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Химия и технология лекарственных препаратов
и биологически активных соединений

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REVIEW ARTICLE

PROTAC® technology and potential for its application in infection control

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Abstract

Objectives. To describe the pharmaceutical technology of controlled degradation of protein molecules (PROTAC®, Proteolysis Targeting Chimera), approaches to the design of the PROTAC® molecule, methods of ligand and linker selection and synthesis, as well as the application of this technology in dealing with a variety of diseases and the possible limitations of its use.

Results. The review covers 77 sources, mostly from 2020–2023. The review outlines the principle of PROTAC® technology: the construction of a chimeric molecule consisting of three fragments. One fragment specifically binds to the biotarget, another recruits the proteolytic system of the host cell, and the third binds them together. The main areas of the current development of the technology are described herein, as well as the opportunities and limitations of chimeric molecules in the fight against different types of infectious diseases.

Conclusion. The potential to use PROTAC® technology to combat cancer as well as neurodegenerative, autoimmune, and infectious diseases is shown.

Keywords

PROTAC, ubiquitin-proteasome system, E3 ligases, molecular design, antiviral drugs

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ОБЗОРНАЯ СТАТЬЯ

Технология PROTAC® и перспективы ее применения в борьбе с инфекциями

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Аннотация

Цели. Описать фармацевтическую технологию направленной деградации белковых молекул (PROTAC®, PROteolysis TArgeting Chimera), подходы к конструированию молекулы PROTAC®, методы подбора и синтеза лигандов и линкера, а также применение данной технологии в борьбе с различными заболеваниями и возможные ограничения ее использования.

Результаты. Обзор охватывает 77 источников, в основном за 2020–2023 гг. В обзоре изложен принцип технологии PROTAC®, который заключается в конструировании химерной молекулы, состоящей из трех фрагментов. Один фрагмент специфически связывается с биомишенью, другой рекрутирует протеолитическую систему клетки-хозяина, а третий связывает их между собой. Описаны направления современного развития технологии, а также возможности и ограничения химерных молекул в борьбе с разными типами инфекционных заболеваний.

Выводы. Показаны перспективы использования технологии PROTAC® в борьбе с онкологическими, нейродегенеративными, аутоиммунными и инфекционными заболеваниями.

Ключевые слова

PROTAC, убиквитин-протеасомная система, лигазы E3, молекулярный дизайн, противовирусные препараты

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INTRODUCTION

Chimeric molecule technology used in the controlled degradation of proteins (PROTAC®, Proteolysis Targeting Chimeras) is one of the most promising developments in rational drug design. The concept of drugs based on controlled degradation of selected target proteins was proposed in 2001 [1], while active development started only a few years ago. In 2016, the PubMed[1] database contained references to only 13 publications with the *PROTAC* keyword. In 2022 there were already 479 of such references. Although, at the moment, no drug based on this technology has yet received FDA (U.S. Food and Drug Administration) approval, at least 15 such drugs, mostly antitumor drugs, are in various stages of clinical trials. The theoretical mechanism of the PROTAC® molecule action is schematically presented in Fig. 1. The target molecule is constructed of 3 blocks: block 1 is responsible for binding to the target protein; block 2 is responsible for interaction with the enzyme ubiquitinligase E3 (EC 2.3.2.27)[2]; and block 3 binds them together. The PROTAC® molecule binds the first ligand fragment to the target protein, while the second fragment interacts with the E3 ligase. Thus, protein molecules are physically brought closer together. The main function of E3 ligases is to trigger the mechanism of labeling different proteins with the peptide fragment ubiquitin. This mechanism is mediated by another enzyme, E2 ligase, and carries out the destruction of unnecessary protein molecules in the cell by a special proteasomal enzyme complex [2]. As a result of PROTAC® molecule action, the target protein molecule

1 https://pubmed.ncbi.nlm.nih.gov/. Accessed February 26, 2024.

2 https://www.brenda-enzymes.org/. Accessed February 26, 2024.

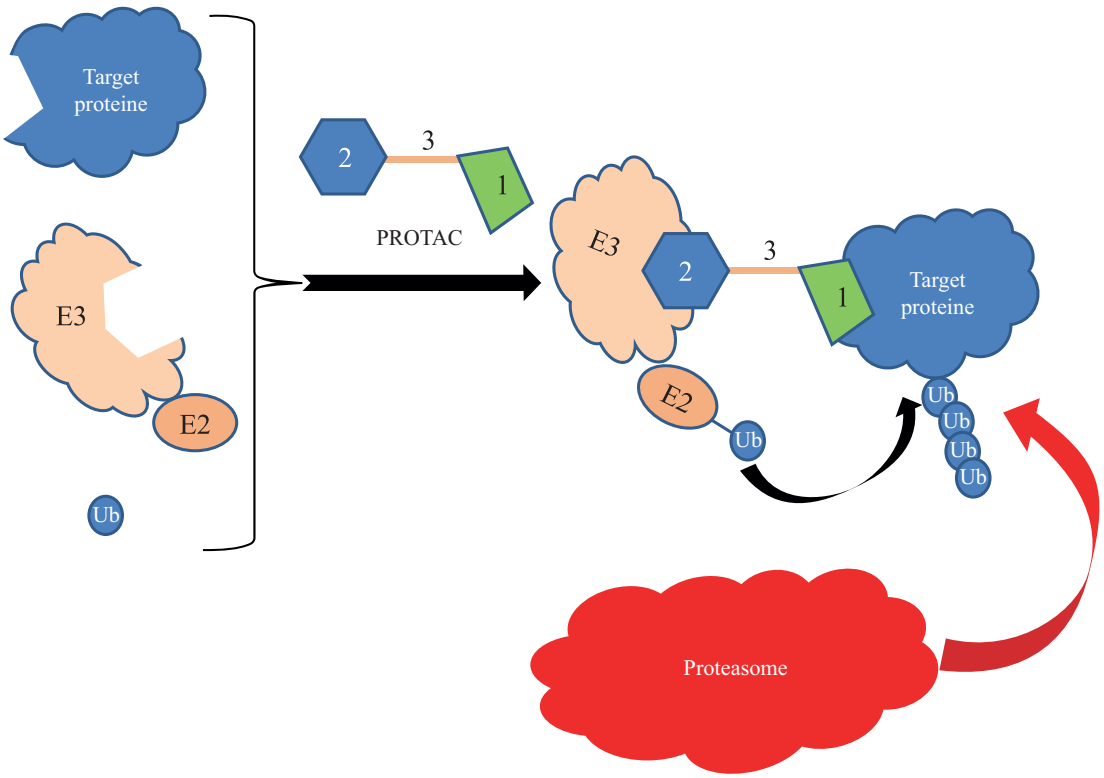


Fig. 1. PROTAC-induced degradation of the target protein by the ubiquitin-proteasome system (Ub — ubiquitin)

is tagged with a polyubiquitin chain and is attacked by the proteasome, resulting in its degradation.

The obvious field of application for the technology is in the treatment of cancer. Selective targeted destruction of tumor cell components is the main area for cancer chemotherapy. PROTAC® technology allows such targets that are inaccessible to conventional drugs to be attacked, i.e., suicide inhibitors. The technology can be used in neurodegenerative diseases such as Alzheimer's disease, autoimmune diseases and in all areas where specifically targeted drugs such as monoclonal antibodies are used. The undoubted advantage of PROTAC® is the relative simplicity and low cost of the active substance which is constructed from small molecules produced by conventional chemical synthesis.

Many reviews published in recent years [3–10] are devoted to the advantages and prospects of this technology. However, the simplicity of the idea hides many difficulties in its realization. This review is devoted to the achievements and problems in the design of chimeric molecules for selective degradation of target proteins, as well as the potential for the application of PROTAC® technology in the fight against infectious agents.

Construction of the PROTAC® molecule

The PROTAC® molecule consists of three structural components. Each of them is selected in accordance with the structure of the biotarget and, in turn, characterizes the pharmacodynamic and pharmacokinetic properties of the chimera. In terms of the design algorithm, well-studied ligands with a proven affinity to the target are chosen most often. A modification point is defined in the ligand structure, preferably at the periphery, where the pharmacophore will not be affected. At this point a linker group is attached to it. For the resulting intermediates, binding to the target is tested and, if successful, an E3 ligand selected from a set of known structures is attached to the other end of the linker. The construction of the PROTAC® molecule is complete, but its performance will depend on many nuances in the selection of all three components.

Selection of ligands to E3 ligase

The number of ubiquitin-transferring ligases in the human body is in excess of 600 [2]. However, only a few of them have low-molecular-weight ligands and are suitable for working with the PROTAC®

molecule. E3 ligase is an enzyme which performs the function of attaching ubiquitin to an arbitrary protein. In this sense there are almost no differences between different types of ligases. However, some of them have their own activator: a binding site for a low molecular weight ligand. Interaction with this ligand activates the enzyme. In fact, out of all the possible varieties, 3 ligases are normally used in practice: CRBN (cereblon), VHL (short for Von Hippel–Lindau) and cIAP (cellular inhibitor of apoptosis). They account for more than 95% of the described active PROTAC® chimeras, and more than half of them—for CRBN [6]. The known synthetic ligands to these three proteins are shown in Fig. 2.

Thalidomide **1** and its derivatives **2**–**5** are CRBN ligands. Their binding to CRBN is responsible for the antitumor activity of these compounds [12]. The ligands of other enzymes used are pseudopeptide molecules containing non-natural amino acids. A comparison of ligand structures explains the reasons for the popularity of CRBN: simplicity, synthetic availability and activity in racemic form. Another reason for this choice is that the activity of PROTAC® molecules targeting the same protein but designed for different ligases differs [3]. The most efficient chimeras are constructed on the basis of CRBN. However, the choice of ligase should be determined primarily by the biotarget, since the proteome has significant differences in different organs and tissues [13, 14].

Synthesis of ligands to CRBN

According to a review [11], the frequency of ligands to CRBN in successful PROTAC® molecules varies depending on the attachment point and linker type (Fig. 3).

The most common ligands **15**–**17** are based on the structure of pomalidomide **2**. The methods for

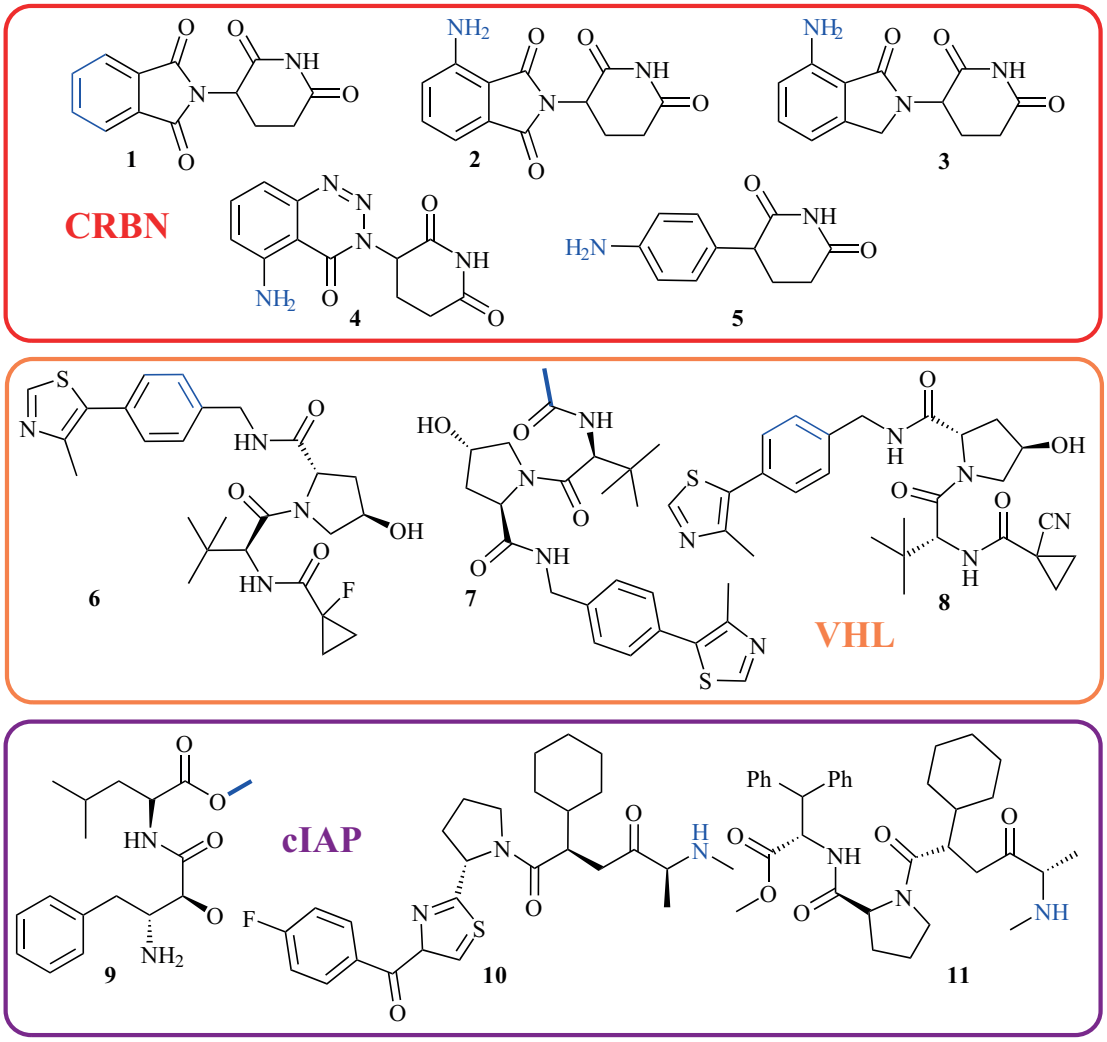


Fig. 2. Ligands of ligases E3. Possible modification points are marked in blue [11]

their synthesis are presented in Scheme 1. From the most available Boc-L-glutamine in the presence of a condensing agent (usually carbonyldiimidazole), a cyclic derivative **12** is obtained. After removal of the protecting group, it is acylated with 3-substituted phthalic anhydride. Linker groups are attached to the resulting derivatives **14**. This is achieved either by direct substitution of fluorine for amine **15**, or the nitro group of compound **14b** is first reduced to an amine, whereupon pomalidomide **2** is obtained. This is then acylated or alkylated at the amino group. Similarly, 4-hydroxyphthalidomide **14c** is prepared from 3-hydroxyphthalic anhydride, which is alkylated on the phenolic hydroxyl to synthesize ligands of type **18**. Ligands of types **19**–**20**, in which the linker is attached via a carbon chain, are prepared by Pd-catalyzed cross-coupling with terminal acetylenes. There are a few alternative routes to these structures, but almost all are based on the condensation of substituted phthalic anhydride with glutamine, glutamic acid, or cyclic 3-aminopiperidine-2,6-dione **13**. The differences are mainly determined by the convenience of linker chain attachment and the overall yield of the synthetic scheme.

Similarly, derivatives substituted at the 4 position of the phenyl ring of phthalic anhydride are obtained. More details on the methods of synthesis of E3 ligands can be found in the review article by Bricelj *et al.* [11].

Selection of linker group and assembly of PROTAC® molecule

The efficiency of the chimeric molecule depends not only on the affinity of ligands to the target protein and E3 ligase, but also on the proper selection of the linker group binding them. A number of studies [15, 16] have shown that the length, flexibility, and structural features of the linker group play a critical role for the formation of the ternary complex "target protein–PROTAC–ligase E3." Simple and relatively short hydrocarbon chains or polyethylene glycols are most often chosen as the initial linker which are gradually modified in the process of structure optimization. The attachment point of the linker to the ligands and the linker chain orientation should be selected in such a way as not to reduce the affinity of the ligands. Most often the selection is carried out by rational design methods, based on the established structure of the binding site. The main rules for selecting

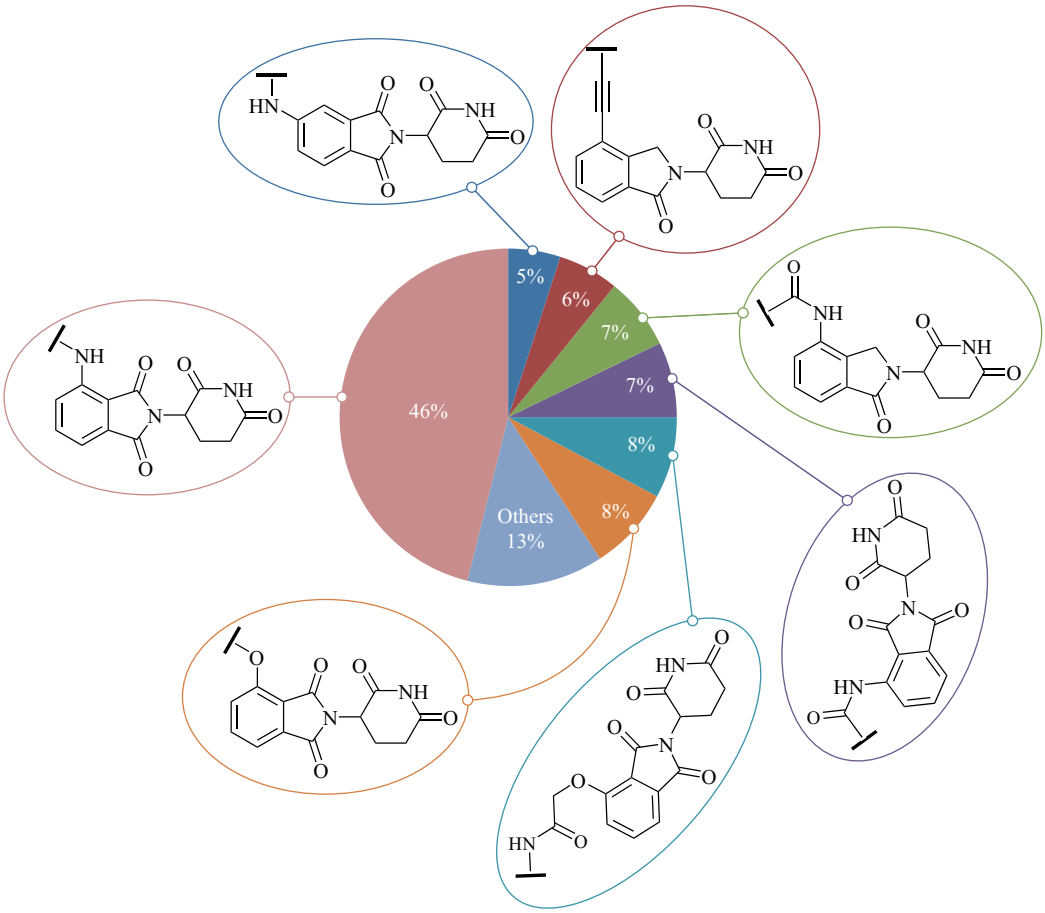
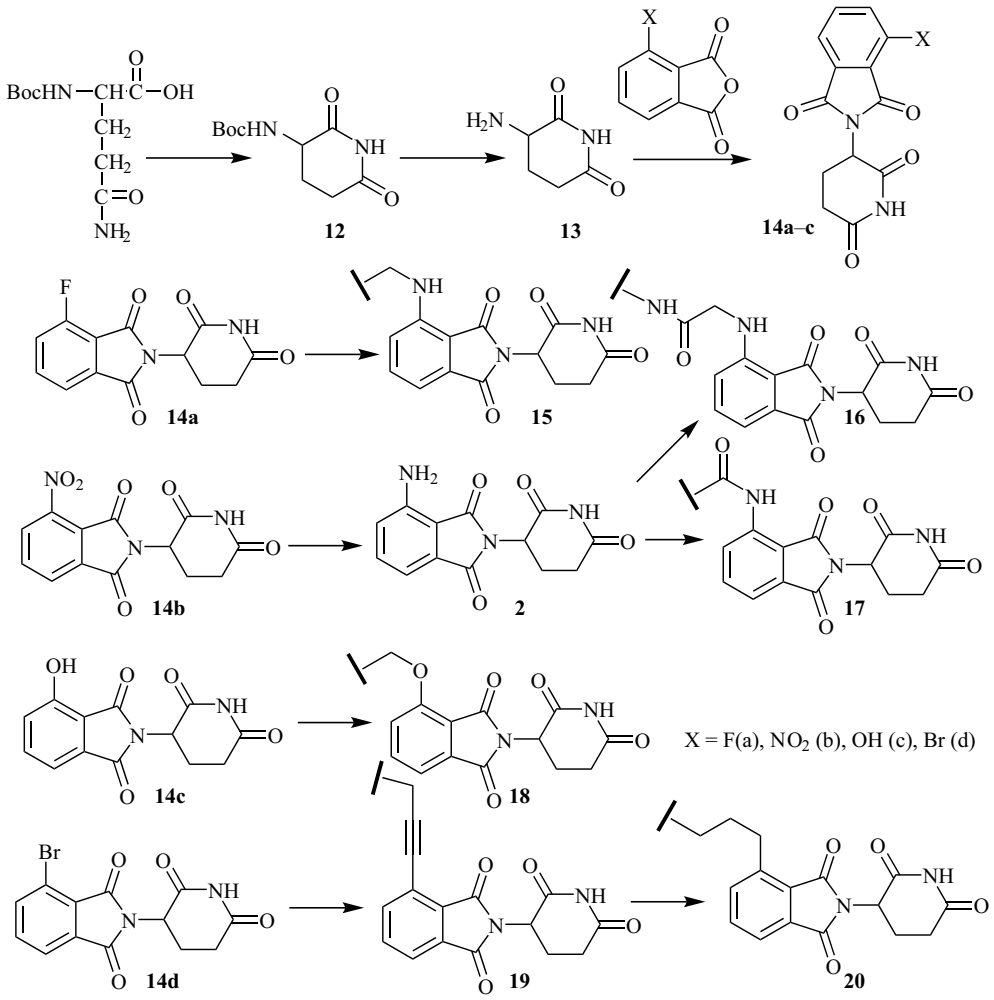


Fig. 3. Structures of synthetic ligands to CRBN in successful PROTAC® [11]



Scheme 1. Synthesis of CRBN ligands based on 3-substituted phthalic anhydride

the attachment point are as follows: (1) the molecular fragment of the ligand should not be changed significantly so as not to lose affinity; (2) the linker should enter the active center from the side available for solvation [6]. An example of the effect of linker on the activity of a chimeric molecule is shown in Cao *et al*. [17] (Fig. 4). The chimeric molecule SK-575 **22** was designed to degrade the nuclear protein PARP1 (poly(ADP-ribose) polymerase), a validated cancer target, and was based on the structure of inhibitor **21** (Olaparib). It showed

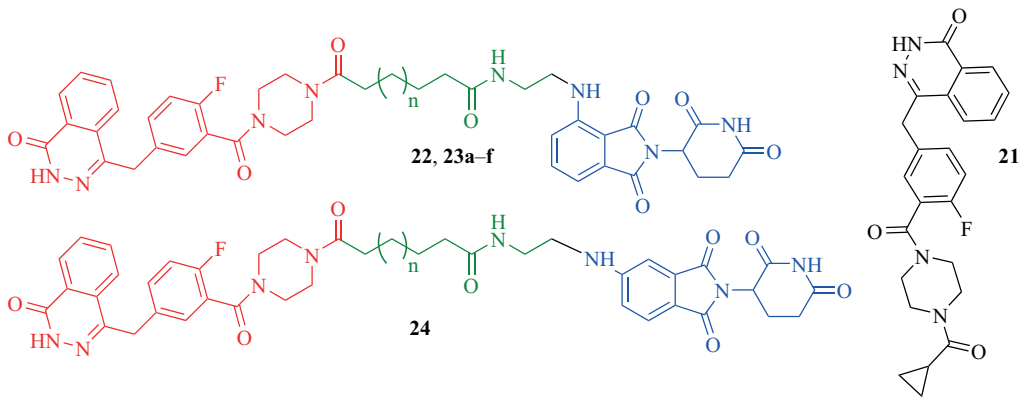


Fig. 4. Structures of PROTACs® for degradation of PARP1 (blue is the CRBN ligand, red is the ligand to PARP1, green is the spacer group) [17] and the initial inhibitor

Table. IC_{50} (μM) value depending on linker length

Compound	**22** *n* = 7	**23a** *n* = 1	**23b** *n* = 3	**23c** *n* = 5	**23d** *n* = 6	**23e** *n* = 8	**23e** *n* = 9	**24** *n* = 7
IC_{50}, μM	**0.019 ± 0.006***	>10	0.83 ± 0.26	0.123 ± 0.071	0.029 ± 0.008	0.021 ± 0.003	0.025 ± 0.004	0.035 ± 0.015

Note: n is the number of carbon groups in the chain. IC_{50} (μM) is concentration of half-maximal inhibition.

* Parameters show the high efficiency of compound **22**.

efficient degradation of the target protein (>99%) at a concentration of 100 nM in a model cell system, although its homologs had lower activity. The **23c–e** homologs, which had 1–2 atoms different spacer chain lengths, were comparable in activity. Shorter or longer linkers markedly decreased the activity of the chimera. Isomer **24** at the same concentration degraded only 77% of the target protein. It can be assumed that the attachment point of the linker affects the stability of the ternary complex. To a large extent, the degradation efficiency of the target protein is influenced by the type of linker. Analogs of compound **22** with polyethylene glycol linkers were 3–5 times less active (Table).

The degree of the target protein destruction depends on many factors. Affinity to the target protein is not a direct indicator of PROTAC® molecule efficiency. Affinity is necessary for the PROTAC® molecule to work, but a high binding constant to the target protein does not guarantee its efficiency.

The sequence of work on the design of PROTAC® molecules to describe the experimental techniques and test systems used, is presented in the form of a protocol in Carmony and Kim [18]. The design principles of PROTAC® molecules with different targets are discussed in detail in [19, 20]. In most works, the design and assembly of the final molecule is described in a step-by-step sequence (ligand synthesis–spacer selection–chimera assembly–activity studies). However, rapid synthesis of large libraries of target molecules for high-efficiency screening and optimization may be one of the directions of technological development. Examples of technological platforms for highly efficient synthesis of libraries of PROTAC® molecules are given in [21–23].

TARGET SELECTION AND PROSPECTS FOR TECHNOLOGY DEVELOPMENT

The choice of target protein is the main element when designing the PROTAC® molecule and this is determined by the therapeutic goal. The very concept of targeted protein degradation seems to be the most suitable for the fight against cancer [24–26]. Indeed, the first PROTAC® molecules to have passed phase I and II clinical trials target androgen (ARV-110, **25**) [27, 28] and estrogen (ARV-471, **26**) [29] receptors, and are designed to target prostate cancer and breast cancer, respectively (Fig. 5).

An important advantage of PROTAC® technology when compared to traditional drugs is that not only the active site of the target protein, but also any fragment thereof can be used for chimera binding. Thus, the spectrum of biotargets is expanded to include many previously inaccessible targets for therapy.

A focus on well-studied targets unites all successful examples of the development of chimeric

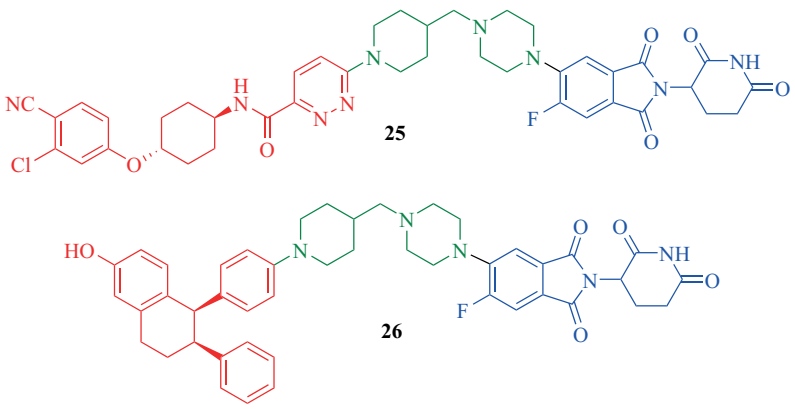


Fig. 5. The first clinically successful examples of PROTAC® technology application (blue is the CRBN ligand, red is the ligand to the target receptor, green is the spacer group)

molecules—protein disruptors. The targets for PROTAC® molecules are receptors [27, 29, 30], protein kinases [31], bromodomain-containing proteins and protein transducers [3], as well as many other proteins.

Like all successful innovations, PROTAC® technology has generated a whole range of new directions. They are all united by the idea of using the cell's own mechanisms to attack a biotarget. The first such direction was the use of alternative pathways for degradation of target proteins not mediated by the ubiquitin-proteasome system. Autophagy is another way in which cells divest themselves of unnecessary components [32]. Takahashi *et al*. [33] showed that it is possible to design molecules **27**–**28**, named by them as AUTAC (autophagy-targeted chimera) (Fig. 6), which utilize the autophagy mechanism to target protein degradation. Like the PROTAC® molecule, such a chimera acts inside the cell. AUTAC binds a "warhead" for the target protein to a guanine derivative which tags the protein for destruction by autophagy [34]. Targeted proteolysis can be induced by so-called heat shock proteins (HSPs). Chimeras which utilize binding to the HSP90 protein (HEMTAC) are described in a study by Li *et al*. [35]. About 40% of the proteins belong to membrane or extracellular proteins. These targets are not accessible to the proteasome system and are not subject to autophagy. Many of them play an important role in the processes of carcinogenesis, age-related and autoimmune diseases [36]. The lysosomal degradation pathway can be involved against extracellular proteins [37, 38]. A number of structures, known as LYTAC (lysosome-targeted chimera), have been identified in which ligands to specific carrier proteins CI-M6PR [38] or ASGPR **29** [39, 40] are used to transport the extracellular target protein into the lysosome (Fig. 6). Monoclonal antibodies [39] or aptamers [40, 41] were used as ligands to the target protein.

An alternative to PROTAC® technology is the actively developing RIBOTAC (Ribonuclease Targeting Chimeras) technology: chimeric molecules targeting RNA degradation [42]. In this case, not only the method of degradation, but also the type of biotarget is changed. When the target is a nucleotide sequence, binding to it is usually by means of either an antisense oligonucleotide or small interfering RNA (siRNA). Using ligands of this type for chimera targeting means rejecting almost all the advantages of the new technology: simplicity and cheapness of synthesis, stability of the molecule, as well

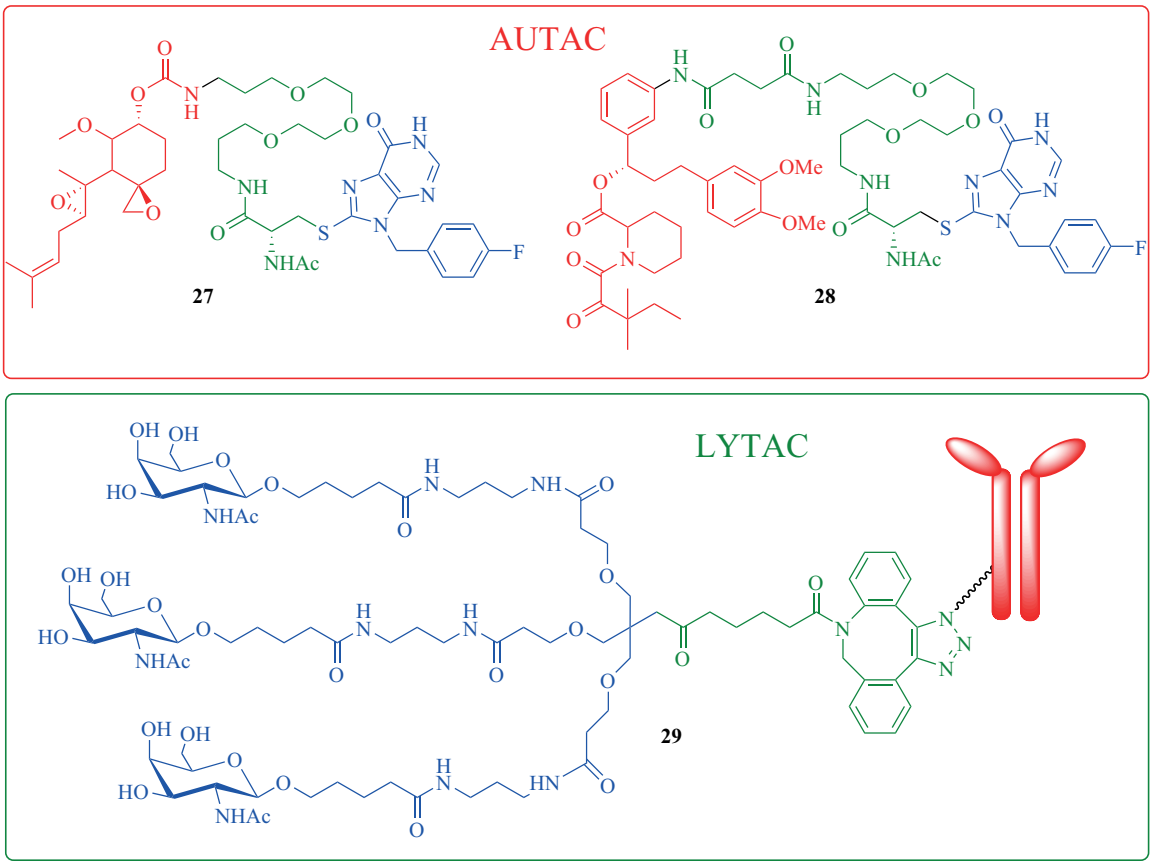


Fig. 6. The structures of AUTAC **27**–**28** (blue is a guanylate marker, red is a ligand to the target receptor, green is a spacer group) [33] and LYTAC **29** (blue is an ASGPR ligand, red is an antibody to the target protein, green is a spacer group) [39]

as the possibility to use enteral routes of administration into the body. Therefore, RIBOTAC technology uses small molecules which bind selectively to RNA, especially to those RNAs which form stable secondary and tertiary structures [43] (Fig. 7). The target disruptor is interferon-dependent ribonuclease L (EC 3.1.26), an enzyme involved in the immune system. It is activated by an oligoadenylate fragment responsible for binding to ribonuclease in the RIBOTAC structure. The search for ribonuclease ligands among other small molecules is described in [45].

Another alternative are chimeras in which different biopolymers, such as peptides, oligonucleotides, or antibodies (non-small molecule PROTACs or NSM-PROTAC), rather than small molecules act as ligands to the target protein [46]. Such constructs lose a number of advantages of the original technology, while instead gainmore precise targeting of previously inaccessible targets.

TECHNOLOGY CHALLENGES AND SOLUTIONS

There exists a set of difficulties inherent in PROTAC® technology which have so far prevented it from attaining a leading position in drug design [47]. The first such problem is the inherently poor pharmacological properties of most chimeric molecules. Almost all of them fall outside the accepted drug-likeness parameters due to their significant size and molecular weight. Low solubility also complicates the development of dosage forms for oral administration. This problem can be partly solved by conventional structure-based design methods [48, 49].

Another difficulty in the design of chimeric molecules is related to the relatively weak set of tools available for this work. While there is a huge variety of physicochemical methods and test systems for searching and optimizing traditional drugs, no such variety of approaches has yet been developed for the new technology. As mentioned earlier, the efficacy of PROTAC® molecule is not directly related to the easily measured affinity, but rather to the stability of the ternary complex and protein-protein interaction parameters. It is not yet fully understood what these values, as well as the selectivity of PROTAC® molecules, depend upon. Thus, it will be some time before the rational design of new chimeras becomes routine procedure. A review on tools and methods for the rational design of PROTAC® molecules is presented by Liu *et al*. [50].

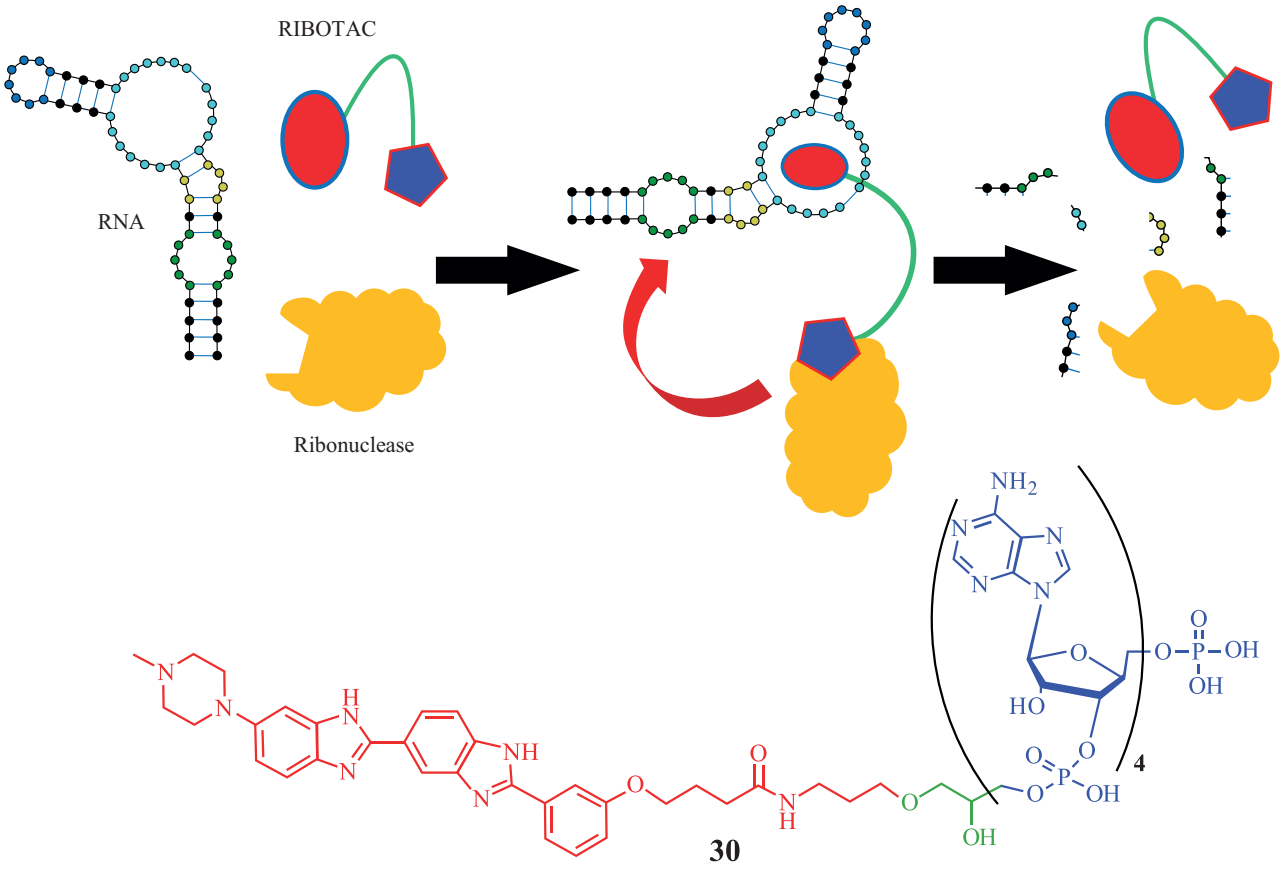


Fig. 7. RIBOTAC-induced degradation of RNA by ribonuclease L. MicroRNA-210 is a targeted chimeric molecule TGP-210-RL **30** [44] (blue is a ligand to ribonuclease L, red is a ligand to microRNA-210, green is a spacer group)

Another problem is related to the mechanism of action of PROTAC® molecules. When traditional suicide inhibitors enter the cell, each drug molecule "kills" only one target molecule (enzyme or receptor). Thus the drug action is directly related to concentration and affinity. However, PROTAC® recruits the cell's own systems, and once the target protein is broken down, the chimera is incorporated into a new catalytic cycle. Thus, the action of the drug will continue until all PROTAC® molecules are completely eliminated or broken down. This opens the way to the highest level of efficacy on the one hand and uncontrollable side effects on the other. It is highly desirable to provide a chemical "switch" as a way of stopping or reactivating the effect of the disrupting molecule at the right moment.

This type of development is currently being carried out in the field of photopharmacology [52]. An example of a photoswitchable PROTAC® molecule is shown in Fig. 8. The initial structure is a chimeric molecule ARV-771 **31** targeting the oncomic target BRD-4. The spacer length is 11 Å, and if changed up or down, the stability of the ternary complex is disturbed and PROTAC® stops working. In the structure of the photoswitchable molecule **32a**, the polyethylene glycol spacer is replaced by a fragment of substituted *trans*-azobenzene of equal length. Upon irradiation with 530 nm light, azobenzene is isomerized to the *cis*-form **32b**. Hereby the distance between the ligands is reduced to 8 Å and the substance loses activity. The reverse transition is initiated by irradiation at 415 nm.

The "switch" may also be purely chemical in nature. Variants of chimeric anticancer molecules utilizing the folate targeting system have been described [53]. In normal cells, folic acid receptors are present in low numbers when compared to many types of tumor cells which actively express these receptors. When the inactive prodrug **33** conjugated to folic acid is transported into cancer cells, the active substance, PROTAC® ARV-771 **31**, is released by the action of endogenous hydrolases (Fig. 9).

Another way to bring the pharmacodynamics of the PROTAC® molecule closer to conventional models is to

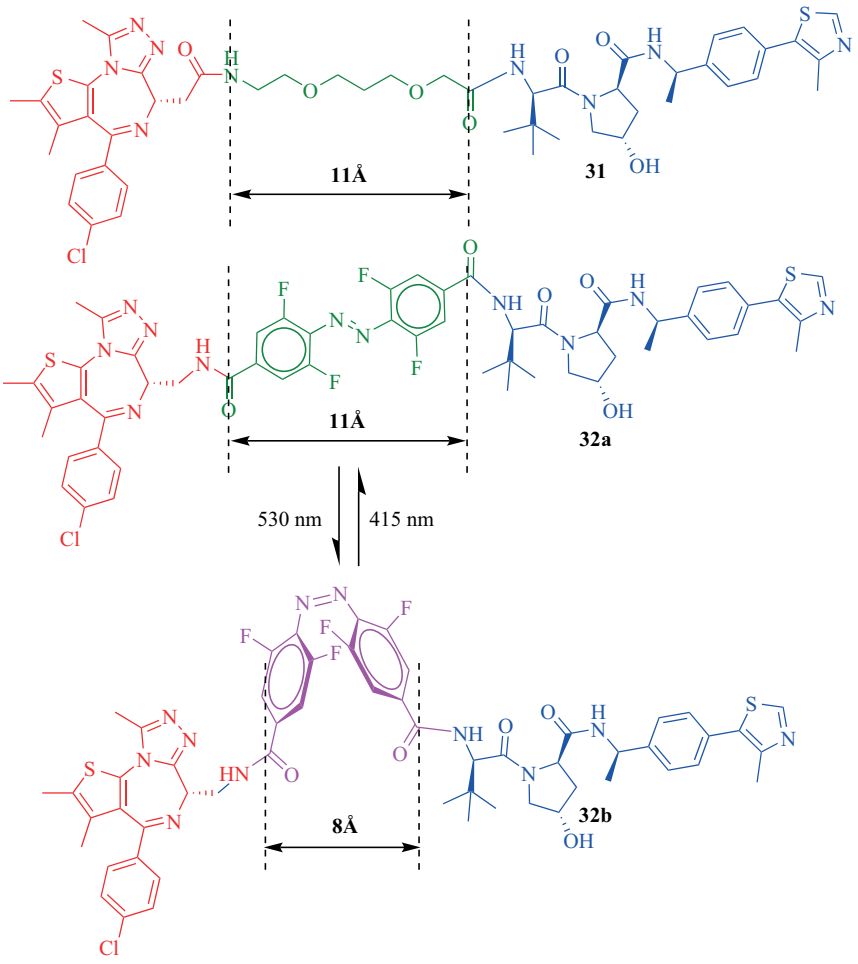


Fig. 8. Photoinduced switching PROTAC® (blue is ligand to the E3 VHL ligase, red is ligand to the target protein BRD4, and green is spacer groups) [51]

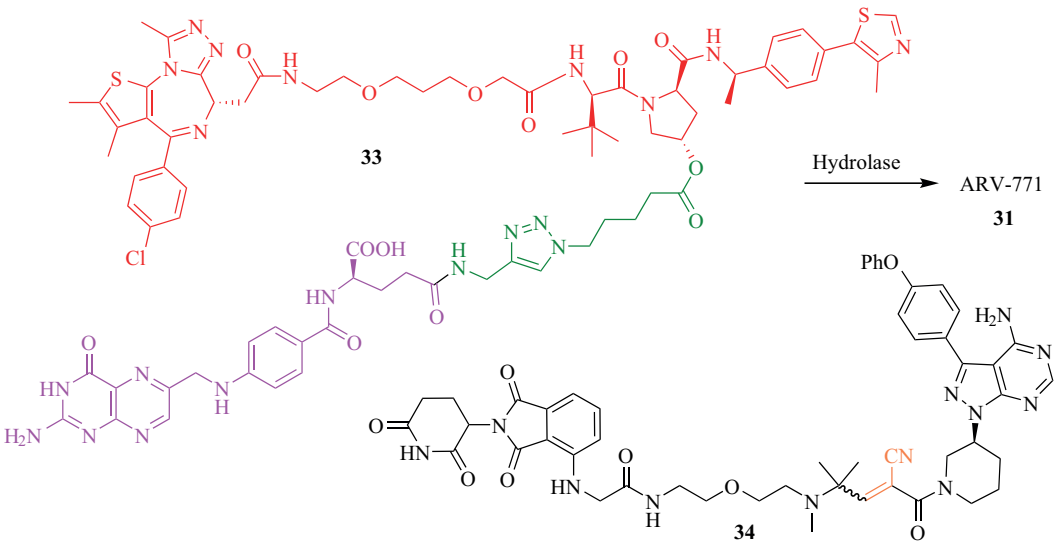


Fig. 9. PROTAC® **33** with folate delivery system to the tumor cell (the fragment of the initial active substance is highlighted in red, the folate group is highlighted in purple, the spacer fragment is highlighted in green) [53]; covalent PROTAC® (an orange fragment is an acrylamide group responsible for covalent binding to the target) [54]

use covalent inhibitors as a "warhead". If the ligand in the chimera binds covalently to the target protein when the proteasome destroys the target, it releases the already spent molecule. It is then unable to re-enter the catalytic cycle. Thus, the PROTAC® molecule begins to function as a conventional suicide inhibitor, while retaining an advantage in the target spectrum. There are other design concepts for PROTAC® technology which utilize covalent binding, including reversible binding [55]. A study by Jin *et al*. [56] proposed controlling the degradation process of the target protein by introducing into the cell a substance which selectively binds the active PROTAC® molecule.

APPLICATION OF PROTAC® TECHNOLOGY IN INFECTION COMBAT: OPPORTUNITIES AND LIMITATIONS

At first glance, the use of the new technology against pathogens and viruses appears very promising. However, the number of publications describing antibacterial or antiviral PROTAC® molecules is still relatively small. Strategies for the application of directed protein degradation against bacterial, viral and protozoan infections should be considered separately due to the significant differences between the biotargets.

Strictly speaking, it is impossible to apply PROTAC® technology in its original form against prokaryotic cells, i.e., bacteria, since the ubiquitin-proteasome system exists only in eukaryotes. However, the very idea of directed degradation of target proteins through activation of the cell's own systems may well be extended to bacterial cells. In 2022, Morreale *et al*. [57] proposed the concept of BacPROTAC, based on the protease system of gram-positive bacteria and mycobacteria ClpCP, similar to the ubiquitin-protease system of eukaryotes. When compared to eukaryotic proteasomes, which recognize complex polyubiquitin chains, the activation mechanism of ClpCP is much simpler. A phosphate group bound to the arginine residue of the target protein serves as a degradation tag. As proof of concept viability, the researchers tested the degradation efficiency of a model protein (streptavidin) *in vitro* by coupling its ligand (biotin) to phosphorylated arginine via a linker in the BacPROTAC-1 **35** compound (Fig. 10).

Compound **35** at a concentration of 100 μM degraded the target protein *in vitro* in the presence of ClpCP in Bacillus subtilis. However, the pharmacokinetics of BacPROTAC-1, based on phosphorylated arginine, is unsatisfactory and the guanidine phosphate group is unstable. The researchers proposed replacing the arginine-phosphate ligand with cyclic peptide molecules similar to cyclomarin A: an antibiotic isolated from a marine actinomycete that has significant affinity for ClpCP .

BacPROTAC is currently more of a fundamental concept than a technology. There are still many hurdles to be overcome before it can be applied in practice. The high selectivity of the PROTAC® molecule in the case of antibacterial therapy is rather a disadvantage. The countless variety of genetically variable pathogenic microorganisms makes it extremely difficult to select a target and a universal approach to chimera design.

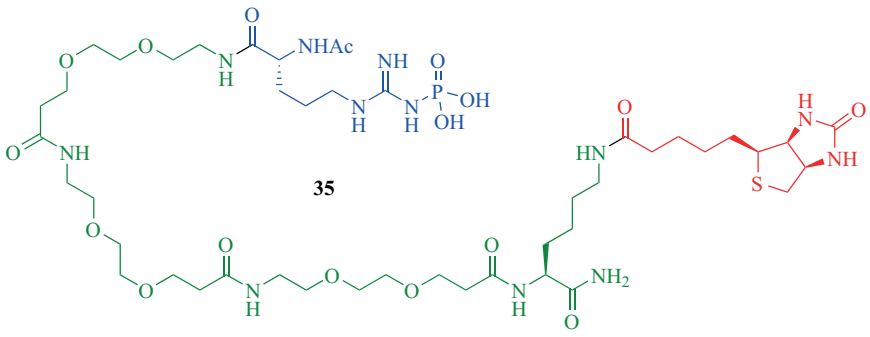


Fig. 10. BacPROTAC-1 is a model chimera using the ClpCP protease system to destroy streptavidin (the ClpCP ligand is blue, the target protein ligand, biotin, is red, and the linker group is green) [57]

Nevertheless, there are authoritative reviews [58–61] which confirm the relevance of such studies.

PROTAC® antiprotozoal molecules appear more likely, since the pathogens are eukaryotes and the ubiquitin-proteasome system is present, although less well understood than in humans. However, studies describing such chimeras have not yet been published.

The largest number of papers focusing on the application of the technology in the fight against infections is focused on the development of PROTAC® antiviral molecules. The life cycle of the virus takes place in a human cell, meaning that the ubiquitin-proteasome system is suitable for destroying the protein components of the virus. RIBOTAC technology also seems promising, since the viral RNA has significant differences. However, a number of unresolved questions remain: are the sites of virus localization in the cell accessible to the proteasome? Can the chimera not only reduce viral load but also prevent infection? Several reviews have considered the problems of using the technology in the fight against viruses [14, 60–64].

There are two possible ways of using the technology in the fight against viral infection: destruction of viral targets themselves or destruction of host cell proteins responsible for pathological processes. However, there are still relatively few examples of PROTAC® being used to degrade virus proteins. The structures of the most active of the described compounds are shown in Fig. 11.

Li *et al*. [65] used pentacyclic triterpenoid oleanolic acid as a "warhead" to target the hemagglutinin of influenza virus. Oleanolic acid exhibits antiviral activity against the influenza A virus and has a moderate affinity for hemagglutinin [66]. Two sets of PROTAC® molecules with ligands to CRBN and VHL ligases and with different spacer groups were synthesized. Destruction of the target protein was carried out *in vitro* in a model cell system. The maximum level of hemagglutinin degradation (mean degradation concentration DC_{50} = 1.44 μM) was shown by compound **36** with VHL ligand.

Oseltamivir is a known influenza drug which inhibits the influenza virus neuraminidase, an enzyme involved in the replication process. Oseltamivir-based compounds have been used to target the neuraminidase of the H1N1 strain of influenza A virus [67]. A large series of compounds were prepared using ligands to CRBN and VHL, a variety of linkers and different type of linker attachment to the oseltamivir molecule. *In vitro*, the best activity was demonstrated by compound **37** (half-maximal effective concentration EC_{50} = 0.33 μM). This is almost the same as the comparison drug, oseltamivir phosphate (EC_{50} = 0.36 μM). The compound showed no cytotoxicity to normal cells at concentrations up to 50 μM.

The function of the serine protease NS3/4A of the hepatitis C virus is to cleave the viral polyprotein: an important step in viral replication. Thus, degradation of the NS3/4A protease by PROTAC® should inhibit virion formation and multiplication. Telaprevir, a peptidomimetic NS3/4A protease inhibitor, was used as the "warhead" of compound **38**, and the tricyclic imide fragment served as the ligand of the E3 CRBN ligase. Compound **38** showed high protease degradation ability (DC_{50} = 50 nM) in a cell model [68].

In order to degrade SARS-CoV2 virus nucleic acids, the RIBOTAC technology described above [69, 70] was used by binding antisense sequences to ligands to ribonuclease L.

Some of the organism's own ways of fighting viruses are similar to the action of PROTAC® technology. For example, one of the E3 ligases (URB5) has an affinity to the MERS-CoV ORF4b coronavirus protein which suppresses the immune system of the cell. As a result of its action, this protein is tagged with a polyubiquitin chain and destroyed by the proteasome, thus increasing the body's resistance to the virus [71]. There are also natural substances which work on a similar principle. The metabolite APL-16-5 (**39**, Fig. 12) isolated from the fungus *Aspergillus sp*. CPCC 400735, has an antiviral

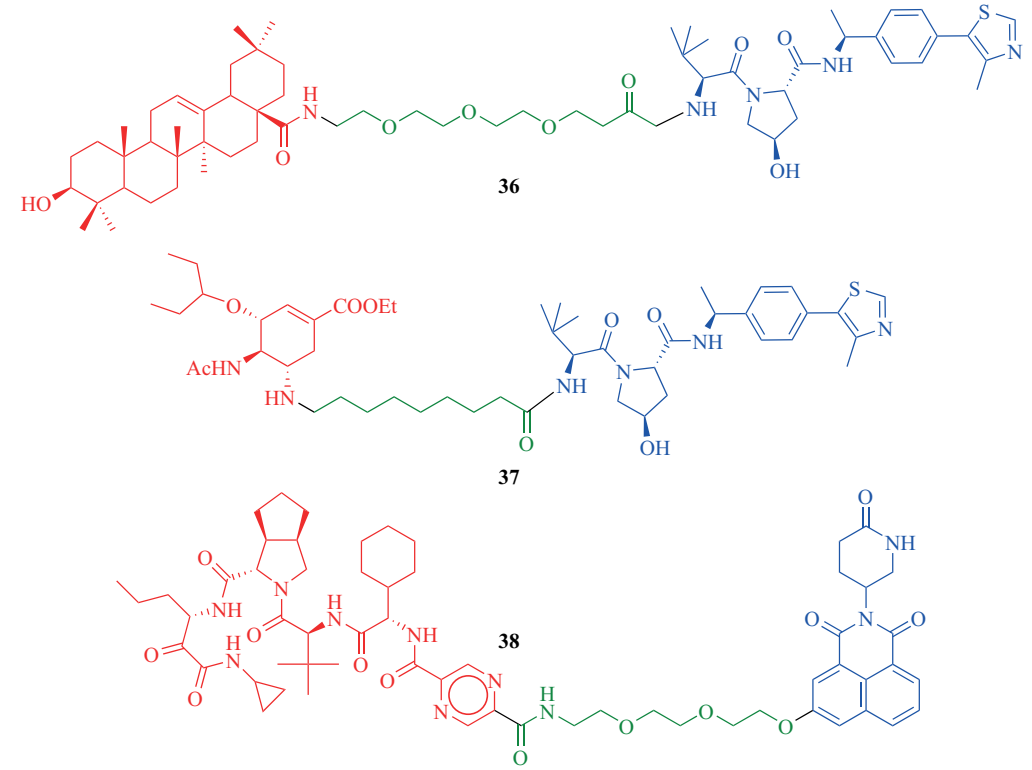


Fig. 11. Structures of PROTACs® aimed at various viral proteins (E3 ligands are blue, ligands to the target protein are red, linker groups are green)

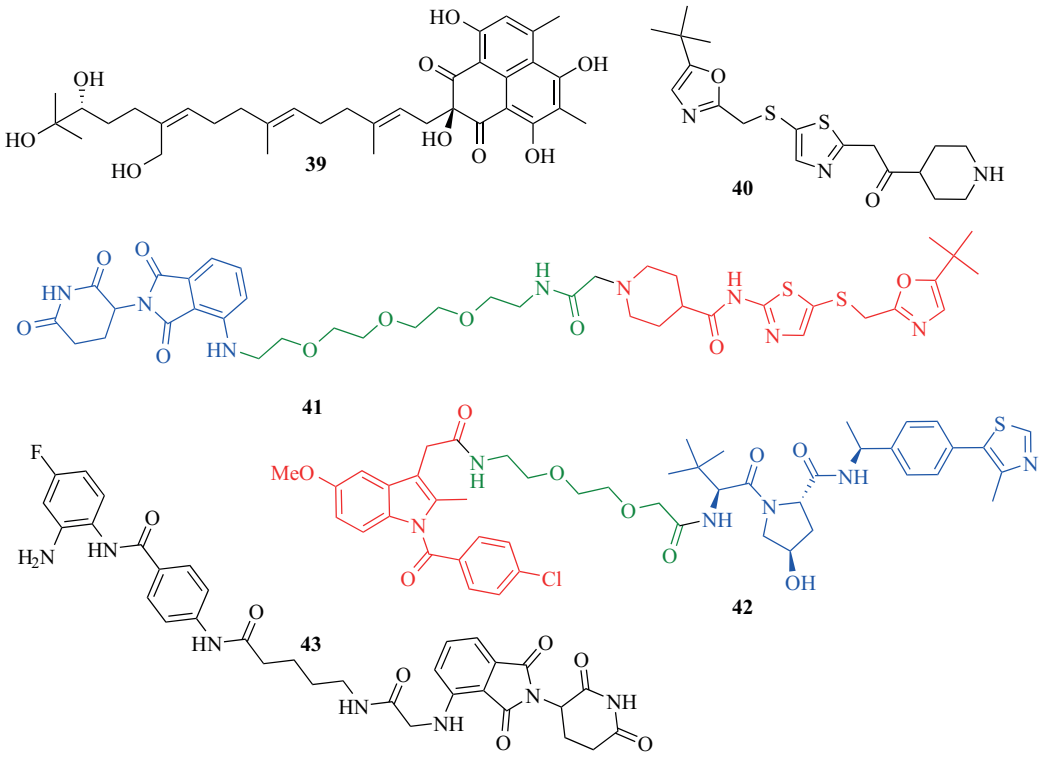


Fig. 12. Structures of antiviral PROTACs® (E3 ligands are blue, ligands to the target protein are red, linker groups are green)

effect against influenza A. This is due to the fact that it is a ligand of both virus polymerase and E3 ligase TRIM25 [72].

Another way of fighting viral infection is to inhibit the pathological cellular processes caused by the virus. In this case, the action of PROTAC® technology is more traditional. Infection caused by cytomegalovirus develops with the participation of cyclin-dependent protein kinases (CDK), inhibitors of which are being tested as antiviral drugs [73]. In particular, compound SNS-032 **40** from *Selleck* (USA), a selective CDK inhibitor, served as the basis for the antiviral PROTAC® drug **41** [74]. Compound **41** (EC_{50} = 0.025 ± 0.001 μM) was almost four times as effective when compared with the original SNS-032 (EC_{50} = 0.105 ± 0.004 μM).

In the search for an effective therapy for COVID-19 during the pandemic, many registered drugs from a wide variety of classes were retested. In particular, indomethacin, an old anti-inflammatory drug, was found to have some efficacy against coronavirus infection. Desantis *et al*. [75] developed several PROTAC® drugs which utilize the structure of indomethacin as a "warhead" targeting prostaglandin-E synthase 2 (PGE-2). This enzyme interacts with the coronavirus protein NSP7 which is required for SARS-CoV2 replication. The exact mechanism of the antiviral action of indomethacin is unclear, but destruction of PGE-2 suppresses replication. The most active compound **42** (EC_{50} = 18.1 μM) is 5 times more effective than indomethacin (EC_{50} = 94.4 μM). Interestingly, these PROTAC® compounds are also active against other types of coronaviruses, e.g., HCoV-OC43, while not exhibiting cytotoxicity against uninfected cells.

One reason for the high mortality rate of COVID-19 is the hyperactivation of the inflammatory response caused by histone deacetylases (HDACs). Inhibition of HDAC-3 reduces inflammation. HDAC-3-targeted chimeras for the treatment of COVID-19 were proposed by Zahid *et al*. [76] based on the anti-inflammatory drug PROTAC® HD-TAC7 **43** (*MedChemExpress*, USA). Computer analysis showed that the proposed molecules could theoretically be used to control inflammatory responses in COVID-19. However, the potential practical applications were limited by unresolved pharmacokinetic problems. Molecular dynamic modeling and computational analysis have also been used in [77] to design possible PROTAC® molecules targeting the SARS-CoV-2 protease, another confirmed viral target. However, the results of the calculations have yet to be verified by chemical synthesis and activity studies on models and *in vivo* studies.

CONCLUSIONS

PROTAC®, a targeted protein degradation technology, is based on the use of heterobifunctional molecules to recruit intracellular protein degradation mechanisms to an intracellular target protein of interest. This chemically induced affinity between the molecular mechanism of protein degradation and the target leads to polyubiquitinylation and proteasomal degradation of the target protein. The PROTAC® chimeric molecule is assembled from three parts: a ligand to the target protein; a ligand to the E3 ligase enzyme recruiting ubiquitin-proteasome system; and a linker that binds them together. The publicly available PROTAC-DB 2.0[3] database contains information on 3270 engineered chimeras, 360 "warheads", 1500 linkers and 80 E3 ligase ligands, as well as data on known crystal structures of ternary complexes.

Originally designed to target cancer and neurodegenerative diseases, this technology can also be directed against infections. New modifications suggest the use not only of the proteasome system, but also other defense mechanisms of the cell. Nucleic acids also act as a biological target. As of the end of 2022, at least 20 PROTAC® projects worldwide were in clinical trials and at least one had reached Phase III. The precise targeting of the body's own defense systems, which is no less effective than monoclonal antibody technology but cheaper, opens the way to treating a wide variety of diseases.

Authors' contribution

All authors equally contributed to the research work.

The authors declare no conflicts of interest.

[3] http://cadd.zju.edu.cn/protacdb/. Accessed February 26, 2024.

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