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Tyrosine kinase ABL1 as a promising molecular target for anticancer drugs

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Tyrosine kinase ABL1 plays an important role in many key cellular processes linked to growth, proliferation, differentiation, survival, apoptosis, cell motility, adhesion, *etc*. However, this protein kinase is also associated with the development of several oncological diseases. In this review we summarize the literature data on the ABL1 structure, function, the role in cancer and known inhibitors of the kinase.

Keywords: protein kinase ABL1, cancer, inhibitor.

Introduction

Tyrosine kinase ABL1 is an ubiquitous non-receptor signaling enzyme that plays a key role in many cellular activities such as division, differentiation, metabolism, survival, apoptosis, *etc*. However, overactivity of this enzyme is associated with the development of oncological diseases [1].

To date, a number of ABL1 inhibitors have been developed which have demonstrated their anticancer activity. However, the effectiveness of therapy with their use decreases with the emergence of resistance [2]. Therefore, the development of new inhibitors using approaches that can reduce the rate of resistance development is of urgent need.

Role and functions of ABL1

ABL1 has been shown to be essential for the normal development of immune system. The experiments on *Abl1* knockout mice showed that it is a necessary component of T and B lymphocytes development [3]. Similar experiments highlighted the role of ABL1 in the development of the thymus and spleen [4].

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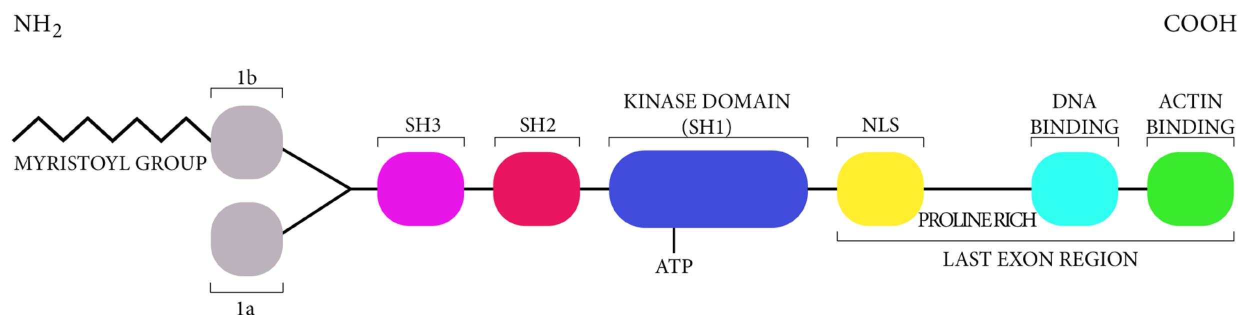

Fig. 1. Domain organisation of ABL1a and ABL1b.

At the cellular level, ABL1 is involved in signal-dependent cytoskeleton remodelling, cell migration and adhesion, receptor endocytosis, autophagy, DNA damage response, and apoptosis [5, 6].

Structure of ABL1

ABL1 is a multidomain protein (Fig. 1). This protein kinase consists of domains homologous to those of the SRC kinase (SH3, SH2, SH1), C-terminus with an approximate length of 600 amino acid residues and N-cap. The SH1 domain contains a phosphate-binding loop (P-loop) and an activation loop (A-loop).

In humans, the *ABL1* gene encodes two isoforms (Ia and Ib). These isoforms differ in the amino acid sequence of the N-terminus, Ib contains a myristoyl group at the N-terminus, whereas Ia does not have this group [7].

The SH1 domain has a kinase function, the SH2 domain recognises phosphorylated tyrosines, and SH3 is involved in the recognition of xPxxP motifs. The C-terminus contains DNA and an actin-binding site. Also, at the C-terminus there are signals of nuclear localization and nuclear export, which are involved in the transportation of the enzyme. N-cap plays an important role in the regulation of kinase activity.

In the inactive state, the SH3 and SH2 domains are localized close to the SH1 domain, although they do not overlap the active site.

An important characteristic feature of ABL1 mutant forms, associated with oncology, particularly BCR-ABL1, is the absence of the N-cap (Fig. 2).

Regulation of ABL1 activity

The inactive conformational state of ABL1 is maintained by intramolecular interactions. The general structure of ABL1 in the autoinhibited state is presented in Fig. 3. In Fig. 3, the AlphaFold model of ABL1 is used as the main scaffold, while structures with PDB IDs: 2fo0 and 5mo4 are used to incorporate myristoyl and Nilotinib, respectively. In details, the SH2 domain interacts with the C-lobe of the kinase domain, and the linker that binds it to the N-lobe, interacts with the SH3 domain. N-cap interacts with the SH3-SH2 connector, and the myristoyl group at the N-terminus enters the hydrophobic cavity of the C-lobe of the kinase domain [8].

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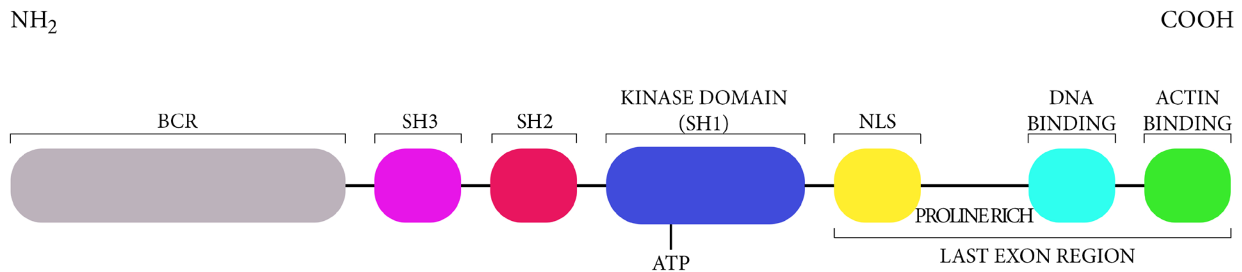


Fig. 2. Domain organisation of BCR–ABL1.

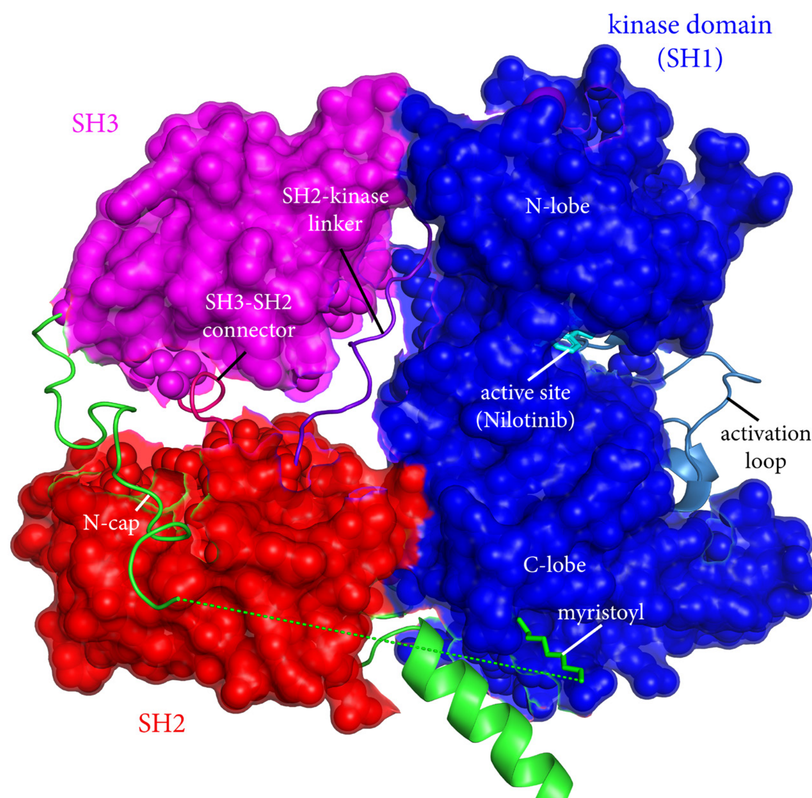


Fig. 3. General structure of ABL1 in the autoinhibited state (AlphaFold model aligned with the elements of crystal structures with PDB IDs: 2fo0 and 5mo4).

One of the key aspects of changing the activity of ABL1 is the connection of SH3 with the SH2-SH1 linker. An important component of this connection is Tyr245, which can be phosphorylated. A mutant form of ABL1 with Tyr245 replaced by phenylalanine exhibits reduced activity [9]. This confirms the role of Tyr245 phosphorylation in the transition of ABL1 to the active form.

Another amino acid residue whose phosphorylation affects ABL1 activity is Tyr412 [10]. This amino acid residue is believed to be phos-

phorylated by the trans-autophosphorylation mechanism [11]. It has been demonstrated that Tyr412 can be also phosphorylated by active forms of Src family kinases, which may indicate their role in the regulation of ABL1 activity [12].

The inactive state of ABL1 can also be maintained by trans-inhibition. F-actin, by binding to the actin-binding site at the C-terminus, induces ABL1 to adopt an inactive conformation [13]. This activity is SH2-dependent. Another protein that can exhibit trans-inhibitory activity is RB (retinoblastoma protein). RB, by binding to the N-terminus of the kinase domain, is able to inhibit even constitutively active mutant forms of ABL1 [14]. This may indicate that the inhibitor activity of RB does not require the adoption of a typical inactive conformation by ABL1. Retinoblastoma protein is phosphorylated by a cyclin-dependent kinase and, interestingly, also by ABL1 [15, 16].

It is likely that the transition of ABL1 to the active state is modulated by the contact of its domains with a specific substrate, which leads to the breakdown of intramolecular interactions and, as a result, destabilisation of the inactive form. Currently, 116 proteins are known to interact with ABL1, 76 of which bind to the domains SH3, SH2, and/or SH2-SH1 linker [17].

In summary, it can be assumed that the activation of ABL1 occurs in two stages. The first step is the release of the inactive structure from the inhibitor, and the second is the binding of a substrate with a simultaneous transition to the active conformation. After activation, the active form can be maintained by phosphorylation of Tyr245 and Tyr412.

ABL1 and oncology

The mutant forms of ABL1, which become constitutively active are associated with the development of the oncological diseases.

A typical example of this form is BCR-ABL1. This form occurs as a result of a reciprocal translocation between the 22nd and 9th chromosomes t(9;22)(q34;q11). This anomaly is called the Philadelphia chromosome (Ph). The principle by which BCR-ABL1 is activated is based on oligomerisation of BCR domains and subsequent trans-autophosphorylation [18]. There are three forms of BCR-ABL1, which differ in the proportion of BCR in the fused protein. Each form is associated with a specific type of leukemia [19, 20]: P210 BCR-ABL1 is a hallmark of chronic myelogenous leukemia (CML) [21]; the transcript encoding P185 BCR-ABL1 (alternative name — P 190 BCR-ABL1) is expressed more often than transcripts encoding other forms in acute lymphocytic leukemia (ALL) [22]; the expression of P230 BCR-ABL1-encoding transcript was detected in neutrophilic-chronic myelogenous leukemia [23], as well as in rare cases of CML [24]. The association of different forms of BCR-ABL1 with different types of leukaemia is not absolute, as a transcript encoding P210 BCR-ABL1 was found in some patients with Ph+ AML [22].

ABL1 is also capable of forming mutant forms with a number of other proteins. In addition to BCR, such proteins are: NUP214, ETV6 (TEL), ZMIZ1, SFPQ, RCSD1, FOXP1 and SNX2 [25–27]. ETV6-ABL1 is associated with acute myeloblastic leukemia and B- and T-acute lymphoblastic leukemia; NUP214-ABL1 and EML1-ABL1 are associated exclu-

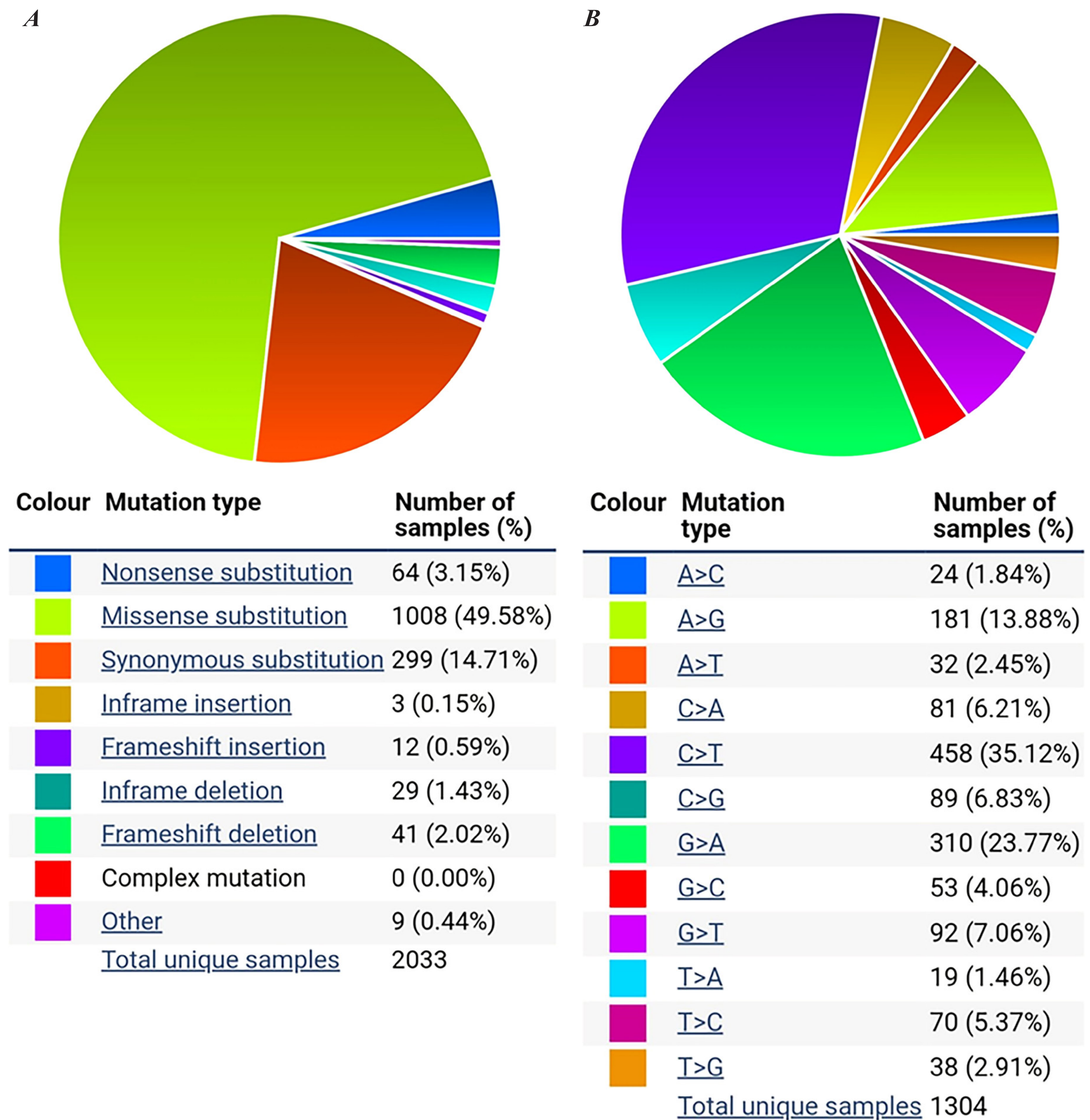
sively with T-acute lymphoblastic leukemia; RCSD1-ABL1, SFPQ-ABL1, ZMIZ1-ABL1, FOXP1-ABL1 and SNX2-ABL1 — with B-acute lymphoblastic leukemia.

In addition to its role in leukemia, there is evidence to suggest a role of *ABL1* amplification in the development of solid tumours [28].

Due to its tyrosine kinase activity, ABL1 has positive or negative effects on malignancies according to the cellular context, thus functioning as a signaling coordinator by (directly or indirectly) regulating the expression and/or phosphorylation levels of many components involved in tumorigenesis. Long-term inhibition of ABL1 in glioblastoma has been shown to promote the cell motility and invasiveness, while the proliferation and tumorigenic properties are reduced. In addition, the inhibition of ABL1 interferes with the formation of the glioma neurosphere and the expression of markers characteristic of stem cell [29]. In breast cancer, ABL1 regulates the response to tamoxifen treatment through a functional interaction with the estrogen receptor. Inhibition of ABL1 activity sensitizes to tamoxifen treatment, which is accompanied by inhibition of cell viability and growth retardation. Thus, today ABL1 is defined as a therapeutic target and prognostic tumor marker of breast cancer [30]. The transformation from gastritis to gastric B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) is epigenetically regulated by miR-203 promoter methylation, and ABL1 appears as a new target for the treatment of this malignancy. It was shown that the treatment with tyrosine kinase inhibitors imatinib and dasatinib in MALT lymphoma prevented the growth of tumor cells. [31].

Analysis of the distribution of ABL1 mutations according to the COSMIC database [32] showed that 49.58% are missense substitutions, 14.71% are synonymous substitutions, 3.15% are nonsense substitutions, all other types of mutations do not exceed three percent (Fig. 4). The mutation rate of the ABL1 gene worldwide is believed to be relatively higher in men than in women. The recent studies have identified a new mutation, namely a deletion in exon 8 of the ABL1 gene, that has been associated with the development of colorectal cancer. In addition, colorectal cancer cells strongly express *ABL1*. Long-term inhibition of ABL1 activity reduces the level of proliferation, apoptosis of cells and reduces the progression of colorectal cancer tumors [33].

Overexpression of *ABL1* is also characteristic of other types of cancer, so according to GEPIA data from the Cancer Genome Atlas and the Genotype Tissue Expression databases (Fig. 5), the highest level of *ABL1* expression is observed in the breast invasive carcinoma. Also, an increased level of expression compared to the control is observed in the bladder urothelial carcinoma, cholangiocarcinoma, colon adenocarcinoma, lung adenocarcinoma, pancreatic adenocarcinoma, ovarian serous cystadenocarcinoma, cervical squamous cell carcinoma and endocervical adenocarcinoma, stomach adenocarcinoma, uterine carcinosarcoma, rectal adenocarcinoma, glioblastoma multiforme, thymoma, low grade glioma, hepatocellular carcinoma, diffuse large B-cell lymphoma. A slight increase in expression is typical for the prostate adenocarcinoma, testicular germ cell tumors and thyroid carcinoma, while in cutaneous melanoma, the expression level of *ABL1*, on the contrary, decreases by almost eighty percent.



Colour	Mutation type	Number of samples (%)
	Nonsense substitution	64 (3.15%)
	Missense substitution	1008 (49.58%)
	Synonymous substitution	299 (14.71%)
	Inframe insertion	3 (0.15%)
	Frameshift insertion	12 (0.59%)
	Inframe deletion	29 (1.43%)
	Frameshift deletion	41 (2.02%)
	Complex mutation	0 (0.00%)
	Other	9 (0.44%)
	Total unique samples	2033

Colour	Mutation type	Number of samples (%)
	A>C	24 (1.84%)
	A>G	181 (13.88%)
	A>T	32 (2.45%)
	C>A	81 (6.21%)
	C>T	458 (35.12%)
	C>G	89 (6.83%)
	G>A	310 (23.77%)
	G>C	53 (4.06%)
	G>T	92 (7.06%)
	T>A	19 (1.46%)
	T>C	70 (5.37%)
	T>G	38 (2.91%)
	Total unique samples	1304

Fig. 4. The COSMIC database was used to analyze the mutation distribution for ABL1. *A* – Distribution of different mutation types for *ABL1*. *B* – A breakdown of the observed substitution mutations in *ABL1*.

Also, a significant decrease in the expression level of ABL1 is characteristic of sarcoma, head and neck squamous cell carcinoma, kidney chromophobe carcinoma, renal clear cell carcinoma, renal papillary cell carcinoma, esophageal carcinoma, adrenocortical carcinoma. In acute myeloid leukemia, as a result of the formation of the Philadelphia chromosome, the

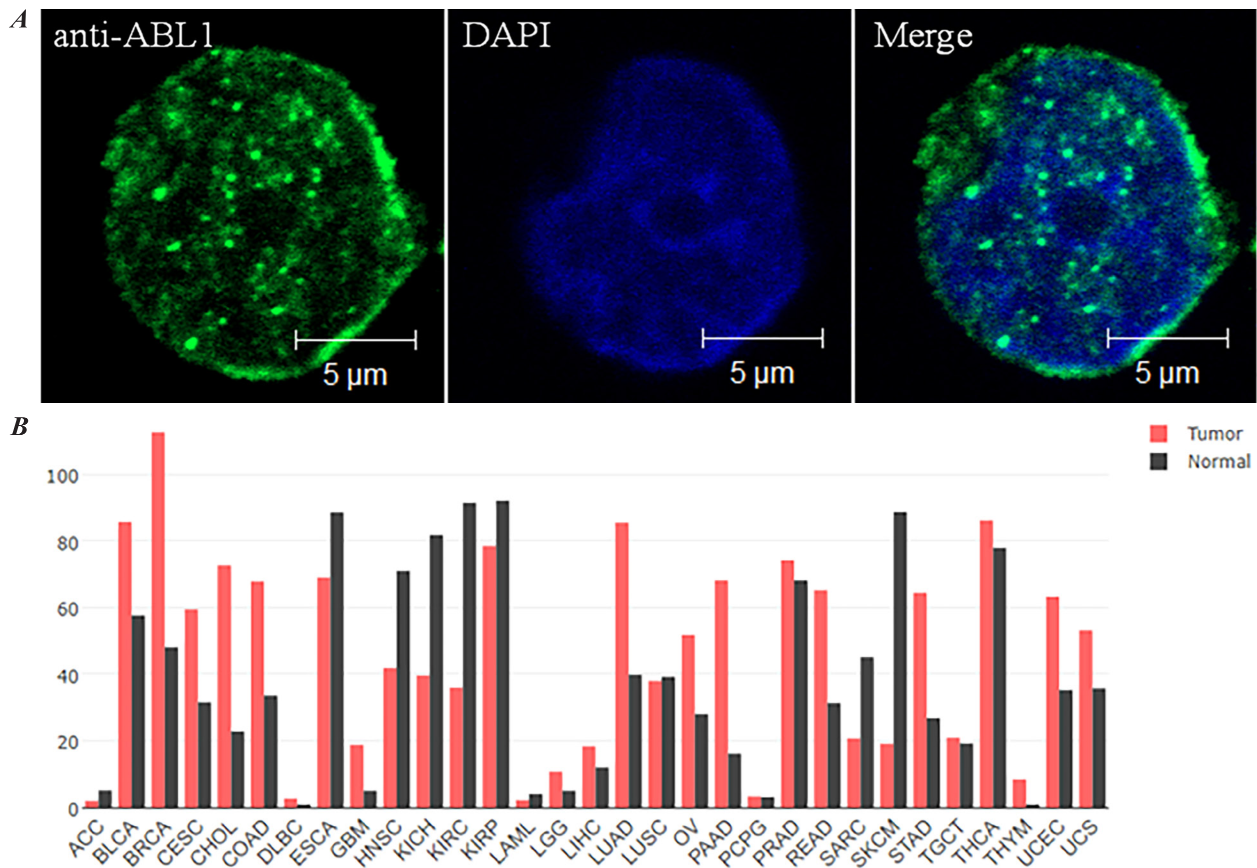


Fig. 5. ABL1 and oncology. *A* — Immunofluorescence analysis, localization of ABL1 and BCR-ABL1 in CML cells. *B* — ABL1 expression in normal samples (grey box) and tumor samples (red box) from patients with cancer compiled by GEPIA data from The Cancer Genome Atlas and the Genotype Tissue Expression databases. ACC — adrenocortical carcinoma, BLCA — bladder urothelial carcinoma, BRCA — breast invasive carcinoma, CESC — cervical squamous cell carcinoma and endocervical adenocarcinoma, CHOL — cholangiocarcinoma, COAD — colon adenocarcinoma, DLBC — diffuse large B-cell lymphoma, ESCA — esophageal carcinoma, GBM — glioblastoma multiforme, HNSC — head and neck squamous cell carcinoma, KICH — kidney chromophobe carcinoma, KIRC — renal clear cell carcinoma, KIRP — renal papillary cell carcinoma, LAML — acute myeloid leukemia, LGG — low grade glioma, LIHC — hepatocellular carcinoma, LUAD — lung adenocarcinoma, LUSC — lung squamous cell carcinoma, OV — ovarian serous cystadenocarcinoma, PAAD — pancreatic adenocarcinoma, PCPG — pheochromocytoma and paraganglioma, PRAD — prostate adenocarcinoma, READ — rectal adenocarcinoma, SARC — sarcoma, SKCM — cutaneous melanoma, STAD — stomach adenocarcinoma, TGCT — testicular germ cell tumors, THCA — thyroid carcinoma, THYM — thymoma, UCEC — uterine corpus endometrial carcinoma, UCS — uterine carcinosarcoma.

level of ABL1 decreases, while its hyperexpression is observed as part of the *BCR-ABL1* oncogene. A slight decrease in *ABL1* expression, not exceeding five percent, is observed in lung squamous cell carcinoma. And only in pheochromocytoma and paraganglioma, the level of *ABL1* expression does not change compared to the control.

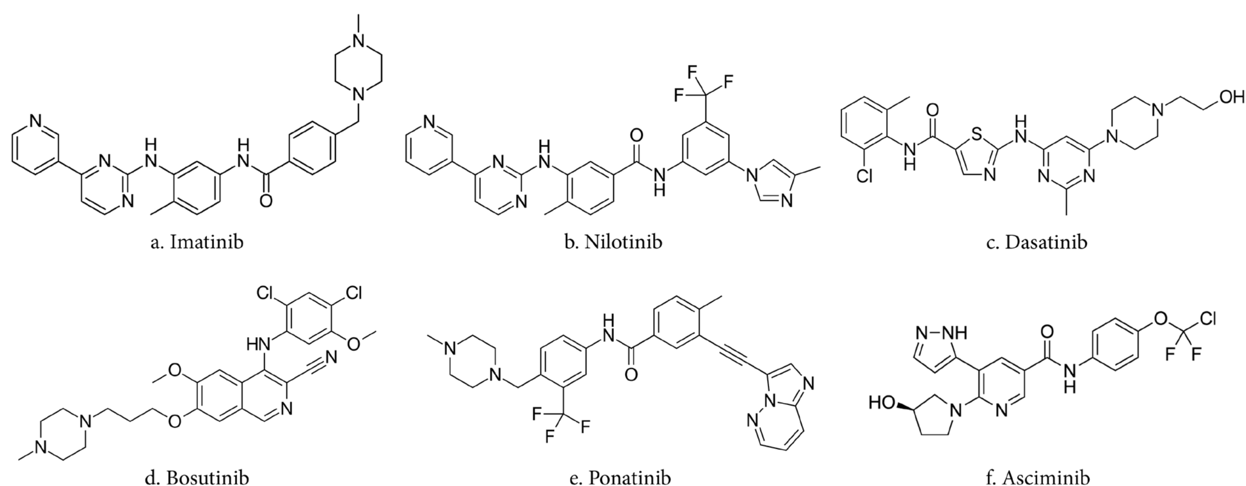


Fig. 6. Chemical structures of ABL1 inhibitors that have been approved for use in clinical practice.

In addition to the role of ABL1 in the development of malignant neoplasms, the recent studies report the involvement of ABL1 in other pathological processes. Thus, pathogenic germline variants of the *ABL1* gene can cause dysmorphic facial features, congenital heart defects, microcephaly, ear abnormalities, pneumothorax, pectoral muscle abnormality, scoliosis, high arch of the palate, and developmental delays, *etc.* [34, 35] Heterozygous ABL1 missense variants characterized by gain-of-function due to loss of autoinhibition are a common cause of congenital heart and skeletal malformation syndrome — congenital heart and skeletal malformation syndrome (CHDSKM) is a rare autosomal dominant disorder characterized by congenital heart defects, abnormalities in skeleton and developmental delay [36, 37].

ABL1 inhibitors

The ABL1 inhibitors are the gold standard for the treatment of chronic myelogenous leukemia. According to the mechanism of action, the inhibitors can be divided into two classes: inhibitors that interact with the allosteric site and the inhibitors which bind to the ATP-binding site of the kinase domain. ATP-competitive inhibitors are divided into two types: inhibitors with higher affinity for the active conformation of ABL1 (type I) and inhibitors with higher affinity for the inactive conformation (type II). To date, six inhibitors have been approved for use in clinical practice: imatinib, dasatinib, nilotinib, bosutinib, ponatinib and asciminib. Their chemical structures are represented in Fig. 6.

First-generation inhibitor: imatinib

Imatinib (STI571) was the first BCR-ABL1 inhibitor approved for the treatment of chronic myelogenous leukemia [38]. The mechanism of its action is based on binding to the ATP-binding site of the catalytic domain of the BCR-ABL1 in its inactive conformation [39].

Imatinib consists of a typical bisarylanilino core, which contains a phenyl ring with a benzamide-piperazine group in the meta-position of the aniline-type nitrogen atom on one side and a pyridine-pyrimidine moiety on the other (Fig. 6a). This scaffold interacts with Thr315 via hydrogen bonding and Van der Waals forces. The two substituents, located at an angle of approximately 120°, correspond to the adenine binding site. The first substituent is protected from the solvent in a "hydrophobic pocket" formed by Tyr253, Phe382 of the activation loop and amino acid residues Leu248, Phe317 and Leu370; the second substituent predominantly forms Van der Waals interactions with the following amino acid residues of BCR-ABL1: Val289, Met290, Asp38, Ile360 and His361 [40, 41].

The main disadvantage of imatinib, like all BCR-ABL1 inhibitors, is the emergence of resistance. The mechanism of drug resistance can be divided into two types: the first, BCR-ABL1-dependent, is based on point mutations that change the structure of the protein; BCR-ABL1-independent, is based on the alteration of signaling pathways and the reduction of the ability of inhibitors to be present in the cell.

Second-generation inhibitors

The second generation inhibitors of BCR-ABL1 were developed for the treatment of imatinib-resistant cases of chronic myelogenous leukemia. There are three second-generation inhibitors approved for clinical use — nilotinib, dasatinib and bosutinib.

Nilotinib (AMN107) has been shown to be effective in almost all imatinib-resistant CML cases [42]. Similar to imatinib, its mechanism of action is based on binding to the ATP-binding site of the BCR-ABL1 catalytic domain in its inactive conformation.

The nilotinib structure was created by modifying the structure of imatinib by inverting the amide linking group, replacing the piperazine ring with 3-methylimidazole and adding a trifluoro-methyl group to the anilinocarbonyl substituent to increase the number of Van der Waals interactions (Fig. 6b). Therefore, the energy contribution of each hydrogen bond to the total energy is reduced, which allows to avoid disruption of inhibitor binding in a case of mutation of key amino residues involved in this interaction. Despite these modifications, the less stringent binding requirements did not affect nilotinib selectivity, and moreover the efficacy compared to imatinib was improved (IC_{50} values of 10–25 nM and 100–500 nM for nilotinib and imatinib, respectively) [41].

Dasatinib (BMS-354825), compared to imatinib, allows to obtain faster response to treatment [42]. The action of dasatinib is based on interaction with the ATP-binding site of the catalytic domain of BCR-ABL1 in active and inactive forms, with higher affinity for the active. To create dasatinib, the phenyl ring of the imatinib scaffold was replaced with an aminothiazole group that occupies the adenine pocket of BCR-ABL1 (Fig. 6c). The pyridine group of imatinib was replaced by hydroxyethyl piperazine, which remains open to solvent after BCR-ABL1 binding [41].

Bosutinib (SKI-606) also provides a faster response to treatment than imatinib and, like dasatinib, binds to the ATP-binding site of the catalytic domain with higher affinity to the active form of BCR-ABL1 [39, 44].

The structure of bosutinib (Fig. 6d) was based on the structure of the Src kinase in-

hibitor 4-[(2,4-dichlorophenyl)amino]-6,7-dimethoxy-3-quinolinecarbonitrile. To the quinoline core was added a hydrophilic protonable N-methylpiperazino moiety. Even though bosutinib does not have full selectivity for BCR-ABL1, it is still approved as a second-line treatment for CML [41, 45, 46].

Third-generation inhibitors

Third-generation inhibitors are effective against the forms of CML resistant to inhibitors of previous generations. To date, two third-generation ABL1 inhibitors were approved for clinical use such as ponatinib and asciminib [47].

Ponatinib (AP24534) was developed to target the ABL1 mutated form T315I. In addition to activity against BCR-ABL1, it is active against Src family kinases.

The structure of ponatinib (Fig. 6e) is similar to that of nilotinib. However, there are some differences: the presence of an ethynyl linker; the methyl imidazole group is replaced by a methyl piperazine moiety; to optimize the formation of hydrogen bonds in the hydrophilic pocket, instead of the pyridine-pyrimidine group of nilotinib, ponatinib has terminal imidazo[1,2-b]pyridazin moiety. Point mutations in the kinase ATP-binding site have less effect on the overall binding affinity and efficacy of this drug [48]. Clinically, all these structural modifications lead to high activity in the patients with Ph+ leukemias who have received extensive prior treatment and are resistant to other inhibitors, including patients with the T315I mutation, other mutations or no mutations [41, 49].

Asciminib (ABL001) (Fig. 6f) differs from all previously approved inhibitors by mechanism of action — it binds with the allosteric site of BCR-ABL1. By interacting with myristate pocket, this inhibitor modulates the transition of the kinase into an inactive conformation. During clinical trials of asciminib, a significant molecular response was achieved or maintained for 12 months in 48% of patients. Among patients with the T315I mutation, the proportion of such cases was 28% [50].

Experimental inhibitors

In addition to the inhibitors approved for clinical use, there are a number of experimental inhibitors. The chemical structures of these compounds are shown in Fig. 7.

Bafetinib (NS-187) was developed to improve the inhibitory efficiency toward BCR-ABL1 mutants and to increase selectivity by reducing side effects. This was achieved by increasing the hydrophobic properties of the benzamide ring of imatinib through the introduction of trifluoro-methyl group in order to enhance Van der Waals interactions in the aforementioned “hydrophobic pocket” [51]. At the same time, the pyridine group of imatinib was replaced by a more hydrophilic pyrimidine ring, which allowed to increase the water solubility without affecting the inhibitory properties against BCR-ABL1 (IC_{50} = 71 nM) [52]. The N-methylpiperazine ring was replaced by a dimethylaminopyrrolidine moiety, which contributes to the formation of a hydrogen bond [51]. Thus, bafetinib is active against a number of mutant forms of BCR-ABL1, with the exception of several mutants, including T315I (IC_{50} > 10 μM) [53]. A phase I clinical trial showed that 19% of patients with CML and Ph+ ALL with resistance or intolerance to

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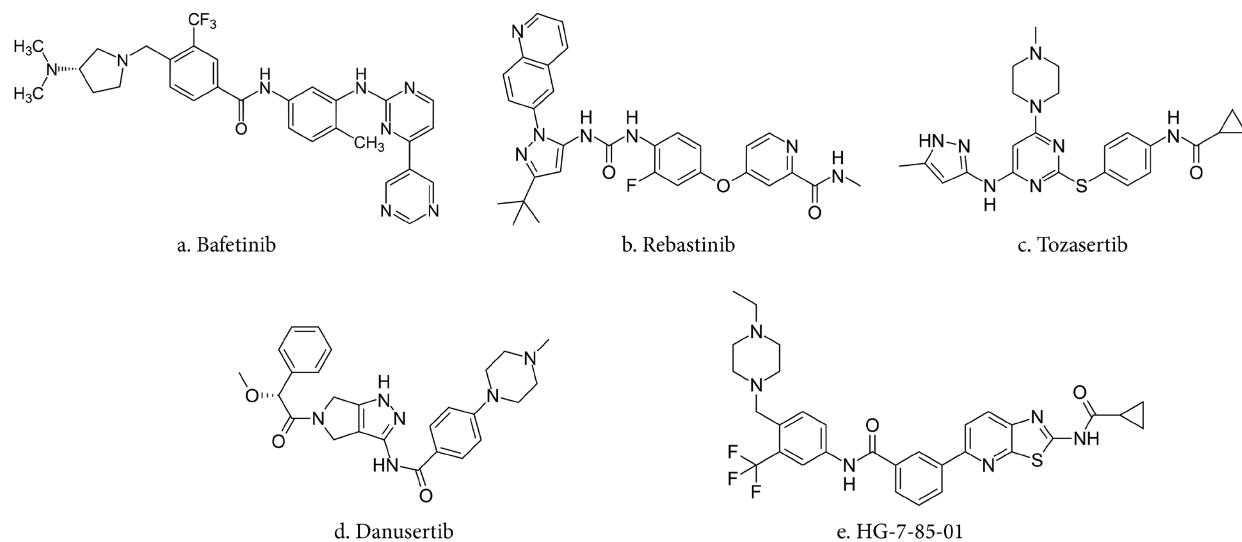

Fig. 7. Chemical structures of experimental inhibitors

imatinib achieved a complete cytogenetic response after treatment with bafetinib as second-line therapy, indicating its potential clinical efficacy [54].

Rebastinib (DCC-2036) is an allosteric inhibitor that was developed to overcome mutations that prevent the transition of BCR-ABL1 to an inactive state [55]. This effect of rebastinib is due to the stabilisation of the bond between Glu282 and Arg386. In rebastinib structure, the central fluorine-substituted phenyl core, which has urea linker in ortho position to the halogen atom, is linked to a carboxamide-substituted pyridine on the one side and a pyrazole, containing 4-tert-butyl and 1-(6-quinolinyl) substituents, on the other side (Fig. 7b).

The crystallographic studies showed that the ureic and carboxamide-pyridine groups form five hydrogen bonds mainly with the amino acid residues Glu282 and Arg386, while the rest of the molecule forms Van der Waals interactions with the hydrophobic amino acid cluster. In the case of the T315I mutation, the hydrophobic interactions are even enhanced, which was confirmed by the sensitivity to rebastinib in cellular assays with clones carrying this mutation (IC_{50} = 13 vs. 19 nM for unmutated ABL1) [56]. However, rebastinib is significantly less active against the E255V P-loop mutation (IC_{50} = = 800 nM) [55]. Clinically, although rebastinib has shown efficacy (among 40 patients with CML 8 complete hematologic responses were achieved, 4 of them had the T315I mutation) [57].

Tozasertib (MK-0457, VX-680) (Fig. 7c) is an ATP-competitive inhibitor of Aurora kinases (IC_{50} = 4–27 nM) [53, 58], which further was found as a potent inhibitor of ABL1 (IC_{50} = 10 nM). It should be noted that tozasertib inhibits Aurora kinases in the inactive

state, while BCR-ABL1 — in the active conformation [53]. Co-crystal structures indicate that this aminopyrazole pyrimidine inhibitor forms four hydrogen bonds with key amino acid residues in the ATP-binding site, including Asp381. Tozasertib demonstrates also high inhibitory activity against the BCR-ABL1 form with the T315I mutation (IC_{50} = 30 nM) [59]. In the second phase of clinical trials tozasertib demonstrated therapeutic efficacy in the patients with T315I BCR-ABL1 CML (44% had a hematologic responses). This result suggests that tozasertib is more effective than ponatinib in the accelerated phase of disease and can be used as a bridge therapy for stem cell transplantation taking into account its high myelosuppressive effect [60].

Danusertib (PHA-739358) (Fig. 7e) is a multikinase ATP-competitive inhibitor that targets protein kinases Aurora, Ret, TrkA, FGFR1 and ABL1 (including ABL1 with the T315I mutation). Danusertib exhibits activity against the active form of BCR-ABL1 and demonstrates promising activity in patients with ALL and CML [61].

HG-7-85-01 is a hybrid compound which was created by combining the structures of nilotinib and dasatinib in order to overcome resistance. During design of HG-7-85-01 structure, the aminothiazole moiety of dasatinib was attached to the pyridine ring, and the resulting scaffold was linked to the phenyl-benzamide group of nilotinib, which is responsible for selectivity toward the inactive conformation of BCR-ABL1 (Fig. 7e). In the cell-based assays, this inhibitor demonstrates the activity against BCR-ABL1 with the T315I mutation [62]. In addition, the target selectivity spectrum of HG-7-85-01 is narrower than that of ponatinib [62, 63], suggesting the potential of this compound to reduce the number of side effects compared to ponatinib. The comparative characteristics of ABL inhibitors are summarized in the Table 1.

Table 1. **The comparative characteristics of ABL inhibitors**

The name of the drug	**Use in therapy**	**ABL mutations that cause resistance to the drug**	**Features/mechanism of action of drugs**	**References**
Imatinib (STI571)	First-line drug in the treatment of CML	M237V, L273M, F311L, E355D/G, V379I, A397P, M244V, E275K/Q, T315I, F359V/I/C, A380T, S417F/Y, L248R, D276G, F317L/V/I/C, D363Y, F382L, I418S/V, G250E/R, T277A, F359V/I/C, L364I, L384M, S438C, Q252R/H, E279K, Y342H, A365V, L387M/F, E453G/K, Y253F/H, V280A/I, M343T, L370P, M388L, E459K/V, V289A, A344V, V371A, E255K/V, V299L, M351T, E373K, Y393C, P480L, E258D, H396R/P, F486S	The mechanism of its action is based on binding to the ATP-binding site of the catalytic domain of the BCR-ABL1 in its inactive conformation	[39, 64]

The name of the drug	Use in therapy	ABL mutations that cause resistance to the drug	Features/mechanism of action of drugs	References
Nilotinib (AMN107)	First- and second-line drug in the treatment of CML	Y253F/H, E255K/V, T315I, F359V/I/C	Similar to imatinib, its mechanism of action is based on binding to the ATP-binding site of the BCR-ABL1 catalytic domain in its inactive conformation	[39, 64]
Dasatinib (BMS-354825)	First- and second-line drug in the treatment of CML	V299L, T315I, F317L/V/I/C	The action of dasatinib is based on interaction with the ATP-binding site of the catalytic domain of BCR-ABL1 in active and inactive forms, with higher affinity for the former	[39, 64]
Bosutinib (SKI-606)	Second-line drug in the treatment of CML	V299L, T315I.	Binds to the ATP-binding site of the catalytic domain with greater affinity to the active form of BCR-ABL1	[39, 44, 64]
Ponatinib (AP24534)	A third-line drug in the treatment of CML	A397P, T315L	Unlike the structure of nilotinib, it has an ethynyl linker; the methylimidazole group is replaced by a methylpiperazine part; instead of the pyridine-pyrimidine group of nilotinib, ponatinib has a terminal imidazo[1,2-b]pyridazine moiety	[64]
Asciminib (ABL001)	The drug in the treatment of CML	T315I	Binds to the myristate pocket, causing the BCR-ABL1 kinase to switch to an inactive conformation	[50]
Bafetinib (NS-187)	Experimental inhibitor	T315I	A trifluoromethyl group is added, as in nilotinib, the pyridine group of imatinib is replaced by a more hydrophilic pyrimidine ring. The N-methylpiperazine ring was replaced by a dimethylaminopyrrolidine moiety	[51, 52]
Rebastinib (DCC-2036)	Experimental inhibitor, since the introduction of ponatinib, the benefit of rebastinib is considered insufficient	No data available	Effect of rebastinib is due to the stabilisation of the bond between Glu282 and Arg386	[55]
Tozasertib (MK-0457, VX-680)	Experimental inhibitor	No data available	An ATP-competitive inhibitor of Aurora kinases that additionally has activity against ABL1	[53, 58]
Danusertib (PHA-739358)	Experimental inhibitor	No data available	ATP-competitive inhibitor that inhibits Aurora, Ret, TrkA, FGFR1 and ABL1 (including ABL1 with the T315I mutation)	[61]
HG-7-85-01	Experimental inhibitor	No data available	The amidazole part of dasatinib is attached to the pyridine ring, the resulting region is connected to the phenylbenzamide group of nilotinib, which provided selectivity for the inactive conformation of BCR-ABL1	[62]

Conclusion

This review is focused on the role of tyrosine kinase ABL1 in cancer development and represents a comprehensive comparison of the currently available BCR-ABL1 inhibitors as anticancer drugs.

First-generation inhibitor, imatinib, has revolutionized the treatment of chronic myelogenous leukemia (CML), but the development of resistance mutations, such as T315I, makes it ineffective. As a result of these limitation, second- and third-generation inhibitors have been developed.

Second-generation drugs, bosutinib, nilotinib and dasatinib, are effective against a wider range of resistant mutations. However, they are still ineffective against certain mutations, like T315I.

The third-generation inhibitor, ponatinib, has shown to be effective against the highly resistant T315I mutation. It provides a valuable treatment option for patients who have developed resistance to earlier therapies. The introduction of allosteric inhibitor, asciminib, provides an alternative mechanism of BCR-ABL1 inhibition. By targeting the myristoyl-binding pocket, rather than the ATP-binding site, asciminib further expands therapeutic possibilities.

Additionally, the experimental inhibitors such as bafetinib and rebastinib, which have enhanced activity against certain BCR-ABL1 mutations, have been introduced. Bafetinib has demonstrated efficacy against several imatinib-resistant mutations, while rebastinib has shown activity in targeting the T315I mutation in cellular assays.

The inhibitors such as ponatinib and asciminib, along with experimental compounds such as bafetinib and rebastinib, represent significant progress in overcoming resistance. The development of new inhibitors with better treatment efficacy and reduced side effects reflects the ongoing effort to improve therapeutic outcomes in ABL1-targeted cancer therapies.

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Протеїнкіназа ABL1 як перспективна молекулярна мішень для протиракових препаратів

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Тирозинкіназа ABL1 відіграє важливу роль у регуляції багатьох клітинних процесів, пов’язаних із ростом, проліферацією, диференціюванням, виживанням, апоптозом, рухливістю клітин, адгезією та ін. Однак, ця протеїнкіназа асоційована із розвитком низки онкологічних захворювань. В огляді зроблено спробу підсумувати літературні дані щодо структури, функцій, ролі ABL1 у розвитку раку та існуючих інгібіторів цієї протеїнкінази.

Ключові слова: протеїнкіназа ABL1, онкологічні захворювання, інгібітор.

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