UDC 546.26-162 doi: 10.33609/2708-129X.90.9.2024.31-56

NEW DRUGS ON THE PHARMACEUTICAL MARKET CONTAINING FLUORINE AND RESIDUES OF TAILOR-MADE AMINO ACIDS.

Jianlin Han[1*], Alicja Wzorek[2], Gagan Dhawan[3,4*], Wei Zhang[5*], Alexander E. Sorochinsky[6*], Daniel Baecker[7*], Taizo Ono[8], Karel D. Klika[9], Vadim A. Soloshonok[10,11*]

[1]Jiangsu Co-Innovation Center of Efficient Processing and Utilization of Forest Resources, College of Chemical Engineering, Nanjing Forestry University, 210037 Nanjing, China;
[2]Institute of Chemistry, Jan Kochanowski University in Kielce, 7 Uniwersytecka, 25–406 Kielce, Poland;
[3]School of Allied Medical Sciences, Delhi Skill and Entrepreneurship University, Dwarka, 110077 New Delhi, India;
[4] Department of Biomedical Science, Acharya Narendra Dev College, University of Delhi, Kalkaji, 110019 New Delhi, India;
[5] Department of Chemistry, University of Massachusetts Boston, 02125 Boston MA, Unites States;
[6]V.P. Kukhar Institute of Bioorganic Chemistry and Petrochemistry, the National Academy of Sciences of Ukraine, 02094 Kyiv, Ukraine
[7] Department of Pharmaceutical and Medicinal Chemistry, Institute of Pharmacy, Freie Universität Berlin, 2+4 Königin-Luise-Straße, 14195 Berlin, Germany;
[8]National Institute of Advanced Industrial Science and Technology (AIST), 2266–98, Anagahora, Shimoshidami, Moriyama-ku, 463–8560 Nagoya, Japan;
[9]Molecular Structure Analysis, German Cancer Research Center (DKFZ), 280 Im Neuenheimer Feld, 69120 Heidelberg, Germany;
[10] Department of Organic Chemistry I, Faculty of Chemistry, University of the Basque Country UPV/EHU, 3 Paseo Manuel Lardizábal, 20018 San Sebastián, Spain;
[11]IKERBASQUE, Basque Foundation for Science, 3 María Díaz de Haro, Plaza Bizkaia, 48013 Bilbao, Spain
**email: vadimsoloshonok@gmail.com*

This article profiles five newly drugs containing fluorine along with fragments of amino acids or their derivatives approved by the FDA in 2024. These pharmaceuticals include Voydeya® (danicopan), Ojemda® (tovorafenib), Itovebi® (inavolisib), Scemblix® (asciminib), and Revuforj® (revumenib). For each drug, we discuss the discovery, therapeutic areas of application, and detailed chemical synthesis.

Key words: Fluorine, Tailor-made amino acids, Pharmaceutical drugs, Drug design, Synthesis, Bioactivity.

INTRODUCTION. Amino acids are fundamental to the development of life as they are the building blocks of proteins, which perform a vast array of functions within living organisms [1]. Proteins are involved in virtually every cellular process, including enzymatic catalysis, structural support, transport, communication, and immune response. Without amino acids, the complex molecules necessary for life as we know it would notexist [2–18]. They play a crucial role in maintaining the structure and function of cells, tissues, and organs, making them essential for growth, repair, and overall health [19–32].

In the modern pharmaceutical industry, amino acids are invaluable due to their versatility and their influence on drug design and development. Tailor-made amino acids (AAs) [33] can be incorporated into drugs to enhance their efficacy, stability, and specificity. By manipulating the structure of amino acids, pharmaceutical researchers can design drugs that precisely target specific biological pathways, reduce side effects, and improve patient outcomes [34–41]. Additionally, amino acids are used in the synthesis of peptide-based drugs, which are increasingly important in treating a range of conditions from cancer to metabolic disorders [42–48]. Their role in the pharmaceutical industry underscores the profound impact of amino acids not only on life itself but also on the advancement of medical science and therapeutics [49–51].

Another trend in the design of modern pharmaceuticals is a selective incorporation of fluorine atoms or/and fluorine-containing groups [52–63]. Thus, fluorine plays a crucial role in modern drug design due to its unique chemical properties, such as high electronegativity, small atomic size, and ability to form stable bonds. These properties allow fluorine to enhance the potency, selectivity, metabolic stability, and pharmacokinetics of drugs. Incorporating fluorine into drug molecules can improve their efficacy and reduce side effects, making them more effective therapeutic agents [64–69].

Fluorine-containing amino acids are particularly valuable in drug design because they combine the benefits of fluorine with the structural versatility of amino acids [70–74]. These tailor-made amino acids can be used to fine-tune the activity and pharmacokinetics of drug candidates, leading to more targeted and efficient treatments. The synthesis of tailor-made fluorinated α- [75–100] and β-amino acids [101–121] has been one of the areas of intense research activity in the last 20+ years [122–143]. The selective introduction of fluorine into bioactive compounds has become a mature strategy in drug development, resulting in numerous FDA-approved fluorinated drugs [64, 66–69].

Overall, the incorporation of fluorine and amino acids into pharmaceuticals represents a significant advancement in the field of medicinal chemistry, offering new opportunities for the development of more effective and safer drugs. In the present article, we profile five newly FDA-approved (2024) small-molecule pharmaceuticals (Figure 1) that contain fluorine and a residue of an amino acid or its derivative. These include: Voydeya® (danicopan) **1**, Ojemda® (tovorafenib) **2**, Itovebi®(inavolisib) **3**, Scemblix® (asciminib) **4**, and Revuforj® (revumenib) **5**. For each drug, we discuss the discovery, therapeutic areas of application, and detailed chemical synthesis.

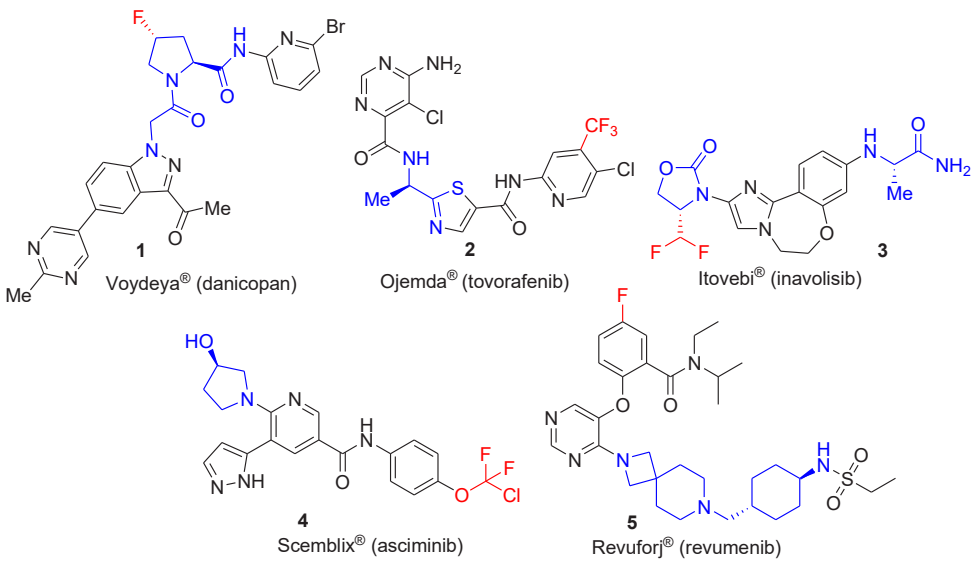


Fig. 1. Chemical structures of new pharmaceutical drugs **1**-**5** containing fluorine (marked in red) and a residue of an amino acid or its derivative (marked in blue).

Voydeya® (Danicopan) (1)

Danicopan, marketed under the name Voydeya®, is a drug derived from γ-fluorine-substituted proline. The FDA approved this compound on March 29, 2024. Developed by Alexion Pharmaceuticals, a subsidiary of AstraZeneca, this drug targets rare diseases, with Alexion being renowned for their expertise in orphan drugs [144]. Cyclic amino acids, such as those used in this compound, are particularly important in drug design because they are more sterically constrained than their linear counterparts [145, 146]. Adding fluorine [147] or CF_3 groups [148–150] on five-membered rings further restricts the range of accessible conformations, enabling the fine-tuning of biological properties. The introduction of a fluorine atom into the pyrrolidine-2-carboxamide framework, as compared to non-fluorinated analogs like compounds **6** and **7** (Figure 2), significantly boosts activity, achieving an IC_{50} of 0.027 μM. This modification demonstrates exceptional potency and underscores the compound's potential to surpass other molecules in its class [151, 152].

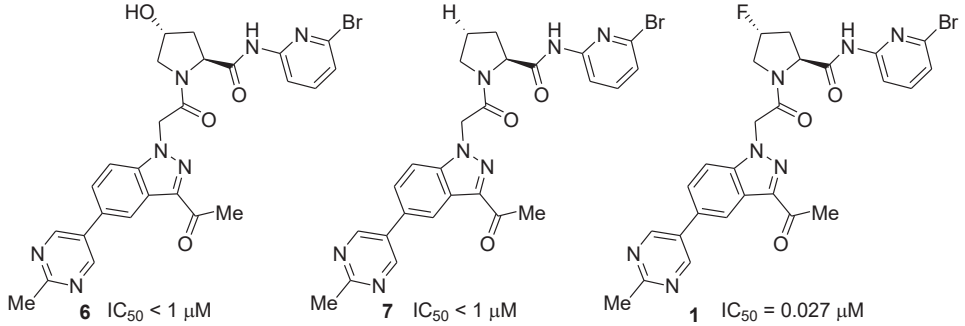
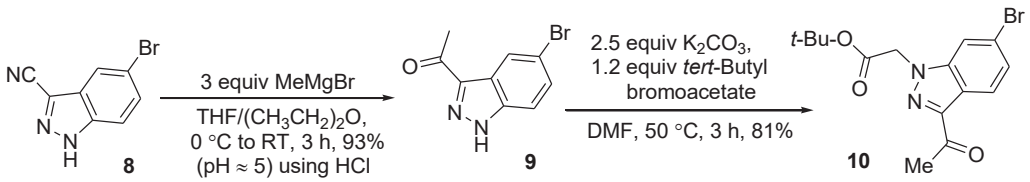


Fig. 2. Structures of Voydeya® (Danicopan) **1** and its fluorine-free analogs **6** and **7**.

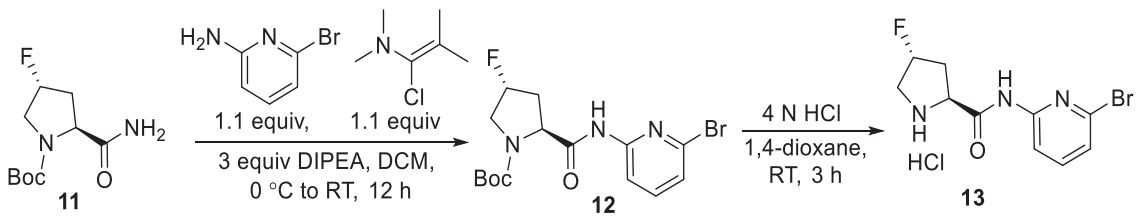
Voydeya, an oral complement factor D inhibitor, serves as an add-on therapy to the complement C5 inhibitors Ravulizumab and Eculizumab for treating extravascular hemolysis (EVH) in adults with paroxysmal nocturnal hemoglobinuria (PNH) [153,154]. PNH is a rare condition where the immune system's complement attacks red and white blood cells and platelets, leading to intravascular hemolysis and a heightened risk of thrombosis and organ damage. Although C5 inhibitors are the primary treatment, some patients still experience residual extravascular hemolysis and anemia [155]. Danicopan received its initial approval in Japan on January 18, 2024, for treating adults with PNH in combination with C5 inhibitors [156]. On February 23, 2024, the European Medicines Agency also recommended its market authorization for patients with residual hemolytic anemia despite C5 inhibition therapy [157].

The synthesis of Voydeya® (Danicopan) was developed by Alexion Pharmaceuticals [158–160]. This process starts with the creation of several key intermediates. As outlined in Scheme 1, 5-bromo-1*H*-indazole-3-carbonitrile **8** reacts with methyl magnesium bromide forming an imine magnesium salt intermediate. This intermediate is then hydrolyzed with acid treatment at pH 5 to produce ketone **9**. Following this, a Michael addition is carried out, yielding the ester **10** with an 81% yield.



Scheme 1. Synthesis of key intermediate **10**.

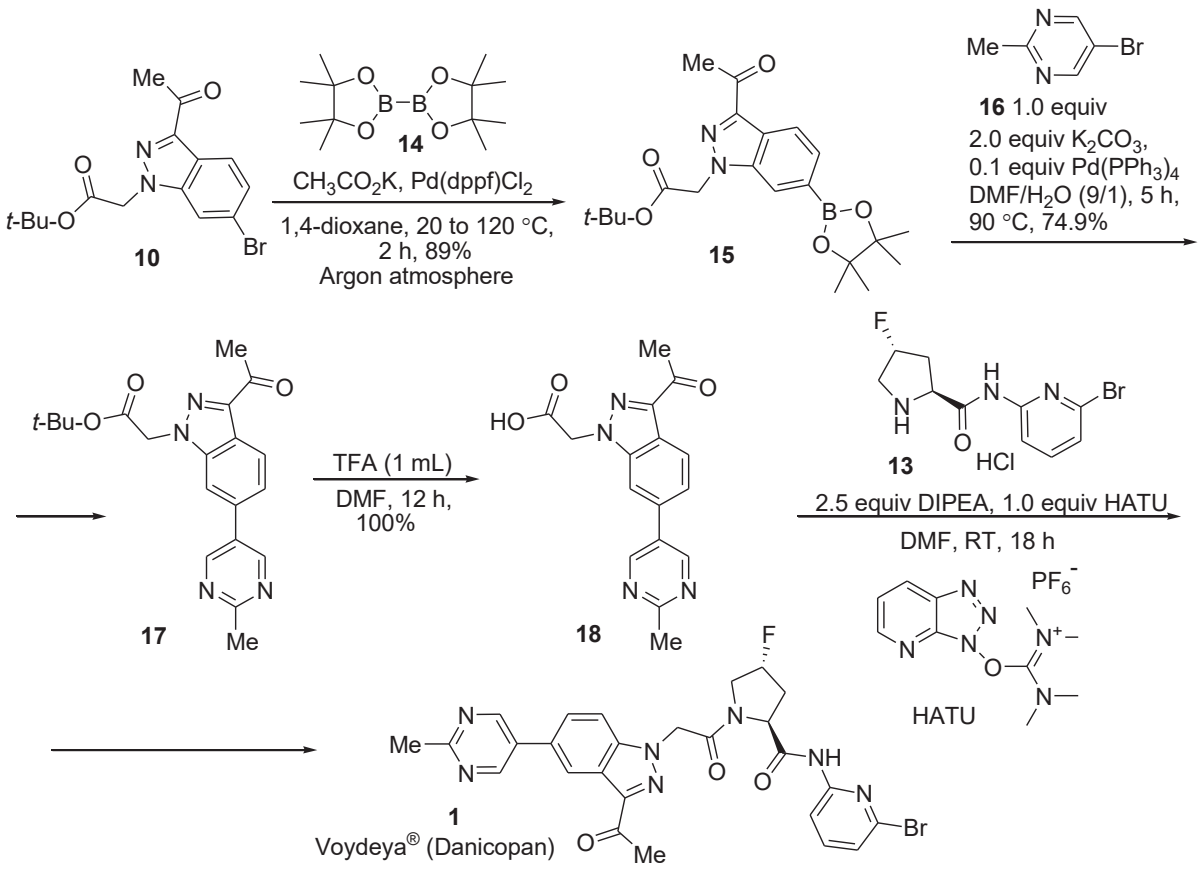
The synthesis of another important compound **13**, is detailed in Scheme 2. Boc-protected fluoropyrrolidine **11** undergoes amide alkylation using Ghosez reagent and diisopropylethylamine (DIPEA) [161]. This is followed by deprotection of the amino group, resulting in the precursor **13**.



Scheme 2. Synthesis of key intermediate **13**.

ISSN 2708-129X. Укр. хім. журн., 2024

The assembly of Danicopan's structure using key compounds **10** and **13** is detailed in Scheme 3. Initially, bromide **10** reacts with **14**, forming intermediate **15**. This is followed by a Suzuki – Miyaura coupling reaction with compound **16** in the presence of a palladium catalyst and a base, resulting in ester **17**. Ester hydrolysis with trifluoroacetic acid (TFA) then produces carboxylic acid **18** in quantitative yield. Finally, a coupling reaction with fluoro-proline derivative **13** leads to the synthesis of Voydeya® (Danicopan) (**1**).

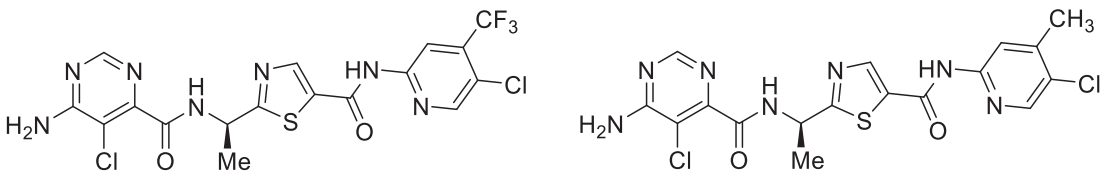


Scheme 3. Synthesis of Danicopan**1**.

Ojemda® (Tovorafenib) (2)

Tovorafenib, branded as Ojemda® (**2**), is an aromatic trifluoromethyl-containing complex structure developed by Day One Biopharmaceuticals Inc (California, USA) under a license agreement with Takeda Oncology (Massachusetts, USA). This drug, also known as DAY101, is a targeted therapy for cancers with RAF alterations, including pediatric low-grade glioma [162–164]. Tovorafenib**2** has shown the most effective inhibitory activity against RAF kinases like BRAF and CRAF when compared

to non-fluorinated analogs, such as **19** (Figure 3) [165, 166]. It received FDA approval on April 23, 2024. Ojemda is an oral kinase inhibitor that targets mutant BRAF V600E, wild-type BRAF, and wild-type CRAF kinases. It is intended for patients aged 6 months and older with relapsed or refractory pediatric low-grade glioma (pLGG) harboring BRAF fusions, rearrangements, or V600 mutations [167, 168]. This accelerated approval was granted based on clinical responses and the duration of response observed in the phase 2 FIREFLY-1 trial (NCT04775485; PNOC026) [169]. The recommended dose is 380 mg/m² taken orally once weekly (maximum 600 mg) until disease progression or unacceptable toxicity [170].



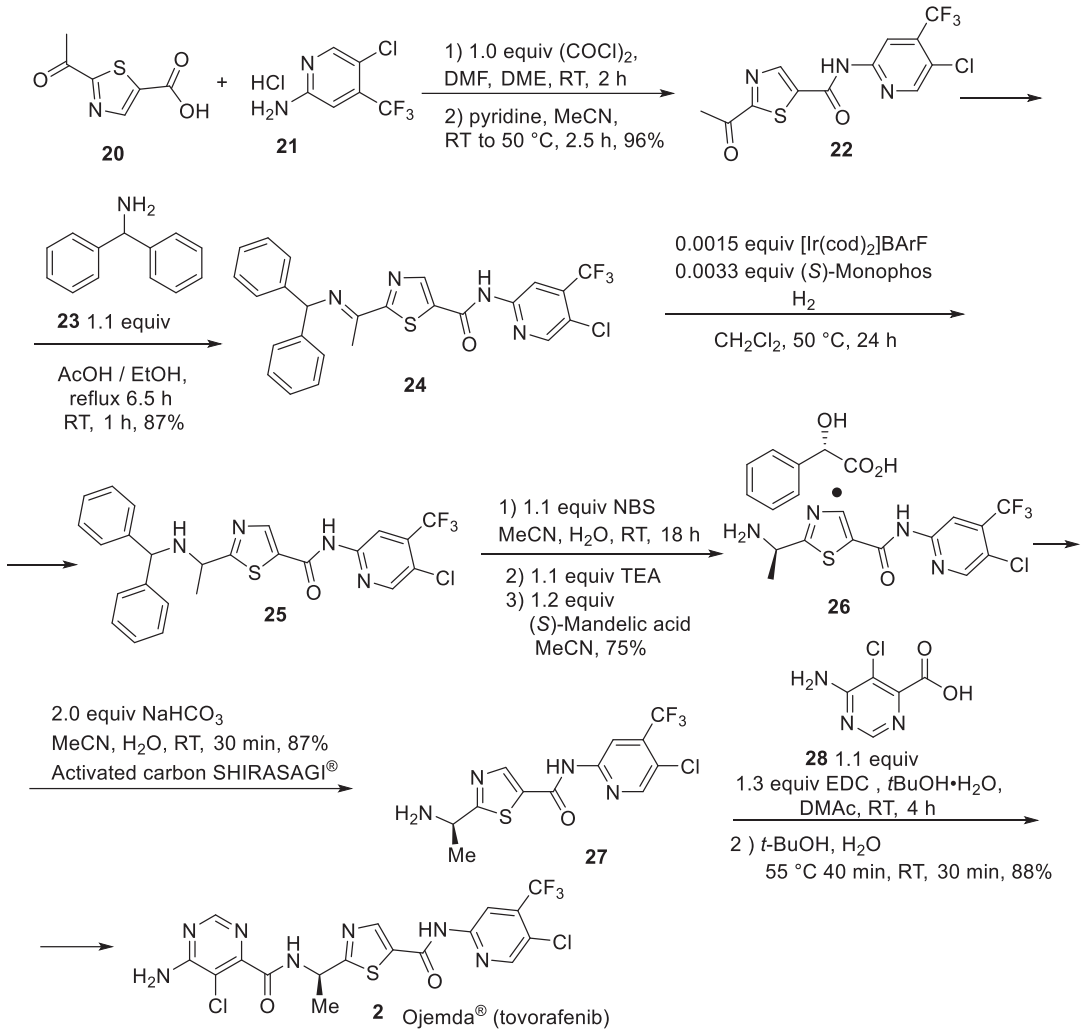
2 Ojemda®(tovorafenib) **19**

Fig. 3. Structures of Tovorafenib**2** and its non-fluorinated analog **19**.

Scheme 4 outlines the synthesis of Ojemda® (Tovorafenib) [171]. The process begins with the reaction of thiazole **20** with compound **21** using oxalyl chloride as the activating reagent, yielding target amide **22** with a 96% yield. Compound **22** is then mixed with ethanol, 1.1 equivalents of diphenylmethanamine **23**, and acetic acid in a flask equipped with a Dean–Stark trap, and the mixture is refluxed for 6.5 hours. After cooling and stirring for 1 hour, Schiff base **24** is obtained with an 87% yield. Next, compound **24** is dissolved in dichloromethane and combined with [Ir (cod)$_2$] BArF and (*S*)-Monophos, then placed in an autoclave. Hydrogen is introduced, and the mixture is heated to 50°C and stirred for 24 hours, resulting in compound **25**. Acetonitrile and water are added, followed by 1.1 equivalents of *N*-bromosuccinimide, and the reaction proceeds at room temperature for 18 hours to generate the corresponding free amino compound in situ. Optical resolution [172] is performed using (*S*)-mandelic acid, yielding crystallized product **26** with a 75% yield. Subsequent purification involving 2.0 equivalents of sodium bicarbonate and activated carbon in a water–acetonitrile mixture produces compound **27**. Finally, intermediate **27** is coupled with 6-amino-5-chloropyrimidine-4-carboxylic acid **28** under EDC/*t*-BuOH conditions, resulting in Ojemda® (Tovorafenib) **2** with an 88% yield [171].

Itovebi® (inavolisib)(3)

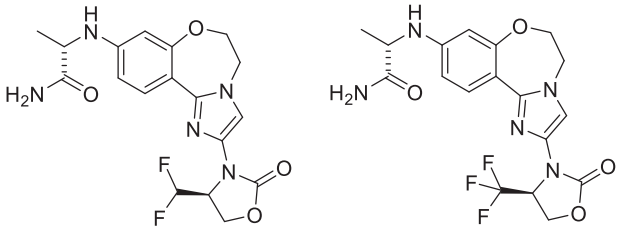
Inavolisib, marketed under the brand name Itovebi®, has been approved by the FDA for treating locally advanced or metastatic breast cancer [173]. It functions as an inhibitor of the phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K) pathway, representing a new generation of inhibitors with an improved toxicity profile compared to the previously approved inhibitor alpelisib [174, 175].



Scheme 4. Synthesis of Ojemda® (Tovorafenib) **2**.

PI3K enzymes play a crucial role in cell growth and differentiation, consisting of regulatory and catalytic subunits [176]. There are four isoforms: PI3Kα, PI3Kβ, PI3Kγ, and PI3Kδ. PI3Kα is most closely linked to tumorigenesis due to mutations and amplifications in the PIK3CA gene encoding the p110α unit [177, 178]. Approximately one-third of breast cancer cases exhibit such pathway disorders [179], which are considered poor prognostic factors [173].Therefore, selective inhibitors of PI3Kα, which do not induce side effects by blocking other PI3K isoforms, are highly desirable [180]. Inavolisib demonstrates an enzyme inhibitory concentration (IC_{50}) of 0.034 nM for PI3Kα, 100 nM for PI3Kβ, 18 nM for PI3Kγ, and 12 nM for PI3Kδ, indicating a more than 350-fold selectivity for PI3Kα [181]. Additionally, inavolisib promotes the degradation of the mutated p110α subunit [182].

It is note worthy that the introduction of a trifluoromethyl group in compound **29** (Figure 4), which has a PI3Kα IC_{50} of 0.095 nM and a PI3Kδ/PI3Kα ratio of 171, resulted in less selectivity towards the α isoform compared to the difluoromethyl group in compound **3** (PI3Kα IC50 of 0.034 nM and a PI3Kδ/PI3Kα ratio of 361) [183].



Itovebi® (inavolisib) **3**

PI3Kα = 0.034 nM;
PI3Kδ/PI3Kα ratio = 361

29

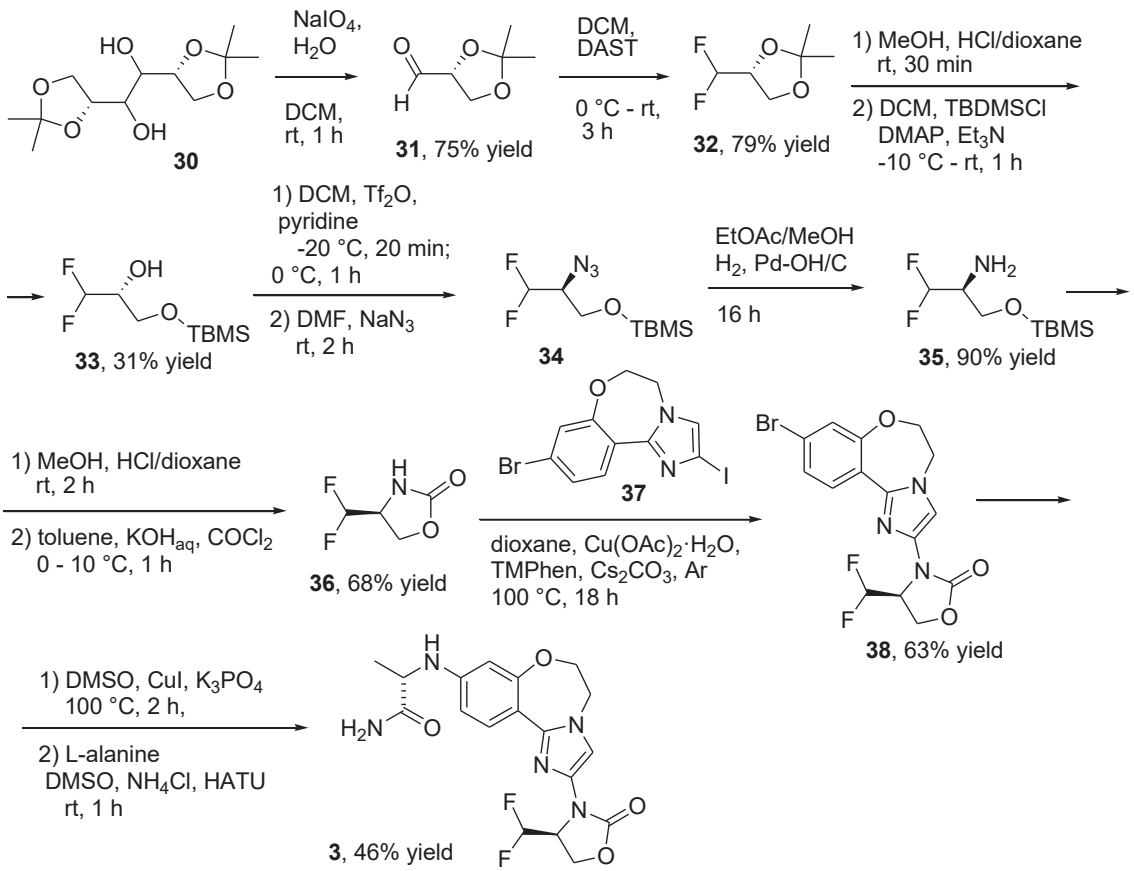
PI3Kα = 0.095 nM;
PI3Kδ/PI3Kα ratio = 171

Fig. 4. Structures of Itovebi® (inavolisib)**3** and its CF_3-containing analog **29**.

Chemically, inavolisib features a benzoxazepine oxazolidinone core, an alanine amide moiety, and an amino alcohol derived from difluoroalanine. This difluoroalanine derivative is particularly favored by PI3Kα, enhancing the selectivity for this isoform. The precise interactions of inavolisib with its target are facilitated by hydrogen bonds from the amide and amino groups of the alanine fragment. Additionally, the difluoromethyl group of inavolisib interacts with the hydroxyl group of Ser774 within the p110α pocket [181]. Thus, fluorination plays a crucial role in the unique effectiveness of this next-generation PI3Kα inhibitor.

The synthetic route to prepare inavolisib (Scheme 5) starts with 1,2:5,6-bis-*O*-(1-methylethylidene)-D-mannitol **30**, which serves as a source for the desired stereochemical configuration [183]. Sodium periodate ($NaIO_4$) in hot water is added to silica, forming a powder. This mixture is then combined with compound **30** dissolved indichloromethane (DCM) and stirred at room temperature for 1 hour, producing carbaldehyde **31**. To the cooled carbaldehyde **31** solution in DCM, diethylaminosulfur trifluoride (DAST) is added dropwise and stirred at room temperature for 3 hours, yielding (*R*)-4-difluoromethyl-2,2-dimethyl [1,3] dioxolane **32**. This intermediate is dissolved in methanol (MeOH), and hydrochloric acid (HCl) in dioxane is added, stirring at room temperature for 30 minutes. The acetal is cleaved to form the respective diol. After work-up, the residue is dissolved in DCM, followed by the addition of *tert*-butyldimethylsilyl chloride(TBDMS), Et_3N, and catalytic amounts of 4-Dimethylaminopyridine(DMAP). Compound **33** was obtained after stirring for 1 hour at room temperature. Following this, trifluoromethanesulfonic anhydride (Tf_2O) was added dropwise to a solution of **33** and pyridine in DCM. The temperature was maintained at -20 °C for 20 minutes, then brought to 0 °C for 1 hour while stirring. After extraction and work-up, the residue was dissolved in DMF, and sodium azide (NaN_3) was added, stirring for 2 hours at room temperature to produce intermediate **34**. The azide was then reduced using

palladium hydroxide on carbon (Pd-OH/C) under hydrogen (H_2) by stirring for 16 hours in ethyl acetate (EtOAc) and MeOH, yielding primary amine **35**. This product was dissolved in MeOH and stirred in a solution of HCl (in dioxane) for 2 hours at room temperature to remove the protective group. After work-up, the crude product was dissolved in toluene and aqueous potassium hydroxide (KOH) at 0°C. Phosgene ($COCl_2$) was added gradually, followed by stirring for 1 hour to obtain (*S*)-4-difluoromethyloxazolidin-2-one **36**. This was combined with 9-bromo-2-iodo-5,6-dihydrobenzo[*f*]imidazo[1,2-*d*][1,4]-oxazepane **37**, copper acetate monohydrate ($Cu(OAc)_2{\cdot}H_2O$), 3,4,7,8-tetram ethyl-1,10-phenanthroline (TMPhen), and cesium carbonate (Cs_2CO_3) in dioxane. The mixture was heated to 100 °C for 18 hours under an argon (Ar) atmosphere, resulting in compound **38**. The reagent **37** can be obtained as described in the literature [184]. Compound **38** was then suspended in dimethyl sulfoxide (DMSO) with L-alanine, cuprous iodide (CuI), and potassium phosphate tribasic (K_3PO_4), and heated at 100 °C for 2 hours. After cooling to room temperature, DMSO, ammonium chloride (NH_4Cl), and Et_3N were added. To this suspension, 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]-pyridinium 3-oxide hexafluorophosphate (HATU) was added dropwise and stirred at room temperature for 1 hour. Finally, inavolisib**3** was obtained [183].



Scheme 5. Synthesis of Itovebi® (inavolisib) **3**.

Scemblix® (asciminib)(4)

Asciminib is an efficacious, small-molecule, orally bioavailable, and a selective allosteric inhibitor discovered and developed by Novartis for the treatment of hematologic malignancies, including Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) [185,186]. In October 2021, the U.S. FDA approved Scemblix® for two distinct indications in CML [185]. In vitro anticancer activity tests against MV411 (ATCC) and K562 (ATCC) leukemia cells demonstrated that asciminib exhibited potent inhibitory activity, with cellular IC_{50} values of 8.65 μmol/L for K562 and 0.32 μmol/L for MY411. However, its structurally similar analog, compound **39** (Figure 5), showed moderate activity against the leukemia cell lines (K562 IC_{50} > 30 μmol/L and MY411 IC_{50} > 30 μmol/L).

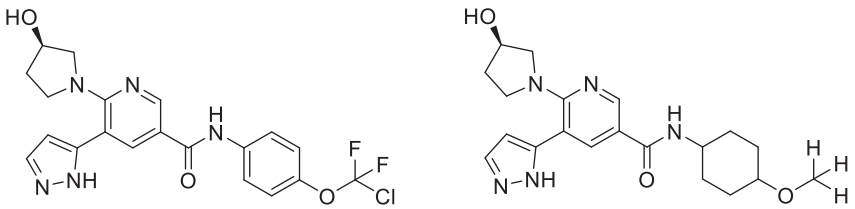
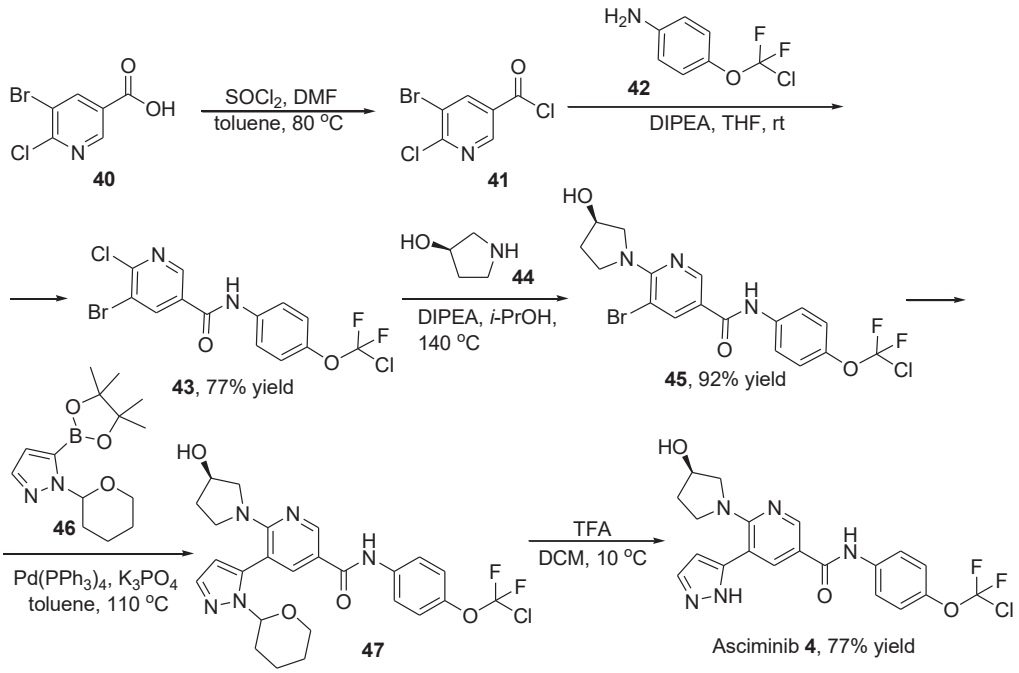


Fig. 5. Structures of Scemblix® (asciminib) **4** and its fluorine-free analog **39**.

This study indicated that the CF_2Cl group in the asciminib structure is crucial for inducing inactive conformations. Additionally, the pyrazole ring in its structure reduces hERG toxicity [186, 187]. As an allosteric inhibitor targeting ABL1, asciminib binds to the myristoyl pocket of ABL1 to inhibit BCR-ABL1 activity, differing from competitive inhibitors that target the ATP-binding site, such as imatinib, dasatinib, and nilotinib, which are associated with risks of resistance and site mutations [188–191]. Due to its unique allosteric regulatory mechanism, asciminib not only inhibits wild-type ABL1 kinase but also exhibits high activity against the T315I-mutated ABL1, significantly reducing the potential off-target effects of ATP-binding site inhibitors. In October 2024, the U.S. FDA granted accelerated approval to asciminib for the treatment of newly diagnosed adult patients with Philadelphia chromosome-positive chronic myeloid leukemia in chronic phase (Ph+ CML-CP) [192].

The synthesis of asciminib **4** has been documented by several groups [186, 193, 194]. One efficient method, illustrated in Scheme 6, begins with 5-bromo-6-chloronicotinic acid **40** as the starting material [186]. Chlorination of 5-bromo-6-chloronicotinic acid **40** using thionyl chloride in the presence of DMF in toluene at 80 °C produces acid chloride **41**. This intermediate then undergoes insitu condensation with 4-(chlorodifluoromethoxy)aniline **42** in the presence of DIPEA in THF at room temperature, forming amide **43** with a 77% yield. Next, compound **43** is reacted with (*R*)-pyrrolidin-3-ol **44** in the presence of DIPEA and isopropanol at 140 °C for 1 hour, producing derivative **45** with a 92% yield. Compound **45** is then

subjected to a standard Suzuki – Miyaura coupling reaction with the protected (1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-5-yl)boronic acid pinacol ester **46**, resulting in compound **47**. Finally, the protecting group is removed at 10 °C in the presence of trifluoroacetic acid in DCM, yielding the target product, asciminib **4**, with a 77% yield.



Scheme 6. Synthesis of Scemblix® (asciminib) **4**.

Revuforj® (revumenib)(5)

Revumenib, an orally administered and first-in-class menin inhibitor developed by Syndax Pharmaceuticals, received FDA approval in November 2024 for the treatment of patients with relapsed or refractory (R/R) acute leukemia harboring lysine methyltransferase 2A (KMT2A) gene translocations [195, 196]. Before this approval, revumenib was granted orphan drug designation by the FDA for the treatment of acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), and acute undifferentiated leukemia (ALAL), as well as by the European Commission for the treatment of AML [197].

This novel drug disrupts the interaction between menin and KMT2A fusion proteins, which are key drivers of leukemogenesis [195,198]. By inhibiting this interaction, revumenib helps restore normal gene expression, effectively halting cancer cell proliferation and promoting cell differentiation.

In cellular experiments, revumenib demonstrated an IC_{50} of 10–20 nmol/L for inhibiting Menin-MLL, whereas its structurally similar compounds **48** and **49** (Figure 6) showed poorer inhibitory activity with IC_{50} values for Menin-MLL exceeding 20 nmol/L. The superior inhibitory activity of revumenib **5** against Menin-MLL may be attributed to the fluorine atom in its structure [199].

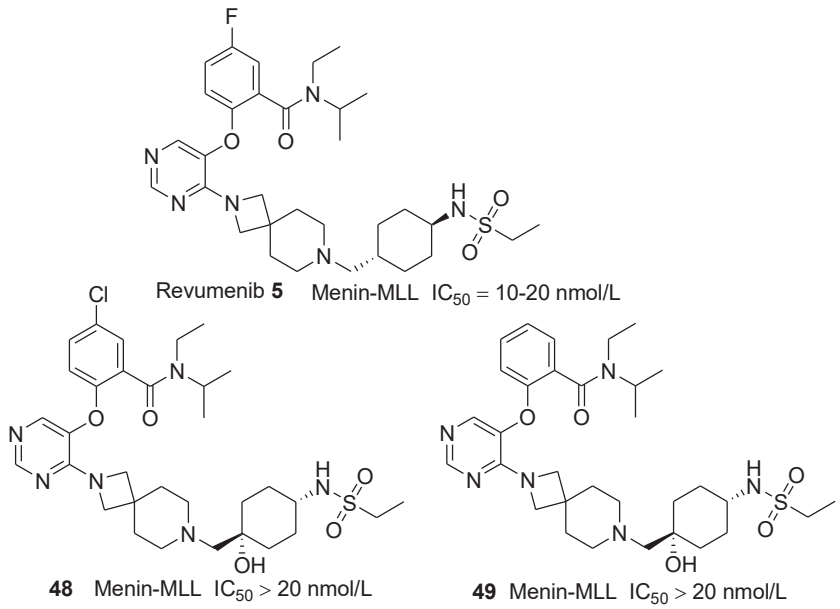
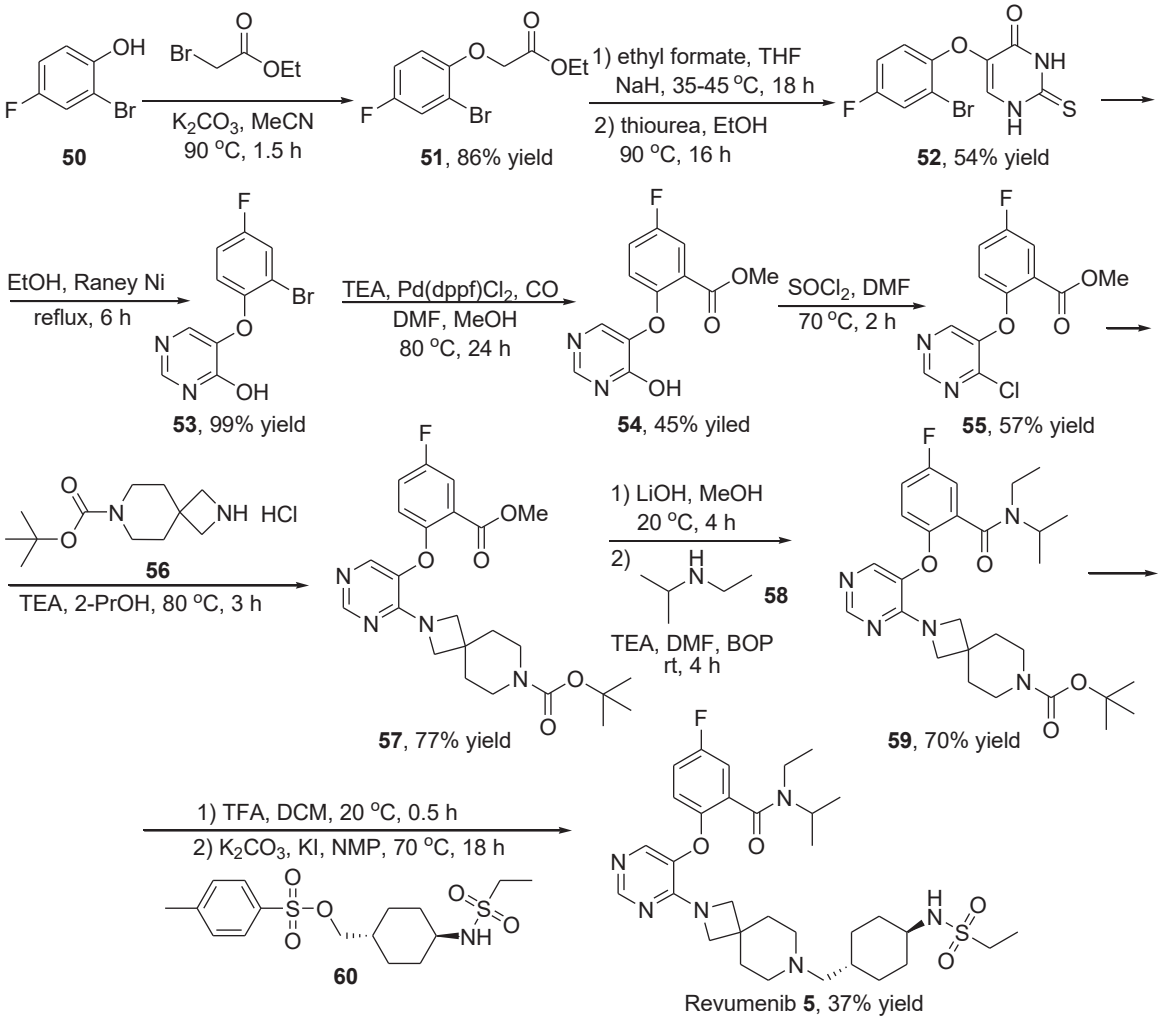


Fig. 6. Structures of Revuforj® (revumenib) **5** and its fluorine-free analogs **48** and **49**.

Clinical trials have shown promising results. When used as monotherapy for relapsed or refractory AML, revumenib **5** demonstrated significant efficacy, particularly in cases with nucleophosmin 1 (NPM1) mutations. This approval marks a significant advancement in the field of leukemia treatment, offering new hope for patients with limited therapeutic options [200, 201].

The synthetic route for the preparation of revumenib (**5**) is outlined in Scheme 7, starting with 2-bromo-4-fluorophenol **50** as the initial material [202]. Compound **50** underwent a substitution reaction with ethyl 2-bromoacetate in the presence of K_2CO_3, yielding compound **51** with an 86% yield. Compound **51** was first reacted in anhydrous THF, using ethyl formate and NaH as reagents. It then underwent a cyclization condensation reaction with thiourea at 90°C, resulting in the pyrimidinone compound **52** with a 54% yield.

Subsequently, compound **52** was subjected to a desulfurization reduction reaction in the presence of Raney Ni, yielding compound **53** with a 99% yield. Compound **53** was then reacted with CO and methanol under the catalysis of $Pd(dppf)Cl_2$, affording compound **54** with a 45% yield. In the presence of $SOCl_2$, compound **54** underwent a substitution reaction, resulting in derivative**55** with a 57% yield. Ester **55** was then reacted with bicyclic properly protected diamine **56** in the presence of TEA, using isopropanol as the solvent, to yield compound **57** with a 77% yield. Precursor **57** first underwent a hydrolysis reaction in the presence of LiOH, followed by an amidation reaction with amine **58** in the presence of BOP, yielding product **59** with a 70% yield. Derivative **59** was first deprotected of its Boc-protecting group in the presence of TEA and DCM as solvents. It subsequently reacted with activated cyclic amino alcohol **60** in the presence of K_2CO_3, KI, and NMP, giving rise torevumenib **5** with a 37% yield [202].



Scheme 7. Synthesis of Revuforj® (revumenib) **5**.

CONCLUSIONS. This year's crop of FDA-approved small-molecule drugs containing fluorine and amino acid residues consists of five pharmaceuticals: Voydeya® (danicopan) **1**, Ojemda® (tovorafenib) **2**, Itovebi® (inavolisib) **3**, Scemblix® (asciminib) **4**, and Revuforj® (revumenib) **5**. Four of these drugs (**2**-**5**) were developed to fight various types of cancer, while danicopan (**1**) was approved for the treatment of a rare form of blood disease.

The tailor-made amino acidsinclude 3-substituted proline (**1**), alanine (**2**, **3**), and amino acid-derived cyclic amino alcohols (**3**, **4**) and diamines (**5**). The types of fluorination are represented by cyclic CHF (**1**), hetero-aromatic CF_3 (**2**), aliphatic CHF_2 group (**3**), aromatic $CClF_2$-O group (**4**), and aromatic fluorine (**5**).

An important trend observed in new small-molecule pharmaceuticals, and this group of drugs in particular, is that all five compounds

under discussion are chiral, possessing one (**2**, **3**) or two (**1**, **3**, **4**) stereogenic carbons. Considering the FDA requirements for chiral drugs, continuous advances in the asymmetric synthesis and characterization of chiral fluorine-containing compounds are of great importance. In this regard, particular attention should be given to the phenomenon of the self-disproportionation of enantiomers (SDE), a non-linear behavior of enantiomerically enriched compounds [203–205]. The SDE properties of chiral drugs, especially those containing fluorine [206–208] and/or AA residues [209–211], are a critical public safety issue, requiring additional scrutiny in evaluating their enantiomeric purity [212–215].

We gratefully acknowledge the financial support from the National Natural Science Foundation of China (No. 21761132021), the Qing-Lan Project of Jiangsu Province (for Han) and IKERBASQUE, Basque Foundation for Science (for Soloshonok).

НОВІ ПРЕПАРАТИ НА ФАРМАЦЕВТИЧНОМУ РИНКУ, ЩО МІСТЯТЬ ФТОР І ЗАЛИШКИ СПЕЦІАЛЬНО СТВОРЕНИХ АМІНОКИСЛОТ

Ц. Хань[1*], А. Взорек[2], Г. Дхаван[3,4*], В. Зханг[5*], О. Є. Сорочинський[6*], Д. Бекер[7*], Т. Оно[8], К. Д. Клика[9], В. А. Солошонок[10,11*]

[1]Спільний інноваційний центр Цзянсу з ефективного оброблення та використання лісових ресурсів, Коледж хімічної інженерії, Нанкінський лісотехнічний університет, 210037 Нанкін, Китай;
[2]Інститут хімії, Університет імені Яна Кохановського в Кельцях, Кельці, Польща;
[3] Школа медичних наук, Університет підприємництва, Делі, 110077 Нью-Делі, Індія
[4]Коледж Ачаріа Нарендра Дев, Університет Делі, 110019 Нью-Делі, Індія;
[5]Департамент хімії, Массачусетський університет, Бостон, 02125 Массачусетс, США;
[6]Інститут біоорганічної хімії та нафтохімії ім. В. П. Кухаря НАН України, Київ, Україна;
[7]Департамент фармацевтичної та медичної хімії, Інститут фармації, Вільний університет Берліна, 14195 Berlin, Germany;
[8]Національний інститут передових промислових наук і технологій, 463–8560 Нагоя, Японія
[9]Німецький центр дослідження раку (DKFZ), 69120 Гейдельберг, Німеччина;
[10]Хімічний факультет, Університет Країни Басків, 20018 Сан-Себастьян, Іспанія;
[11]ІКЕРБАСК, Баскський фонд науки, 48013 Більбао, Іспанія
**email: vadimsoloshonok@gmail.com*

У статті розглянуто п’ять нових препаратів, схвалених FDA, що містять фтор і фрагменти амінокислот або їхніх похідних. До цих лікарських засобів належать: Voydeya® (danicopan), Ojemda® (tovorafenib), Itovebi® (inavolisib), Scemblix® (asciminib) та Revuforj® (revumenib). Описано відкриття кожного препарату, терапевтичне застосування та детальний хімічний синтез.

Ключові слова: фтор, спеціально створені амінокислоти, фармацевтичні препарати, дизайн ліків, синтез, біоактивність.

REFERENCES

1. Vickery H.B., Schmidt C.L.A. The history of the discovery of the amino acids. *Chem. Rev*. 1931. **9**(2): 169–318. doi: 10.1021/cr60033a001.
2. Luisi P.L. *The Emergence of Life: From Chemical Origins to Synthetic Biology*. Cambridge University Press. 2006. doi: 10.1017/CBO9780511817540
3. Anfinsen C.B., Edsall J.T., Richards F.M. *Advances in Protein Chemistry*. New York: Academic Press. 1972.
4. Michal G., Schomburg D., eds. *Biochemical Pathways: An Atlas of Biochemistry and Molecular Biology.* 2nd Ed. Oxford: Wiley-Blackwell. 2012.
5. Genchi G. An overview on D-amino acids. *Amino Acids*. 2017. **49**(9): 1521–1533. doi: 10.1007/s00726-017-2459-5.
6. Wong J. T.-F. A Co-Evolution Theory of the Genetic Code. *Proc. Nat. Acad. Sci. USA*. 1975. **72**(5): 1909–1912. doi: 10.1073/pnas.72.5.1909.
7. Trifonov E.N. Consensus temporal order of amino acids and evolution of the triplet code. *Gene*. 2000. **261**(1): 139–151. doi: 10.1016/s0378-1119(00)00476-5.
8. Higgs P.G., Pudritz R.E. A thermodynamic basis for prebiotic amino acid synthesis and the nature of the first genetic code. *Astrobiology*. 2009. **9** (5): 483–90. doi: 10.1089/ast.2008.0280.
9. Meierhenrich U. *Amino acids and the asymmetry of life*. Berlin: Springer. 2008. doi: 10.1007/978-3-540-76886-9.
10. Hanessian S. Reflections on the total synthesis of natural products: Art, craft, logic, and the chiron approach. *Pure Appl. Chem*.1993. **65**(6): 1189–1204. doi: 10.1351/pac199365061189.
11. Blaser H.U. The chiral pool as a source of enantioselective catalysts and auxiliaries. *Chem. Rev*. 1992. **92**(5): 935–952. doi: 10.1021/cr00013a009.
12. Kitadai N., Maruyama S. Origins of building blocks of life: A review. *Geosci. Front*. 2018. **9**(4): 1117–1153. doi: 10.1016/j.gsf.2017.07.007.
13. Danchin A. From chemical metabolism to life: the origin of the genetic coding process. *Beilstein J. Org. Chem*. 2017. **13**(1): 1119–1135. doi: 10.3762/bjoc.13.111.
14. Frenkel-Pinter M., Samanta M., Ashkenasy G., Leman L.J. Prebiotic Peptides: Molecular Hubs in the Origin of Life. *Chem. Rev*. 2020. **120**(11): 4707–4765. doi: 10.1021/acs.chemrev.9b00664.
15. Milner-White E.J. Protein three-dimensional structures at the origin of life. *Interface Focus*. 2019. **9**(6): 20190057. doi: 10.1098/rsfs.2019.0057.
16. Chatterjee S., Yadav S. The Coevolution of Biomolecules and Prebiotic Information Systems in the Origin of Life: A Visualization Model for Assembling the First Gene. *Life*. 2022. **12**(6): 834. doi: 10.3390/life12060834.
17. Kirschning A. The coenzyme/protein pair and the molecular evolution of life. *Nat. Prod. Rep*. 2021. **38**(5): 993–1010. doi: 10.1039/D0NP00037J.
18. Gutteridge A., Thornton J.M. Understanding nature's catalytic toolkit. *Trends in Biochem. Sci*. 2005. **30**(11): 622–629. doi: 10.1016/j.tibs.2005.09.006.
19. McCoy R.H., Meyer C.E., Rose W.C. Feeding experiments with mixtures of highly purified amino acids. VIII. Isolation and identification of a new essential amino acid.*J. Biol. Chem*. 1935. **112**: 283–302.
20. Steinhardt J., Reynolds J. A. *Multiple equilibria in proteins*. New York: Academic Press. 1969.
21. Xie J., Schultz P.G. Adding amino acids to the genetic repertoire. *Curr. Opin. Chem. Biol*. 2005. **9**(6): 548–554. doi: 10.1016/j.cbpa.2005.10.011.
22. Park M.H. The post-translational synthesis of a polyamine-derived amino acid, hypusine, in the eukaryoti c translation initiation factor 5A (eIF5A). *J. Biochem*. 2006. **139**(2): 161–169. doi: 10.1093/jb/mvj034.
23. Curis E., Nicolis I., Moinard C. et al. Almost all about citrulline in mammals. *Amino Acids*. 2005. **29**(3): 177–205.

doi: 10.1007/s00726-005-0235-4.
24. Sakami W., Harrington H. Amino acid metabolism. *Annu. Rev. Biochem.* 1963. **32**(1): 355–398.
doi: 10.1146/annurev.bi.32.070163.002035.
25. Wang X., Li J., Dong G., Yue J. The endogenous substrates of brain CYP_2D. *Eur. J. Pharmacol.* 2014. **724**: 211–218.
doi: 10.1016/j.ejphar.2013.12.025.
26. Petroff O.A. GABA and glutamate in the human brain. *Neurosci.* 2002. **8**(6): 562–573.
doi: 10.1177/1073858402238515.
27. Turner E.H., Loftis J.M., Blackwell A.D. Serotonin a la carte: supplementation with the serotonin precursor 5-hydroxytryptophan. *Pharmacol. Ther*. 2006. **109**(3): 325–338.
doi: 10.1016/j.pharmthera.2005.06.004.
28. Kostrzewa R.M., Nowak P., Kostrzewa J.P. *et al*. Peculiarities of L-DOPA treatment of Parkinson's disease. *Amino Acids*. 2005. **28**(2): 157–164.
doi: 10.1007/s00726-005-0162-4.
29. Leuchtenberger W., Huthmacher K., Drauz K. Biotechnological production of amino acids and derivatives: current status and prospects. *Appl. Microbiol. Biotechnol*. 2005. **69**(1): 1–8.
doi: 10.1007/s00253-005-0155-y.
30. Sanda F., Endo T. Syntheses and functions of polymers based on amino acids. *Macromol. Chem. Phys*. 1999. **200**(12): 2651–2661.
doi: 10.1002/(SICI)1521-3935.
31. Lengyel P., Söll D. Mechanism of protein biosynthesis. *Bacteriol. Rev*. 1969. **33**(2): 264–301.
doi: 10.1128/br.33.2.264-301.1969.
32. Marasco D., Perretta G., Sabatella M., Ruvo M. Past and future perspectives of synthetic peptide libraries. *Curr. Protein Pept. Sci*. 2008. **9**(5): 447–467.
doi: 10.2174/138920308785915209.
33. Soloshonok V.A., Cai C., Hruby V.J., Meervelt L.V. Asymmetric synthesis of novel highly sterically constrained (2*S*,3*S*)-3-methyl-3-trifluoromethyl- and (2*S*,3*S*,4*R*)-3-trifluoromethyl-4-methylpyroglutamic acids. *Tetrahedron*. 1999. **55**(41): 12045–12058.
doi: 10.1016/S0040-4020(99)00711-5.
34. Blaskovich M.A.T. Unusual amino acids in medicinal chemistry. *J Med Chem*. 2016. ***59*** (24): 10807–10836.
doi: 10.1021/acs.jmedchem.6b00319.
35. Han J., Konno H., Sato T. *et al*.Tailor-made amino acids in the design of small-molecule blockbuster drugs. *Eur. J. Med. Chem*. 2021. **220**: 113448.
doi: 10.1016/j.ejmech.2021.113448.
36. Liu J., Han J., Izawa K. *et al*. Cyclic tailor-made amino acids in the design of modern pharmaceuticals. *Eur. J. Med. Chem*. 2020. **208**: 112736.
doi: 10.1016/j.ejmech.2020.112736.
37. Stevenazzi A., Marchini M., Sandrone G., Vergani B., Lattanzio M. Amino acidic scaffolds bearing unnatural side chains: An old idea generates new and versatile tools for the life sciences. *Bioorg. Med. Chem. Lett*. 2014. **24**(23): 5349–5356.
doi: 10.1016/j.bmcl.2014.10.016.
38. Ma J.S. Unnatural amino acids in drug discovery. *Chim. Oggi-Chem. Today*. 2003. **21**(6): 65–68.
39. Liu A., Han J., Nakano A., *et al*. New pharmaceuticals approved by FDA in 2020: Small-molecule drugs derived from amino acids and related compounds. *Chirality*. 2022. **34**(1): 86–103.
doi: 10.1002/chir.23376.
40. Han J., Lyutenko N.V., Sorochinsky A.E., *et al*. Tailor-Made Amino Acids in Pharmaceutical Industry: Synthetic Approaches to Aza-Tryptophan Derivatives. *Chem. Eur. J*. 2021. **27**(70): 17510–17528.
doi: 10.1002/chem.202102485.
41. Yin Z., Hu W., Zhang W. *et al*. Tailor-made amino acid-derived pharmaceuticals approved by the FDA in 2019. *Amino Acids*. 2020. **52**(9): 1227–1261.
doi: 10.1007/s00726-020-02887-4.
42. Hodgson D.R.W., Sanderson J.M. The synthesis of peptides and proteins containing non-natural amino acids. *Chem. Soc. Rev*. 2004. **33**(7): 422–430.
doi: 10.1039/B312953P.
43. Henninot A., Collins J.C., Nuss J.M. The current state of peptide drug discovery: Back to the

future? *J. Med. Chem*. 2018. **61**(4): 1382–1414. doi: 10.1021/acs.jmedchem.7b00318.
44. Han, J., Konno H., Sato T., *et al*. Peptidomimetics and Peptide-Based Blockbuster Drugs. *Curr. Org. Chem*. 2021. **25**(14):1627–1658. doi: 10.2174/1385272825666210610155047.
45. Qiu W., Gu X., Soloshonok, V.A. et al. Stereoselective synthesis of conformationally constrained reverse turn dipeptide mimetics. *Tetrahedron Lett*. 2001. **42**(2): 145–148. doi: 10.1016/S0040-4039(00)01864-5.
46. Fosgerau K., Hoffmann T. Peptide therapeutics: current status and future directions. *Drug Discov. Today*. 2015. **20**(1): 122–128. doi: 10.1016/j.drudis.2014.10.003.
47. Cai M., Cai C., Mayorov A.V. *et al*. Biological and conformational study of β-substituted prolines in MT-II template: steric effects leading to human MC5 receptor selectivity. *J. Pept. Res*. 2004. **63**(2): 116–131. doi: 10.1111/j.1399-3011.2003.00105.x.
48. Craik D.J., Fairlie D.P., Liras S., Price D. The future of peptide-based drugs. *Chem. Biol. Drug Des*. 2013. **81**(1): 136–147. doi: 10.1111/cbdd.12055.
49. Hamley I.W. *Introduction to Peptide Science.* Wiley: Weinheim, Germany. 2020. ISBN: 978-1-119-69817-3.
50. Saladin K. *Anatomy and Physiology: The Unity of Form and Function.* 6th Ed. McGraw-Hill Science/Engineering/Math. 2011.
51. Soloshonok V.A., Izawa K. Eds. *Asymmetric Synthesis and Application of α-Amino Acids. ACS Symposium Series 1009*. Washington, District of Columbia: American Chemical Society, 2009.
52. Wang J., Sánchez-Roselló M., Aceña J.L. *et al*. Fluorine in pharmaceutical industry: Fluorine-containing drugs introduce ed to the market in the last decade (2001–2011). *Chem. Rev*. 2014. **114**(4): 2432–2506. doi: 10.1021/cr4002879.
53. Zhou Y., Wang J., Gu Z. *et al*. Next Generation of Fluorine-Containing Pharmaceuticals, Compounds Currently in Phase II–III Clinical Trials of Major Pharmaceutical Companies: New Structural Trends and Therapeutic Areas. *Chem. Rev*. 2016. **116**(2): 422–518. doi: 10.1021/acs.chemrev.5b00392.
54. Zhu Y., Han J.L., Wang J.*et al*. Modern Approaches for Asymmetric Construction of Carbon–Fluorine Quaternary Stereogenic Centers: Synthetic Challenges and Pharmaceutical Needs. *Chem. Rev*. 2018. **118**(7): 3887–3964. doi: 10.1021/acs.chemrev.7b00778.
55. Zhu W., Wang J., Wang S.*et al*.Recent advances in the trifluoromethylation methodology and new CF_3-containing drugs. *J. Fluorine Chem*. 2014. **167**: 37–54. doi: 10.1016/j.jfluchem.2014.06.026.
56. Gillis E.P., Eastman K.J., Hill M.D. *et al*. Applications of Fluorine in Medicinal Chemistry. *J. Med. Chem*. 2015. **58**(21): 8315–8359. doi: 10.1021/acs.jmedchem.5b00258.
57. Meanwell N.A. Fluorine and Fluorinated Motifs in Design and Application of Bioisosteres for Drug Design. *J. Med. Chem*. 2018. **61**(14): 5822–5880. doi: 10.1021/acs.jmedchem.7b01788.
58. Johnson B.M., Shu Y-Z., Zhuo X., Meanwell N.A. Metabolic and Pharmaceutical Aspects of Fluorinated Compounds. *J. Med. Chem*. 2020. **63**(12): 6315–86. doi: 10.1021/acs.jmedchem.9b01877.
59. Han J., Kiss L., Mei H. *et al*. Chemical aspects of human and environmental overload with fluorine. *Chem. Rev*. 2021. **121**(8): 4678–4742. doi: 10.1021/acs.chemrev.0c01263.
60. Pan Y. The Dark Side of Fluorine. *ACS Med. Chem. Lett*. 2019. **10**(7): 1016–1019. doi: 10.1021/acsmedchemlett.9b00235.
61. Khan M.F., Murphy C.D. Bacterial degradation of the anti-depressant drug produces trifluoroacetic acid and fluoride ion. *Appl. Microbiol. Biotechnol*. 2021. **105**(24): 9359–9369. doi: 10.1007/s00253-021-11675-3.
62. Sun M., Cui J.N., Guo J. *et al*. Fluorochemicals biodegradation as a potential source of trifluoroacetic acid (TFA) to the environment. *Chemosphere*. 2020. **254**: 126894. doi: 10.1016/j.chemosphere.2020.126894.
63. Garnett K., Van Calster G. The Concept of Essential Use: A Novel Approach to Regulating

Chemicals in the European Union. *Transnatl. Environ. Law*. 2021. **10**(1): 159–187. doi: 10.1017/S2047102521000042.
64. Mei H., Han J., Fustero S. Fluorine-Containing Drugs Approved by the FDA in 2018. *Chem. Eur. J.* 2019. **25**(51): 11797–11819. doi: 10.1002/chem.201901840.
65. Han J., Remete A.M., Dobson L.S. *et al*. Next generation organofluorine containing blockbuster drugs. *J. Fluor. Chem*. 2020. **239**: 109639. doi: 10.1016/j.jfluchem.2020.109639.
66. Mei H., Remete A.M., Zou Y. *et al*. Fluorine-containing drugs approved by the FDA in 2019. *Chin. Chem. Lett*. 2020. **31**(9): 2401–2413. doi: 10.1016/j.cclet.2020.03.050.
67. He J., Li Z., Dhawan G. *et al*. Fluorine-containing drugs approved by the FDA in 2021. *Chin. Chem. Lett*. 2023. **34**(1): 107578. doi: 10.1016/j.cclet.2022.06.001.
68. Yu Y., Liu A., Dhawan G. *et al*. Fluorine-containing pharmaceuticals approved by the FDA in 2020: Synthesis and biological activity. *Chin. Chem. Lett.* 2021. **32**(11): 3342–3354. doi: 10.1016/j.cclet.2021.05.042.
69. Wang Q., Bian Y., Dhawan G. *et al*. FDA approved fluorine-containing drugs in 2023. *Chin. Chem. Lett*. 2024. **35**(11): 109780. doi: 10.1016/j.cclet.2024.109780.
70. Han J., Wzorek A., Dhawan G. *et al*. New drugs appearing on the market in 2023: molecules containing fluorine and fragments of tailor-made amino acids. *Ukr. Bioorg. Acta*. 2024. **19**(1): 3–20. Doi: 10.15407/bioorganica2024.01.003.
71. Wang N., Mei H., Dhawan G. *et al*. New Approved Drugs Appearing in the Pharmaceutical Market in 2022, Featuring Fragments of Tailor-Made Amino Acids and Fluorine. *Molecules.* 2023. **28**(9): 3651. doi: 10.3390/molecules28093651.
72. Li J., Zhou S., Wang J. *et al*.Asymmetric synthesis of aromatic and heteroaromatic α-amino acids using recyclable axially chiral ligand. *Eur. J. Org. Chem*. 2016. **2016**(5): 999–1006. doi: 10.1002/ejoc.201501442.
73. Mei H., Han J., White S. *et al*. Tailor-made amino acids and fluorinated motifs as prominent traits in modern pharmaceuticals. *Chem. Eur. J.* 2020. **26**(50): 11349–11390. doi: 10.1002/chem.202000617.
74. Mei H., Han J., Klika K.D. *et al*. Applications of fluorine-containing amino acids for drug design. *Eur. J. Med. Chem*. 2020. **186**: 111826. doi: 10.1016/j.ejmech.2019.111826.
75. Osipov S.N., Artyushin O.I., Kolomiets A.F. *et al*. Synthesis of fluorine-containing cyclic α-amino acid and α-amino phosphonate derivatives by alkene metathesis. *Eur. J. Org. Chem*. 2001. **2001**(20): 3891–3897. doi:10.1002/1099-0690(200110)2001:20<3891::AID-EJO C3891>3.0.CO;2-R.
76. Remete A.M., Nonn M., Fustero S. *et al*. Synthesis of fluorinated amino acid derivatives through late-stage deoxyfluorinations. *Tetrahedron*. 2018. **74**(44): 6367–6418. doi: 10.1016/j.tet.2018.09.021.
77. Konno T., Kanda M., Ishihara T., Yamanaka H. A novel synthesis of fluorine-containing quaternary amino acid derivatives via palladium-catalyzed allylation reaction. *J. Fluorine Chem.*2005. **126**(11–12): 1517–1523. doi: 10.1016/j.jfluchem.2005.08.013.
78. Krause H.W., Kreuzfeld H.J., Döbler C. Unusual amino acids: II. Asymmetric synthesis of fluorine containing phenylalanines. *Tetrahedron: Asymmetry*. 1992. **3**(4): 555–566. doi: 10.1016/S0957-4166(00)80262-1.
79. Tsushima T., Kawada K., Nishikawa J. *et al*. Fluorine-containing amino acids and their derivatives. 3. Stereoselective synthesis and unusual conformational features of threo- and erythro-3-fluorophenylalanine. *J. Org. Chem*. 1984. **49**(7): 1163–1169. doi: 10.1021/jo00181a003.
80. Vine W.H., Hsieh K.H., Marshall G.R. Synthesis of fluorine-containing peptides. Analogs of angiotensin II containing hexafluorovaline. *J. Med. Chem.*1981. **24**(9): 1043–1047. doi: 10.1021/jm00141a005.
81. Sorochinsky A.E., Ueki H., Aceña J.L. *et al*. Chemical deracemization and (*S*) to (*R*) interconversion of some fluorine-containing α-amino acids. *J. Fluorine Chem*. 2013. **152**: 114–118.

doi: 10.1016/j.jfluchem.2013.02.022.
82. Smits R., Cadicamo C.D., Burger K., Koksch B. Synthetic strategies to α-trifluoromethyl and α-difluoromethyl substituted α-amino acids. *Chem. Soc. Rev.* 2008. **37**(8): 1727–1739. doi: 10.1039/B800310F.
83. Gutiérrez-Bonet Á., Liu W. Synthesis of alkyl fluorides and fluorinated unnatural amino acids via photochemical decarboxylation of α-fluorinated carboxylic acids. *Org. Lett*. 2023. **25**(3): 483–487. doi: 10.1021/acs.orglett.2c04144.
84. Soloshonok V. A., Cai C., Hruby V. J. *et al*. Stereochemically defined C-substituted glutamic acids and their derivatives. 1. An efficient asymmetric synthesis of (2*S*, 3*S*)-3-methyl- and -3-trifluoromethylpyroglutamic acids. *Tetrahedron*. 1999. **55**(41): 12031–12044. doi: 10.1016/S0040-4020(99)00711-5.
85. Soloshonok V.A., Avilov D.V., Kukhar V.P. Highly diastereoselective asymmetric aldol reactions of chiral Ni(II)-complex of glycine with alkyl trifluoromethyl ketones. Tetrahedron: Asymmetry. 1996. **7**(6): 1547–1550. doi: 10.1016/0957-4166(96)00177-2.
86. Soloshonok V.A., Kacharov A.D., Hayashi T. Gold(I)-catalyzed asymmetric aldol reactions of isocyanoacetic acid derivatives with fluoroaryl aldehydes. *Tetrahedron*. 1996. **52**(1). 245–254. doi: 10.1016/0040-4020(95)00893-D.
87. Soloshonok V.A., Kukhar V.P. Biomimetic base-catalyzed [1,3]-proton shift reaction. A practical synthesis of β-fluoroalkyl-β-amino acids. *Tetrahedron*. 1996. **52**(20): 6953–6964. doi: 10.1016/0040-4020(96)00300-6.
88. Soloshonok V.A., Hayashi T., Ishikawa K., Nagashima N. Highly diastereoselective aldol reaction of fluoroalkyl aryl ketones with methyl isocyanoacetate catalyzed by silver(I)/triethylamine. *Tetrahedron Letters*. 1994. **35**(7): 1055–1058. doi: 10.1016/S0040-4039(00)79964-3.
89. Soloshonok V.A., Avilov D.V., Kukhar V.P. *et al*. An efficient asymmetric synthesis of (2*S*, 3*S*)-3-trifluoromethylpyroglutamic acid. *Tetrahedron Lett*. 1997. **38**(27): 4903–4904. doi: 10.1016/S0040-4039(97)01054-X.
90. Soloshonok V.A., Kacharov A.D., Avilov D.V. *et al*. Transition metal/base-catalyzed aldol reactions of isocyanoacetic acid with prochiral ketones, a straightforward approach to stereochemically defined β,β-disubstituted-β-hydroxy-α-amino acids. Scope and limitations. *J. Org. Chem.* 1997. **62**(11): 3470–3479. doi: 10.1021/jo9623402.
91. Bravo P., Guidetti M., Viani F. *et al*. Chiral sulfoxide controlled asymmetric additions to C N double bond. An efficient approach to stereochemically defined α-fluoroalkyl amino compounds. *Tetrahedron.*1998. **54**(42): 12789–12806. doi: 10.1016/S0040-4020(98)00779-0.
92. Bravo P., Capelli S., Meille S.V. *et al*. Synthesis of optically pure (*R*)- and (*S*)-α-trifluoromethyl-alanine. *Tetrahedron*: *Asymmetry*. 1994. **5**(10): 2009–2018. doi: 10.1016/S0957-4166(00)86276-X.
93. Soloshonok V.A., Hayashi T. Gold(I)-catalyzed asymmetric aldol reaction of methyl isocyanoacetate with fluorinated benzaldehydes. *Tetrahedron Lett*. 1994. **35**(17): 2713–2716. doi: 10.1016/S0040-4039(00)77013-4.
94. Takeda R., Kawamura A., Kawashima A. *et al*. Chemical dynamic kinetic resolution and *S*/*R* interconversion of unprotected α-amino acids. *Angew. Chem. Int. Ed.* 2014. **53**(3): 12214–12217. doi: 10.1002/anie.201407944.
95. Bravo P., Farina A., Kukhar V. P. *et al*. Stereoselective additions of α-lithiated alkyl-*p*-tolylsulfoxides to *N*-PMP fluoroalkyl aldimines. An efficient approach to enantiomerically pure fluoro amino compounds. *J. Org. Chem*. 1997. **62**(11): 3424–3425. doi: 10.1021/jo970004v.
96. Soloshonok V.A., Hayashi T. Gold(I)-catalyzed asymmetric aldol reaction of fluorinated benzaldehydes with α-isocyanoacetamide *Tetrahedron*: *Asymmetry.* 1994. **5**(6): 1091–1094. doi: 10.1016/0957-4166(94)80059-6.
97. Nian Y., Wang J., Zhou S. *et al*. Recyclable ligands for the non-enzymatic dynamic kinetic resolution of challenging α-amino acids. *Angew.*

Chem. Int. Ed. 2015. **54**(44): 12918–12922. doi: 10.1002/anie.201507273.
98. Soloshonok V.A., Avilov D.V., Kukhar V.P. Asymmetric aldol reactions of trifluoromethyl ketones with a chiral Ni(II) complex of glycine: Stereocontrolling effect of the trifluoromethyl group. *Tetrahedron.*1996. **52**(38): 12433–12442. doi: 10.1016/0040-4020(96)00741-7.
99. Turcheniuk K.V., Poliashko K.O., Kukhar V.P. *et al*. Efficient asymmetric synthesis of trifluoromethylated β-aminophosphonates and their incorporation into dipeptides. *Chem. Commun*. 2012. **48**(94): 11519–11521. doi: 10.1039/C2CC36702E.
100. Röschenthaler G.-V., Kukhar V.P., Kulik I.B. *et al*. Asymmetric synthesis of phosphonotrifluoroalanine and its derivatives using *N-tert*-butanesulfinyl imine derived from fluoral. *Tetrahedron Lett*. 2012. **53**(5): 539–542. doi: 10.1016/j.tetlet.2011.11.096.
101. Brittain W.D., Lloyd C.M., Cobb S.L. Synthesis of complex unnatural fluorine-containing amino acids. *J. Fluorine Chem*. 2020. **239**: 109630. doi: 10.1016/j.jfluchem.2020.109630.
102. Acena J.L., Simon-Fuentes A., Fustero S. Recent developments in the synthesis of fluorinated β-amino acids. *Curr. Org. Chem*. 2010. **14**(9): 928–949. doi: 10.2174/138527210791111777.
103. Ouchakour L., Ábrahámi R.A., Forró E. *et al*. Stereocontrolled synthesis of fluorine-containing piperidine γ-amino acid derivatives. *Eur. J. Org. Chem*. 2019. **2019**(12): 2202–2211. doi: 10.1002/ejoc.201801540.
104. Zhang X.-X., Gao Y., Hu X.-S. *et al*. Recent advances in catalytic enantioselective synthesis of fluorinated α-and β-amino acids. *Adv. Synth. Catal*. 2020. **362**(22): 4763–4793. doi: 10.1002/adsc.202000966.
105. Tolman V. Syntheses of fluorinated amino acids: from the classical to the modern concept. *Amino Acids*. 1996. **11**(1): 15–36. doi: 10.1007/BF00805718.
106. Lin D., Wang J., Liu H. Recent developments in the synthesis of fluorine-containing β-amino acids and β-lactams. *Chin. J. Org. Chem*. 2013. **33**(10): 2098–2107. doi: 10.6023/cjoc201303020.
107. Albler C., Schmid W. Synthetic routes towards fluorine-containing amino sugars: synthesis of fluorinated analogues of tomosamine and 4-amino-4-deoxyarabinose. *Eur. J. Org. Chem*. 2014. **2014**(12): 2451–2459. doi: 10.1002/ejoc.201301614.
108. Vera-Ayoso Y., Borrachero P., Cabrera-Escribano F. *et al*. Towards cyclic, conformationally constrained, fluorine-containing β-amino acid derivatives from D-glucose. *Tetrahedron: Asymmetry*. 2001. **12**(14): 2031–2041. doi: 10.1016/S0957-4166(01)00354-8.
109. Soloshonok V.A., Kirilenko A.G., Fokina N.A. *et al*. Biocatalytic resolution of β-fluoroalkyl-β-amino acids. *Tetrahedron*: *Asymmetry.* 1994. **5**(6): 1119–1126. doi: 10.1016/0957-4166(94)80063-4.
110. Yamada T., Okada T., Sakaguchi K. *et al*. Efficient asymmetric synthesis of novel 4-substituted and configurationally stable analogues of thalidomide. *Org. Lett.* 2006, **8**(24): 5625–5628. doi: 10.1021/ol0623668.
111. Shibata N., Nishimine T., Shibata N. *et al*. Organic base-catalyzed stereodivergent synthesis of (*R*)- and (*S*)-3-amino-4,4,4-trifluorobutanoic acids. *Chem. Commun*. 2012. **48**(34): 4124–4126. doi: 10.1039/C2CC30627A.
112. Soloshonok V.A., Kirilenko A.G., Kukhar V.P., Resnati G. Transamination of fluorinated β-keto carboxylic esters. A biomimetic approach to β-polyfluoroalkyl-β-amino acids. *Tetrahedron Lett*. 1993. **34**(22): 3621–3624. doi: 10.1016/S0040-4039(00)73652-5.
113. Soloshonok V.A., Kirilenko A.G., Fokina N.A. *et al*. Chemo-enzymatic approach to the synthesis of each of the four isomers of α-alkyl-β-fluoroalkyl-substituted β-amino acids. *Tetrahedron: Asymmetry*.1994. **5**(7): 1225–1228. doi: 10.1016/0957-4166(94)80163-0.
114. Soloshonok V.A., Kirilenko A.G., Galushko S.V., Kukhar V.P. Catalytic asymmetric synthesis of β-fluoroalkyl-β-amino acids via biomimetic [1,3]-proton shift reaction. *Tetrahedron-*

Lett. 1994. **35**(28): 5063–5064. doi: 10.1016/S0040-4039(00)73320-X.
115. Soloshonok V.A., Ono T. The effect of substituents on the feasibility of azomethine-azomethine isomerization: New synthetic opportunities for biomimetic transamination. *Tetrahedron.*1996. **52**(47): 14701–14712. doi: 10.1016/0040-4020(96)00920-9.
116. Soloshonok V.A., Kukhar V.P. Biomimetic transamination of α-keto perfluorocarboxylic esters. An efficient preparative synthesis of β,β,β-trifluoroalanine. *Tetrahedron.* 1997. **53**(25): 8307–8314. doi: 10.1016/S0040-4020(97)00517-6.
117. Soloshonok V.A., Ono T., Soloshonok I. V. Enantioselective biomimetic transamination of β-keto carboxylic acid derivatives. An efficient asymmetric synthesis of β-fluoroalkyl β-amino acids. *J. Org. Chem*. 1997. **62**(22): 7538–7539. doi: 10.1021/jo9710238.
118. Soloshonok V.A., Ohkura H., Yasumoto M. Operationally convenient asymmetric synthesis of (*S*)- and (*R*)-3-amino-4,4,4-trifluorobutanoic acid: Part II. Enantioselective biomimetic transamination of 4,4,4-trifluoro-3-oxo-*N*-[(*R*)-1-phenylethyl)butanamide. *J. Fluorine Chem*. 2006. **127**(7): 930–935. doi: 10.1016/j.jfluchem.2006.04.004.
119. Soloshonok V.A., Soloshonok I.V., Kukhar V.P., Svedas V.K. Biomimetic transamination of α-alkyl β-keto carboxylic esters. Chemoenzymatic approach to the stereochemically defined α-Alkyl β-Fluoroalkyl β-Amino Acids. *J. Org. Chem*. 1998. **63**(6): 1878–1884. doi: 10.1021/jo971777m.
120. Sorochinsky A., Voloshin N., Markovsky A. *et al*. Convenient asymmetric synthesis of β-substituted α,α-difluoro-β-amino acids via Reformatsky reaction between Davis'*N*-sulfinylimines and ethyl bromodifluoroacetate. *J. Org. Chem*. 2003. **68**(19): 7448–7454. doi: 10.1021/jo030082k.
121. Soloshonok V.A., Ohkura H., Sorochinsky A. *et al*. Convenient, large-scale asymmetric synthesis of β-aryl-substituted α,α-difluoro-β-amino acids. *Tetrahedron Lett*. 2002. **43**(31): 5445–5448. doi: 10.1016/S0040-4039(02)01103-6.
122. Kukhar VP. Fluorine-containing amino acids. *J. Fluorine Chem*. 1994. **69**(3): 199–205. doi: 10.1016/0022-1139(94)03131-2.
123. Qiu X.-L., Qing F.-L. Recent advances in the synthesis of fluorinated amino acids. *Eur. J. Org. Chem*. 2011. **2011**(18): 3261–3278. doi: 10.1002/ejoc.201100032.
124. Qiu X.-L, Meng W.-D, Qing F.-L. Synthesis of fluorinated amino acids. *Tetrahedron*. 2004. **60**(32): 6711–6745. doi: 10.1016/j.tet.2004.05.051.
125. Sutherland A., Willis C.L. Synthesis of fluorinated amino acids. *Nat. Prod. Rep*. 2000. **17**(6): 621–631. doi: 10.1039/A707503K.
126. Kiss L., Fülöp F. Selective synthesis of fluorine-containing cyclic β-amino acid scaffolds. *Chem. Rec.* 2018. **18**(3): 266–281. doi: 10.1002/tcr.201700038.
127. Zhou M., Feng Z., Zhang X. Recent advances in the synthesis of fluorinated amino acids and peptides. *Chem. Commun*. 2023. **59**(11): 1434–1448. doi: 10.1039/D2CC06787K.
128. Moschner J., Stulberg V., Fernandes R.*et al*. Approaches to obtaining fluorinated α-amino acids. *Chem. Rev*. 2019. **119**(18): 10718–10801. doi: 10.1021/acs.chemrev.9b00024.
129. Mykhailiuk P.K. Fluorine-containing prolines: Synthetic strategies, applications, and opportunities. *J. Org. Chem*. 2022. **87**(11): 6961–7005. doi: 10.1021/acs.joc.1c02956.
130. Otaka A., Mitsuyama E., Watanabe J. *et al*. Synthesis of fluorine-containing bioisosteres corresponding to phosphoamino acids and dipeptide units. *Pept. Sci.* 2004. **76**(2): 140–149. doi:10.1002/bip.10570.
131. Tarui A., Sato K., Omote M. *et al*. Stereoselective synthesis of α-fluorinated amino acid derivatives. *Adv. Synth. Catal*. 2010. **352**(16): 2733–2744. doi: 10.1002/adsc.201000506.
132. Wang Y., Song X., Wang J. *et al*. Recent approaches for asymmetric synthesis of α-amino acids via homologation of Ni(II) complexes. *Amino Acids*. 2017. **49**(9): 1487–1520.

doi: 10.1007/s00726-017-2458-6.
133. Soloshonok V.A. Highly diastereoselective Michael addition reactions between nucleophilic glycine equivalents and β-substituted-α,β-unsaturated carboxylic acid derivatives; a general approach to the stereochemically defined and sterically χ-constrained α-amino acids. *Curr. Org. Chem.* 2002. **6**(4): 341–364. doi: 10.2174/1385272024605014.
134. Han J., Sorochinsky A.E., Ono T., Soloshonok V.A. Biomimetic transamination - a metal-free alternative to the reductive amination. Application for generalized preparation of fluorine containing amines and amino acids. *Curr. Org. Synth*. 2011. **8**(2): 281–294. doi: 10.2174/157017911794697277.
135. Soloshonok V.A., Sorochinsky A.E. Practical methods for the synthesis of symmetrically α,α-disubstituted α-amino acids. *Synthesis*. 2010. **2010**(14): 2319–2344. doi: 10.1055/s-0029-1220013.
136. Mikami K., Fustero S., Sánchez-Roselló M. *et al.* Synthesis of fluorinated β-amino acids. *Synthesis*. 2011. **2011**(19): 3045–3079. doi: 10.1055/s-0030-1260173.
137. Sorochinsky A.E., Soloshonok V.A. Asymmetric synthesis of fluorine-containing amines, amino alcohols, α- and β-amino acids mediated by chiral sulfinyl group. *J. Fluorine Chem*. 2010. **131**(2): 127–139. doi: 10.1016/j.jfluchem.2009.09.015.
138. Sorochinsky A.E., Aceña J.L., H. Moriwaki H. *et al*. Asymmetric synthesis of α-amino acids via homologation of Ni(II) complexes of glycine Schiff bases; Part 1: alkyl halide alkylations. *Amino Acids.* 2013. **45**(4): 691–718. doi: 10.1007/s00726-013-1539-4.
139. Aceña J.L., Sorochinsky A.E., Soloshonok V.A. Recent advances in asymmetric synthesis of α-(trifluoromethyl)-containing α-amino acids. *Synthesis*. 2012. **44**(11): 1591–1602. doi: 10.1055/s-0031-1289756.
140. Sorochinsky A.E., Aceña J.L., Moriwaki H. *et al*. Asymmetric synthesis of α-amino acids via homologation of Ni(II) complexes of glycine Schiff bases. Part 2: Aldol, Mannich addition reactions, deracemization and (*S*) to (*R*) interconversion of α-amino acids. *Amino Acids*. 2013. **45**(5): 1017–1033. doi:10.1007/s00726-013-1580-3.
141. Aceña J.L., Sorochinsky A.E., Moriwaki H. *et al*. Synthesis of fluorine-containing α-amino acids in enantiomerically pure form via homologation of Ni(II) complexes of glycine and alanine Schiff bases. *J. Fluorine Chem*. 2013. **155**: 21–38. doi:10.1016/j.jfluchem.2013.06.004.
142. Aceña J.L., Sorochinsky A.E., Soloshonok V. Asymmetric synthesis of α-amino acids via homologation of Ni(II) complexes of glycine Schiff bases. Part 3: Michael addition reactions and miscellaneous transformations. *Amino Acids.* 2014. **46**(9): 2047–2073. doi: 10.1007/s00726-014-1764-5.
143. Kukhar V.P., Sorochinsky A.E., Soloshonok V.A. Practical synthesis of fluorine-containing α- and β-amino acids: recipes from Kiev, Ukraine. *Future Med. Chem.* 2009. **1**(5): 793–819. doi: 10.4155/fmc.09.70.
144. Drug Trials Snapshots: VOYDEYA. Available at https://www.fda.gov/drugs/drug-approvals-and-databases/drug-trials-snapshots-voydeya (accessed, December, 2024).
145. Hao J., Milcent T., Retailleau P. *et al*. Asymmetric synthesis of cyclic fluorinated amino acids. *Eur. J. Org. Chem*. 2018. **2018**(27–28): 3688–3692. doi: 10.1002/ejoc.201800255.
146. Sato T., Izaw K., Aceña J.L. *et al*. Tailor-made α-amino acids in pharmaceutical industry: synthetic approaches to (1*R*,2*S*)-1-amino-2-vinylcyclopropane-1-carboxylic acid (vinyl-ACCA). *Eur. J. Org. Chem*. 2016. **2016**(16): 2757–2774. doi: 10.1002/ejoc.201600112.
147. Yamada T., Okada T., Sakaguchi K. *et al*. Efficient asymmetric synthesis of novel 4-substituted and configurationally stable analogues of thalidomide. *Org. Lett*. 2006. **8**(24): 5625–5628. doi:10.1021/ol0623668.
148. Cai C., Soloshonok V.A., Hruby V.J. Michael addition reactions between chiral Ni(II) complex of glycine and 3-(*trans*-Enoyl)oxazolidin-2-ones. A case of electron donor–acceptor

attractive interaction-controlled face diastereoselectivity. *J. Org. Chem*. 2001. **66**(4): 1339–1350.
doi: 10.1021/jo0014865.

149. Soloshonok V.A., Ueki H., Tiwari R. *et al*. Virtually complete control of simple and face diastereoselectivity in the Michael addition reactions between achiral equivalents of a nucleophilic glycine and (*S*)- or (*R*)-3-(*E*-enoyl)-4-phenyl-1,3-oxazolidin-2-ones: practical method for preparation of β-substituted pyroglutamic acids and prolines.*J. Org. Chem*. 2004. **69**(15): 4984–4990.
doi: 10.1021/jo0495438.
150. Soloshonok V.A., Ueki H., Ellis T.K. *et al*. Application of modular nucleophilic glycine equivalents for truly practical asymmetric synthesis of β-substituted pyroglutamic acids. *Tetrahedron Lett*. 2005. **46**(7): 1107–1110.
doi: 10.1016/j.tetlet.2004.12.093.
151. Wiles J.A., Phadke A.S., Deshpande M., Agarwal A., Chen D., Gadhachanda V.R., Hashimoto A., Pais G., Wang Q., Wang X. Achillion Pharmaceuticals Inc. 2018. *Aryl, heteroaryl, and heterocyclic compounds for treatment of medical disorders*. U.S. Patent Application 2018305375 A1.
152. Wiles J.A., Phadke A.S., Deshpande M., Agarwal A., Chen D., Gadhachanda V. R., Hashimoto A., Pais G., Wang Q., Wang X. Achillion Pharmaceuticals Inc. 2020. *Aryl, heteroaryl, and heterocyclic compounds for treatment of medical disorders*. U.S. Patent 10822352 B2.
153. Kang C. Danicopan: first approval. *Drugs*. 2024. **84**(5): 613–618.
doi:10.1007/s40265-024-02023-6.
154. Verdin P. FDA new drug approvals in Q1 2024. *Nat. Rev. Drug. Discov*. 2024. **23**(5): 331.
doi:10.1038/d41573-024-00063-x.
155. Kulasekararaj A.G., Lazana I. Paroxysmal nocturnal hemoglobinuria: Where are we going. *Am. J. Hematol*. 2023. **98**(S5): 33–43.
doi:10.1002/ajh.26882.
156. Voydeya (danicopan) granted first-ever regulatory approval in Japan for adults with PNH to be used in combination with C5 inhibitor therapy. Available at https://www.astrazeneca.com./media-centre/press-releases/2024/voydeya-danicopan-granted-first-ever-regulatory-approval-in-japan-for-adults-with-pnh-to-be-used-in-combination-with-c5-inhibitor-therapy.html(accessed, December, 2024).
157. First oral treatment against residual haemolyticanaemia in patients with paroxysmal nocturnal haemoglobinuria. Available at https://www.ema.europa.eu/en/news/first-oral-treatment-against-residual-haemolytic-anaemia-patients-paroxysmal-nocturnal-haemoglobinuria(accessed, December, 2024).
158. Wiles J. A., Phadke A.S., Deshpande M., Agarwak A., Chen D., Gadhachanda V.R., Hashimoto A., Pais G., Wang Q., Wang X. Achillion Pharmaceuticals Inc. 2017. *Aryl, heteroaryl, and heterocyclic compounds for treatment of medical disorders*. WO2017035353A1.
159. Phadke A., Hashimoto A., Andres M. Achillion Pharmaceuticals Inc. 2020. *Morphic forms of complement factor D inhibitors*. WO2020069024A1.
160. Phadke A. Achillion Pharmaceuticals Inc. 2020. *Morphic forms of complement factor D inhibitors*. WO2020051538A1.
161. Moore J.L., Taylor S.M., Soloshonok V.A. An efficient and operationally convenient general synthesis of tertiary amines by direct alkylation of secondary amines with alkyl halides in the presence of Huenig'sbase. *Arkivoc*. 2005. **2005**(6): 287–292.
doi: 10.3998/ark.5550190.0006.624.
162. Drug Trials Snapshots: OJEMDA. Available athttps://www.fda.gov/drugs/drug-approvals-and-databases/drug-trials-snapshots-ojemda(accessed, December, 2024).
163. Verdin P. FDA new drug approvals in Q2 2024. *Nat. Rev. Drug Discov*. 2024. **23**(8): 573.
doi:10.1038/d41573-024-00118-z.
164. Dhillon S. Tovorafenib: First Approval. *Drugs*. 2024. **84**(8). 985–993.
doi:10.1007/s40265-024-02069-6.
165. Chen W., Cossrow J., Franklin L. et al. Biogen Idec Inc.; Sunesis Pharmaceuticals Inc. 2010. *Compounds useful as RAF kinase inhibitors*. Chinese Patent CN101784545A.
166. Chen W., Cossrow J., Franklin L. et al. Biogen

Idec Inc.; Sunesis Pharmaceuticals Inc. 2010. *Compounds useful as RAF kinase inhibitors*. Chinese Patent CN101784545B.
167. Zhang T., Xu B., Tang F., He Z., Zhou J. Type II RAF inhibitor tovorafenib for the treatment of pediatric low-grade glioma. *Expert Rev. Clin. Pharmacol*. 2024. **17**(11): 999–1008. doi:10.1080/17512433.2024.2418405.
168. Sun Y., Alberta J.A., Pilarz C. *et al*. A brain-penetrant RAF dimer antagonist for the noncanonical BRAF oncoprotein of pediatric low-grade astrocytomas. *Neuro Oncol*. 2017. **19**(6): 774–785. doi:10.1093/neuonc/now261.
169. FDA grants accelerated approval to tovorafenib for patients with relapsed or refractory BRAF-altered pediatric low-grade glioma. Available athttps://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-tovorafenib-patients-relapsed-or-refractory-braf-altered-pediatric(accessed, December, 2024).
170. Drugs@FDA: FDA-Approved Drugs. Available at https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=218033 (accessed, December, 2024).
171. Hirano S., Takeda Y., Nakamoto K., Ikeuchi M., Kitayama M., Yamada M., Kawakami J. Day One Biopharmaceuticals Inc. 2020. *Method for producing optically active compound.* U.S. Patent Application 2020/0317659 A1.
172. Han J., Takeda R., Sato T. Optical Resolution of Rimantadine. *Molecules*. 2019. **24**(9): 1828. doi:10.3390/molecules24091828.
173. Turner N.C., Im S.-A., Saura C. et al. Inavolisib-based therapy in *PIK$_3$CA*-mutated advanced breast cancer. *N. Engl. J. Med*. 2024. **391**(17):1584–1596. doi: 10.1056/NEJMoa2404625.
174. Bartsch R. Next generation of drugs in breast cancer. *Memo - Mag. Eur. Med. Oncol.* 2024. **17**(4): 280–286. doi: 10.1007/s12254-024-00999-1.
175. Singh S., Bradford D., Li X. *et al*. FDA approval summary: Alpelisib for PIK$_3$CA-related overgrowth spectrum. *Clin. Cancer Res*. 2024. **30**(1):23–28. doi: 10.1158/1078-0432.CCR-23-1270.
176. Sirico M., D'Angelo A., Gianni C. *et al*. Current State and Future Challenges for PI3K Inhibitors in Cancer Therapy. *Cancers*. 2023. **15**(3): 703. doi: 10.3390/cancers15030703.
177. Salphati L., Pang J., Plise E.G. *et al*. Preclinical assessment of the PI3Kα selective inhibitor inavolisib and prediction of its pharmacokinetics and efficacious dose in human. *Xenobiotica*. 2024. **54**(10): 808–820. doi: 10.1080/00498254.2024.2415103.
178. Shan K.S., Bonano-Rios A., Theik N.W.Y. *et al*. Molecular targeting of the phosphoinositide-3-protein kinase (PI3K) pathway across various cancers. *Int. J. Mol. Sci.* 2024. **25**(4): 1973. doi: 10.3390/ijms25041973.
179. Belli C., Repetto M., Anand S. *et al*. The emerging role of PI3K inhibitors for solid tumour treatment and beyond. *Br. J. Cancer*. 2023. **128**(12): 2150–2162. doi: 10.1038/s41416-023-02221-1.
180. Yu M., Chen J., Xu Z. *et al*. Development and safety of PI3K inhibitors in cancer. *Arch. Toxicol*. 2023. **97**(3): 635–650. doi: 10.1007/s00204-023-03440-4.
181. Vanhaesebroeck B., Perry M.W.D., Brown J.R. *et al*. PI3K inhibitors are finally coming of age. *Nat. Rev. Drug Discov.* 2021. **20**(10): 741–769. doi: 10.1038/s41573-021-00209-1.
182. Song K.W., Edgar K.A., Hanan E.J. *et al*. RTK-dependent inducible degradation of mutant PI3Kα drives GDC-0077 (Inavolisib) efficacy. *Cancer Discov*. 2022. **12**(1): 204–219. doi: 10.1158/2159-8290.CD-21-0072.
183. Hanan E.J., Braun M.-G., Heald R.A. et al. Discovery of GDC-0077 (Inavolisib), a highly selective inhibitor and degrader of mutant PI3Kα. *J. Med. Chem.* 2022. **65**(24): 16589–16621. doi: 10.1021/acs.jmedchem.2c01422.
184. Ndubaku C.O., Heffron T.P., Staben S.T. *et al*. Discovery of 2-{3-[2-(1-isopropyl-3-methyl-1*H*-1,2–4-triazol-5-yl)-5,6-dihydrobenzo[f]imidazo[1,2-*d*][1,4]oxazepin-9-yl]-1*H*-pyrazol-1-yl}-2-methylpropanamide (GDC-0032): A β-sparing phosphoinositide 3-kinase inhibitor with high unbound exposure and robust

in vivo antitumor activity. *J. Med. Chem*. 2013. **56**(11): 4597–4610. doi:10.1021/jm4003632.
185. Deeks E.D. Asciminib: First Approval. *Drugs*. 2022. **82**(2): 219–226. doi: 10.1007/s40265-021-01662-3.
186. Schoepfer J., Jahnke W., G. Berellini G. et al. Discovery of Asciminib (ABL001), an allosteric inhibitor of the tyrosine kinase activity of BCR-ABL1. *J. Med. Chem*. 2018. **61**(18): 8120–8135. doi: 10.1021/acs.jmedchem.8b01 040.
187. Mulik B.M., Srivastava N., Pendharkar D., Guin M. Design, aynthesis, and anticancer activity of novel methoxycyclohexylnicotinamides. *Russ. J. Org. Chem.* 2024. **60**(1): 173–184. doi: 10.1134/S1070428024010226.
188. Kurzrock R., Gutterman J.U., Talpaz M. The molecular genetics of Philadelphia chromosome-positive leukemias. *N. Engl. J. Med*. 1988. **319**(15): 990–998. doi: 10.1056/NEJM198810133191506.
189. Schuld P., Grzesiek S., Schlotte J. *et al*. Structural and biochemical studies confirming the mechanism of action of Asciminib, an agent specifically targeting the ABL myristoyl pocket (STAMP). *Blood*. 2020. **136** (Supplement 1): 34–35. doi: 10.1182/blood-2020-140968.
190. Wylie A.A., Schoepfer J., Jahnke W. *et al*. The allosteric inhibitor ABL001 enables dual targeting of BCR-ABL1. *Nature*. 2017. **543**(7647): 733–737. doi: 10.1038/nature21702.
191. Milojkovic D., Apperley J. Mechanisms of resistance to Imatinib and second-generation Tyrosine inhibitors in chronic myeloid leukemia. *Clin. Cancer Res*. 2009. **15**(24): 7519–7527. doi: 10.1158/1078-0432.CCR-09-1068.
192. Novartis Scemblix® FDA approved in newly diagnosed CML, offering superior efficacy, and favorable safety and tolerability profile. Available athttps://www.novartis.com/news/media-releases/novartis-scemblix-fda-approved-newly-diagnosed-cml-offering-superior-efficacy-and-favorable-safety-and-tolerability-profile(accessed, December, 2024).
193. Blank J., Koecher C., Pachinger W.H. *et al*. Novartis AG. 2020. *Process for the preparation of N-[4-(chlorodifluoromethoxy)phenyl]-6-[(3R)-3-hydroxypyrrolidin-1-yl]-5-(1H-pyrazol-5-yl) pyridine-3-carboxami de*. WO 2020230100 A1.
194. Dodd S.K., Furet P., Grotzfeld R.M. *et al*. Novartis AG. 2013. *Benzamide derivatives for inhibiting the activity of abl1, abl2 and bcr-abl1*. WO 2013171639 A1.
195. Issa G.C., Aldoss I., Di Persio J. *et al*. The menin inhibitor revumenib in *KMT2A*-rearranged or*NPM1*-mutant leukaemia. *Nature*. 2023. **615**(7954): 920–924. doi: 10.1038/s41586-023-05812-3.
196. Issa G.C., Aldoss I., Di Persio J.F. *et al*. The menininhibitor SNDX-5613 (revumenib) leads to durable responses in patients (Pts) with KMT2A-rearranged or NPM1 mutant AML: Updated results of a phase (Ph) 1 study. *Blood*. 2022. **140** (Supplement 1): 150–152. doi: 10.1182/blood-2022-164849.
197. Fareed A., Inam N., Faraz F. Breakthrough treatment choice for acute myeloid leukemia in pediatric and adult patients: Revumenib, an oral selective inhibitor of KMTA 2Ar. *Rare Tumors*. 2023. **15**: 20363613231183785. doi:10.1177/20363613231183785.
198. Candoni A., Coppola G.A. 2024. update on menininhibitors. A new class of target agents against KMT2A-rearranged and NPM1-mutated acute myeloid leukemia. *Hematol. Rep*. 2024. **16**(2): 244–254. doi: 10.3390/hematolrep16020024.
199. Zhou G., Liu K., Wei Y., Yuan H. Acerand Therapeutics (Hong Kong) Ltd. 2022. *Diazaspirobicylic compounds as protein-protein interaction inhibitors and applications thereof.* WO2022257047 A1.
200. Fleischmann M., Bechwar J., Voigtländer D. *et al*. Synergistic effects of the RAR *alpha* agonist Tamibarotene and the menininhibitor Revumenib in acute myeloid leukemia cells with KMT2A rearrangement or NPM1 mutation. *Cancers*. 2024. **16**(7):1311. doi: 10.3390/cancers16071311.
201. Thomas X. Small molecule menininhibitors:

Novel therapeutic agents targeting acute myeloid leukemia with *KMT2A* rearrangement or*NPM1* mutation. *Oncol. Ther.* 2024. **12**(1): 57–72.
doi: 10.1007/s40487-024-00262-x.

202. Cacatian S., Claremon D.A., Dillard L.W. *et al.* Vitae Pharmaceuticals Inc. 2017. *Inhibitors of the menin-MLL interaction.* WO2017214367 A1.
203. Soloshonok V.A. Remarkable amplification of self-disproportionation of enantiomers on achiral-phase chromatography columns. *Angew. Chem. Int. Ed*. 2006. **45**(5): 766–769. doi: 10.1002/anie.200503373.
204. Soloshonok V.A, Ueki H., Yasumoto M. *et al.* Phenomenon of optical self-purification of chiral non-racemic compounds. *J. Am. Chem. Soc*. 2007. **129**(40): 12112–12113. doi: 10.1021/ja065603a.
205. Soloshonok V.A., Klika K.D. Terminology related to the phenomenon 'self-disproportionation of enantiomers' (SDE). *Helv. Chem Acta*. 2014. **97**(11): 1583–1589. doi: 10.1002/hlca.201400122.
206. Ueki H., Yasumoto M., Soloshonok V.A. Rational application of self-disproportionation of enantiomers via sublimation–a novel methodological dimension for enantiomeric purifications. *Tetrahedron: Asymmetry*. 2010. **21**(11–12): 1396–1400. doi: 10.1016/j.tetasy.2010.04.040.
207. Sorochinsky A.E., Katagiri T., Ono T. *et al.* Optical purifications via self-disproportionation of enantiomers by achiral chromatography; Case study of a series of α-CF_3-containing secondary alcohols. *Chirality*. 2013. **25**(6): 365–368. doi: 10.1002/chir.22180.
208. Sorochinsky A.E., Aceña J.L., Soloshonok V.A. Self-disproportionation of enantiomers of chiral, non-racemic fluoroorganiccompounds: Role of fluorine as enabling element. *Synthesis*. 2013. **45**(2): 141–152. doi: 10.1055/s-0032-1316812.
209. Han J., Wzorek A., Kwiatkowska M. *et al*. The self-disproportionation of enantiomers (SDE) of amino acids and their derivatives. *Amino Acids*. 2019. **5 1**(6): 865–889. doi: 10.1007/s00726-019-02729-y.
210. Wzorek A., Sato A., Drabowicz J. *et al*. Remarkable magnitude of the self-disproportionation of enantiomers (SDE) via achiral chromatography; application to the practical-scale enantiopurification of β-amino acid esters. *Amino Acids*. 2016. **48**(2): 605–613. doi: 10.1007/s00726-015-2152-5.
211. Hosaka T., Imai T., Wzorek A. *et al.* The self-disproportionation of enantiomers (SDE) of α-amino acid derivatives; facets of steric and electronic properties. *Amino Acids*. 2019. **51**(2): 283–294. doi: 10.1007/s00726-018-2664-x.
212. Soloshonok V.A., Wzorek A., Klika K.D. A question of policy: should tests for the self-disproportionation of enantiomers (SDE) be mandatory for reports involving scalemates? *Tetrahedron: Asymmetry*. 2017. **28**(10): 1430–1434. doi: 10.1016/j.tetasy.2017.08.020.
213. Han J., Soloshonok V.A., Klika K.D. *et al*.. Chiral sulfoxides: advances in asymmetric synthesis and problems with the accurate determination of the stereochemical outcome. *Chem. Soc. Rev*. 2018. **47**(4): 1307–1350. doi: 10.1039/c6cs00703a.
214. Soloshonok V.A., Roussel C., Kitagawa O., Sorochinsky A.E. Self-disproportionation of Enantiomers via achiral chromatography: a warning and extra dimension in optical purifications. *Chem. Soc. Rev*. 2012. **41**(11): 4180–4188. doi:10.1039/C2CS35006H.
215. Han J., Kitagawa O., Wzorek A. *et al.* The self-disproportionation of enantiomers (SDE): a menace or an opportunity? *Chem. Sci*. 2018. **9**(7): 1718–1739. doi: 10.1039/C7SC05138G.

Стаття надійшла 10.07.2024.