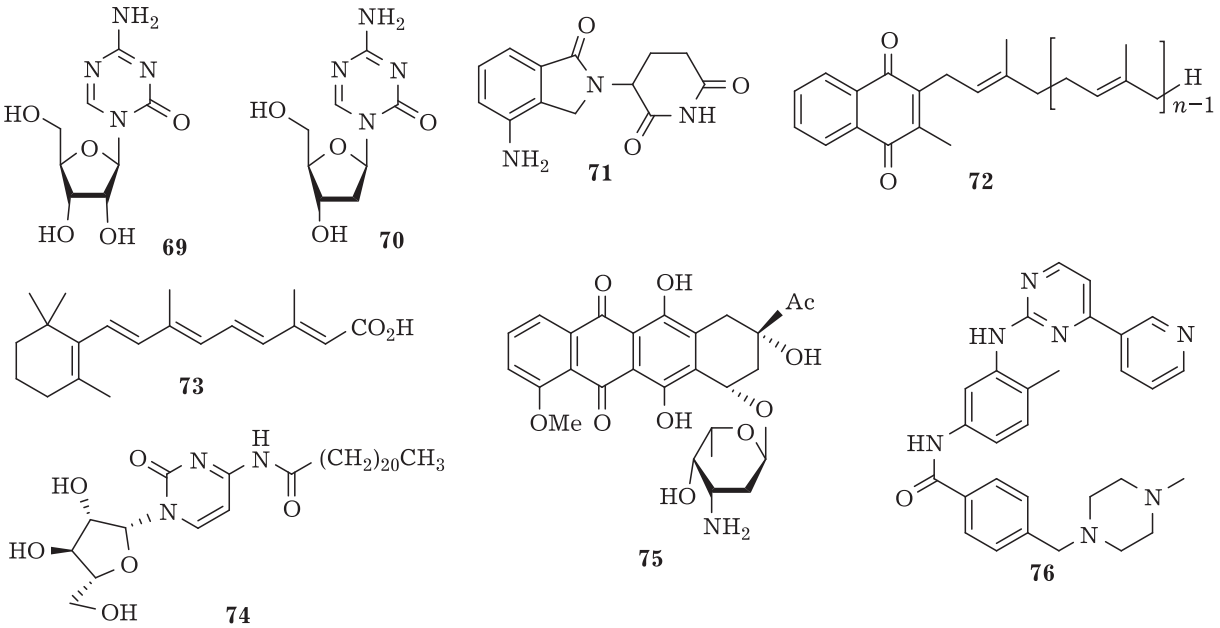

Fig. 8. Structures of azacytidine **69**; decitabinum **70**; lenalidomide **71**; vitamin K_2 **72**; retinoic acid **73**; enocitabin **74**; daunorubicin **75** and imatinib **76**.

by suppressing the transcription of *HIF-1a* [103], and the acid itself regulates the functions of hematopoietic stem cells and leukemogenesis [104].

Other researchers showed that retinoic acid **73** inhibits the clonal growth of human myeloid leucosis, and it was assumed that this acid may be effective in the treatment of leucosis [105]. It was established in a clinical trial that *trans*-retinoic acid serves as an efficient inductor for the achievement of complete remission of acute promyelocytic leucosis with a practically complete absence of side effects [106]. A combination of *trans*-retinoic acid with chemotherapy (anthracyclins) even better improved 5 year total survival in comparison with monochemotherapy. Along with this, the use of arsenic oxide (As_2O_3) for the treatment of recurrent acute promyelocytic leucosis in patients also caused a noticeable effect. Arsenic oxide has a dose-dependent and dual effect on the cells of acute promyelocytic leucosis: in low concentrations, As_2O_3 potentiates partial differentiation of weakly differentiated cells, while in relatively high concentration it causes apoptosis. The authors of the investigation pointed to possible complete recovery from this kind of leucosis [107]. A combination of arsenic oxide (0.1–0.15 mg/kg) and *trans*-retinoic acid (45 mg/m^2) for 60 days with supporting therapy provides a more efficient treatment of recurrences of the acute promyelocytic leucosis than chemotherapy does [108].

Melatonin **15** promotes the survival of normal granulocytes and B-lymphocytes. In mice with leucosis of medium activity degree, the daily introduction of melatonin resulted in 30–40 % survival, to compare with 0 % for non-treated mice. Because of this, melatonin may be useful as an auxiliary antitumour immunotherapeutic agent [109].

Enocitabine **74** demonstrated excellent therapeutic results against acute leucosis in mice [110]. In a subsequent clinical trial, the following pharmacological features of this agent were revealed: minimal toxicity and the ability to cause complete remission of acute leucosis in the dose up to 5.0 mg/kg [111].

Daunorubicin **75** is an anthracycline antibiotic, a cytostatic preparation known since the early 1960-es. Daunorubicin causes complete remission in about 50 % of patients with acute promyelocytic leucosis. The average duration of this remission is 26 months. Complications during therapy are mainly connected with hemorrhages during the first 5 days (25 %) as a result of the development of the syndrome of disseminated intravascular coagulation or as a result of sepsis during the 2nd or 3rd week (25 %). Therapy with daunorubicin is characterized by better survival of patients with acute promyelocytic leucosis than the patients with other kinds of acute granulocytic leucosis [112].

Imatinib **76** (antileukemic cytostatic preparation from the group of selective inhibitors of protein kinases) belongs to the first-line preparations. Imatinib is efficient in inhibiting hybrid tyrosin kinase BCR-ABL, with its gene located at the Philadelphia chromosome formed as a result of a reciprocal translocation between the 9th and 22nd chromosomes. Treatment with the preparation demonstrated a favourable safety profile and was highly tolerable, though separate cases of severe cytopenia were observed. Imatinib is applied to treat BCR-ABL-positive chronic myeloleucosis, and the preparation demonstrated specific clinical activity in the subgroup of patients with acute myeloid leucosis [113].

The inhibitor FLT3 of the second generation, AC220 or quizartinib **77** (Fig. 9) was compared with FLT3 inhibitors of the first generation (for example, CEP-701 **61**) with respect to the efficiency of the treatment of acute myeloleucosis. AC220 became the first candidate for the role of medicinal agent with the profile corresponding to the characteristics desirable for a clinical FLT3 inhibitor [114]. It was reported in 2012 that the results of the II phase of the clinical trial of AC220 for the treatment of resistant acute myeloid leucosis were good. Another FLT3 inhibitor, midostaurin **78**, was also administered to patients during the clinical trial. In 2017, the FDA approved midostaurin for the treatment of adult patients with recently diagnosed acute myeloid leucosis.

Several years ago, a new highly efficient inhibitor of kinase FLT3 was discovered, CHMFL-FLT3-165 **79**, which demonstrated strong biochemical inhibition of the enzyme, strong antiproliferative effects with respect to FLT3-ITD-positive strains of leucosis cells and the primary culture of leucosis cells of the patient, as well as substantial suppression of tumour *in vivo* [115].

One more cytostatic preparation, cytarabinum **80**, was recommended as a component for combined chemotherapy of acute leucosis. For example, a clinical trial of a combination of cytarabine and barasertib (AZD1152) **81** for the treatment of acute myeloid leucosis was carried out [116]. AZD1152 (a new selective inhibitor of kinase Aurora B) manifested itself as a very promising agent to treat patients with leucosis [117]. In the III

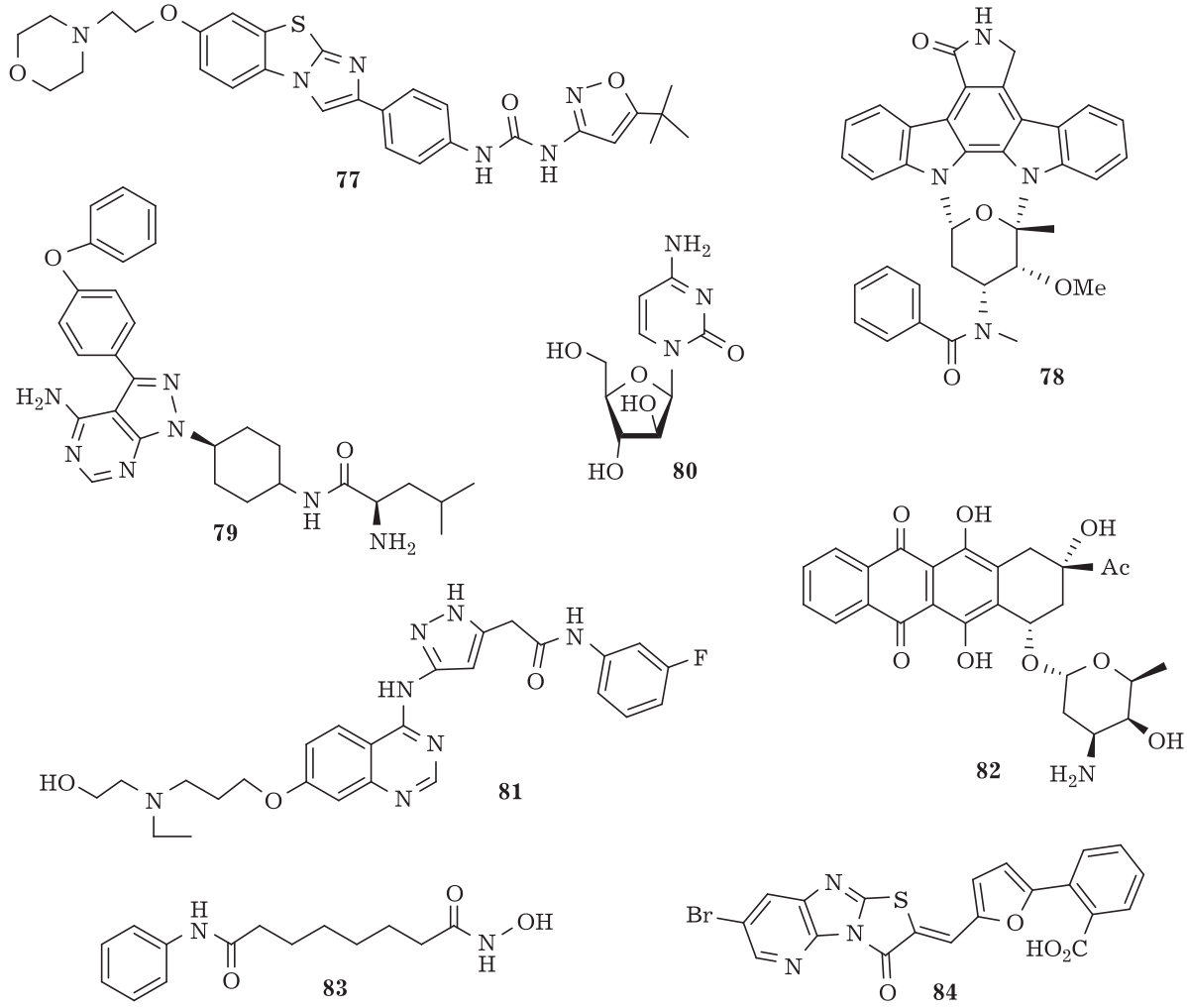

Fig. 9. Structures of quizartinib **77**; midostaurin **78**; CHMFL-FLT3-165 **79**; cytarabin **80**; barasertib **81**; idarubicin **82**; vorinostat **83** and compound **84**.

phase of randomized investigation with respect to relatively young patients with acute myeloid leucosis, a combination of cytarabine and daunorubicin hydrochloride **75** was studied, or a combination of anthracyclin antibiotic idarubicin **82** and cytarabine with the inhibitor of histone deacetylase vorinostat **83** or without it. Preparations used in chemotherapy, such as cytarabine, daunorubicin hydrochloride, idarubicin and vorinostat, provide different actions but are aimed at stopping the growth or at eliminating cancer cells by stopping their fission or propagation. The introduction of more than one medicinal agent (combined chemotherapy), as well as the introduction of preparations in different doses and in different combinations, may kill more cancer cells. However, it has not been established yet what combination is more efficient for chemotherapy of acute myeloid leucosis [118].

A powerful and relatively specific chemical compound **84** was discovered, which affects the negative regulators ERK1/2 and p38 MAPK – activated kinases in hematopoietic cells. This is the first case when a low-molecular inhibitor of protein tyrosine phosphatase was used successfully for the control of the activation of MAPK kinases *in vivo*. Investigations are carried out to determine whether compound **84** may be transformed into a medicine to treat malignant hematopoietic formations, such as acute myelogenous leukemia or T cell acute lymphoblastic leukemia [119].

Chemical screening *in vivo* is a widely applied approach not only to reveal the genetic ways regulating hematopoiesis and hematological diseases but also to discover critical regulators of these ways, which may be subject to pharmacological modulation. Compounds established during the screening of *Danio rerio* fish became promising

therapeutic candidates against leukemia and are included in the clinical trial for the improvement of engraftment of hematopoietic stem cells during transplantation [120].

CONCLUSION

Elimination of hematopoietic disorders caused by various factors and leading to the development of diseases of different complication degrees is a very important problem, and the search for preparations stimulating hematopoiesis is an urgent task. Increased attention is paid in this search to low-molecular compounds due to their simplicity and availability. Some of these stimulating agents exhibited sufficient efficiency in eliminating disorders of hematopoiesis, in particular in case of cytostatic therapy and the treatment of hemolytic pathologies.

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