


 Cite this: *RSC Adv.*, 2024, 14, 33429

# The significance of chirality in contemporary drug discovery-a mini review

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More than half of drugs are chiral compounds with their chirality determining their molecular interactions, ecofriendly environmental safety and efficacy. Overall nearly 90% of chiral compounds are marketed as racemates consisting of an equimolar mixture of two enantiomers. Despite having identical chemical structure and bonding, racemates function differently when exposed to chiral environments and demonstrate notable variances in biological properties such as pharmacology, toxicology, metabolism and pharmacokinetics, etc. Advancements in asymmetric synthesis in recent years have led to considerable interest in the development of single enantiomers of chiral drug molecules for medicinal chemistry settings. In this review, we want to compile examples of chiral medicines approved by the FDA in the years 2022 and 2023 with an emphasis on their synthesis along with information on chiral induction as well as enantiomeric excess.

 Received 6th August 2024  
 Accepted 15th October 2024

DOI: 10.1039/d4ra05694a

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## 1 Introduction

Chirality influences a drug's binding affinity and interactions with its target, hence defining its pharmacology. As a result, in 1992, the Food and Drug Administration (FDA) established a set of criteria for the pharmaceutical evolution of single enantiomers and racemates.<sup>1</sup> Since then, the majority of medications on the market have been chiral, but the number of single-enantiomer and single-diastereomer pharmaceuticals has steadily increased.<sup>2,3</sup> Fig. 1 depicts examples of chiral FDA-approved medications, as well as current clinical trial disclosures. Atropisomerism is an important system of chirality that results from a partial bond rotation, typically inside a  $sp^2$ - $sp^2$ . The FDA-approved small-molecule medicines since 2011 signified that 30% of these molecules include at least one atropisomeric axis.<sup>4</sup> Natural products contain a higher  $sp^3$  fraction ( $F_{sp^3}$ ) and more chiral centers than many drug-like small compounds that have been created so far. It has been proposed that improved drug-like qualities, such as greater solubility<sup>5</sup> and fewer off-target hits (reduced promiscuity), are positively

correlated with a higher degree of  $F_{sp^3}$ , which is defined as the proportion of  $sp^3$ -hybridized carbons.<sup>6,7</sup> Fully  $sp^2$  compounds can occasionally have a high 3D character; a high  $F_{sp^3}$  number does not always correspond to an increased 3D shape.

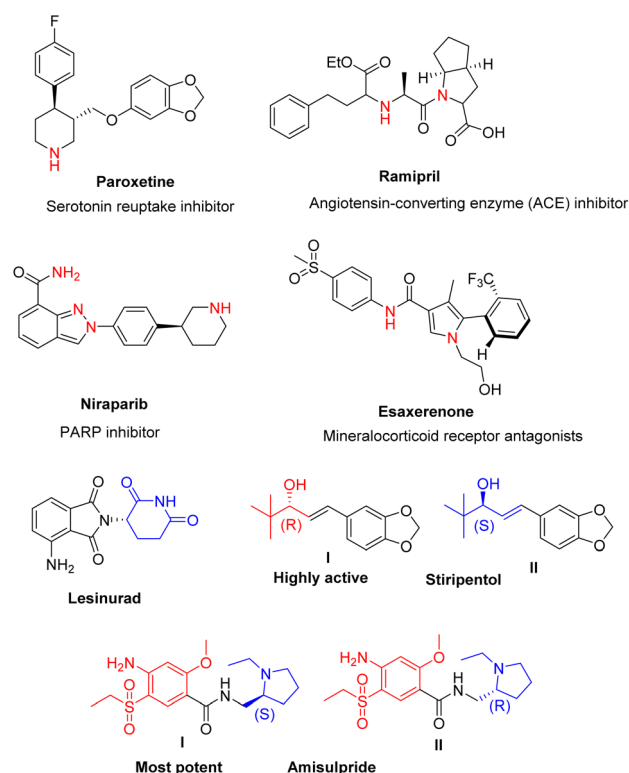


Fig. 1 Few examples of FDA-approved chiral small-molecule drugs.

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Single enantiomers have gained popularity in recent decades. In 2015, the FDA approved lesinurad as Zurampic to treat hyperuricaemia in gout patients. It was also proposed that (–)-lesinurad could be a more effective activity for hyperuricaemia than racemate. Additionally, the FDA authorized stiripentol in 2018. When used concurrently, it also inhibits the metabolism of other anticonvulsant medications. The *R*(+)-enantiomer of stiripentol (I) was discovered to be 2.4 times more potent than the *S*(–)-enantiomer of stiripentol (II), with the racemate's potency falling between the two enantiomers (Fig. 1). On the contrary, several FDA-approved racemic medicines outperform single enantiomers. The FDA approved amisulpride under the brand name Barhemsys in 2020 for the treatment of nausea and vomiting following surgery. The *S*(–)-enantiomer of amisulpride (I) is 40 times more efficient for the D2 receptor than the *R*(+)-enantiomer of amisulpride (II), but II is 50 times more potent for the 5-HT7 receptor. As a result, the racemic version of amisulpride has a poly-pharmaceutical potential benefit over its single enantiomers.<sup>8</sup> Therefore, structure–activity relationship studies (SAR) along with chiral synthesis is of furthestmost importance and anticipated to ease therapeutic activity of lead compounds. With the changes of chirality, structure of the compound will be changed. As a result of that the mode of action of particular compound will vary accordingly. Thus, chirality is paramount to determine the structure of the compounds.

Nature is handed. The complexity of life arises owing to the handedness of nature. Attempts to mimic the biologically active molecules in the lab are difficult, as living things are made up of sugars (mostly D-) and amino acids (mostly L-) that are chiral. Chiral chemistry was discovered in 1848 by French chemist Louis Pasteur.<sup>9</sup> The pharmaceutical industry took almost a century to understand the importance of chiral molecules in human existence, agriculture, and the medicinal field. Chirality has a significant influence on the design and synthesis of medicines, as the database shows that about 50% of drugs launched so far contain stereochemical elements. The presence of chirality in receptors and enzymes demands stereoselective interaction of drug molecules. Employment of single enantiomers in medical treatment has brought asymmetric synthesis as a major theme in drug discovery.

One of the first utilized drug for the morning sickness of a pregnant women was Thalidomide. This drug was used for few years after that it was removed from the market due to its detrimental effect on fetal development. Here, the scenario was different, one of the enantiomers (*R*) of Thalidomide was actively potent for health, while other one (*S*-enantiomer) was less potent for that particular action. Recently, this drug has been introduced again and it works effectively to cure severe diseases, like cancer, specifically the multiple myeloma. It is so obvious that chirality act as a paramount role in the binding interaction and affinity between drug and its target. Since, then most of the marketed drugs are single enantiomer rather mixture of enantiomer.

Asymmetric synthesis has recently attracted significant interest across the global pharmaceutical market as it facilitates scalable and efficient routes to the synthesis of potent drug

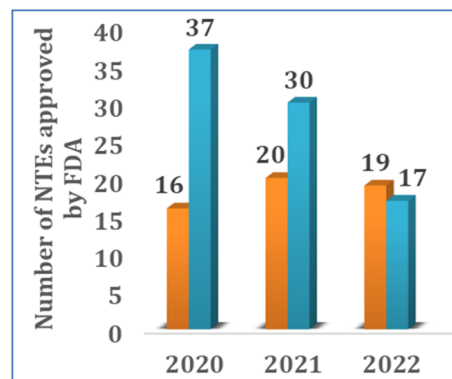


Fig. 2 The total number of biologic (blue) and small molecule (orange) NTEs approved by the FDA between 2020 and 2022.

candidates (Fig. 2). Asymmetric synthesis can be approached in three ways: (1) chiral pool synthesis: synthesis from inexpensive and naturally available chiral substrates such as sugars and amino acids (2) chiral resolution: resolving the racemic mixture to produce a single enantiomer by adopting chiral chromatographic techniques (3) enantioselective induction: asymmetric induction achieved by employing chiral auxiliary, chiral catalyst, or chiral reagent (Fig. 3).<sup>10</sup>

## 2 Pharmaceutical approvals and chirality

During past decades, the total drugs were approved by FDA was mentioned in Table 1. FDA approved 37 new drugs in the year of 2022, 55 drugs in the year 2023 and almost 30 drugs in the year of 2024. The brand names, active ingredients, indications, and therapeutic area of some of the chiral drugs approved by the FDA in the years 2022, 2023 and 2024 (Fig. 4–6) were summarized and presented in Tables 2–4.<sup>12,13</sup>

### 2.1 Chiral drugs and schematic route

Chiral drugs are very important in pharmaceutical drug delivery system. Here some of the drugs were developed by research

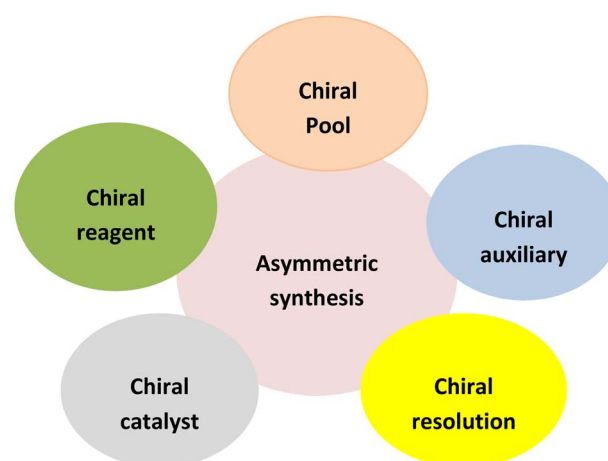


Fig. 3 Methods of asymmetric synthesis.



Table 1 The total numbers of FDA approved achiral, single enantiomer, and racemic NMEs from 2002–2022<sup>11</sup>

Year	Achiral		Single enantiomer		Racemate		Total no.
	No.	%	No.	%	No.	%	
2003–2012	68	32	120	57	23	11	211
2013–2022	105	38	163	59	10	3.6	278
2002–2022	180	36	291	58	35	6.9	506

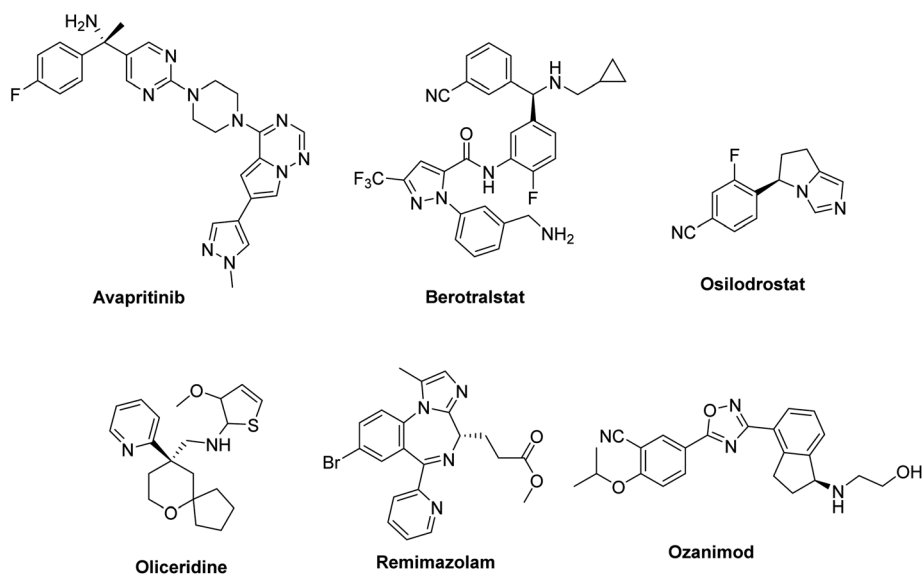


Fig. 4 Few examples of structure of chiral drugs approved by FDA in 2000–2021.

groups and approved by FDA before 2022–2023. Feldman and co-workers reported that after treating A85 with the chiral substrate A86 in chloroform, the secondary product was produced. This product then underwent condensation aided by acetic acid and base-promoted Fmoc-deprotection, ultimately forming the cyclized intermediate Remimazolam A87 in three stages.<sup>14</sup> Yamashita and co-workers mentioned, the decarboxylic reaction yields the chiral intermediate in the complete synthesis of oliceridine, which is then separated chirally by SFC.<sup>15</sup> Chiral HPLC osilodrostat separation of the intermediate directly results in drug formation was reported by Zhang and co-workers.<sup>16</sup> El-Kattan and co-workers explained about the synthesizing berotralstat in its pure enantiomeric form using supercritical fluid chromatography,<sup>17</sup> using the same process as avapritinib, Ohsawa and co-workers, reported a method for the synthesis of enantiopure avapritinib is produced in a 68% yield using the chiral resolution process using supercritical fluid chromatographic separation of the intermediate.<sup>18</sup>

**2.1.1 Oteseconazole (Vivjoa™).** Mycovia oteseconazole (a fluorine-rich polyheterocyclic anti-fungal drug molecule) sold under the brand name Vivjoa is used for the treatment of recurrent vulvovaginal candidiasis (RVVC), an infection caused by vulvovaginal candidiasis in women with no reproductive potential in the years 2016 and 2022.<sup>19,20</sup> Hoekstra William and co-workers reported a method for the synthesis of

oteseconazole. The total synthesis of oteseconazole is carried out in 7 steps. Oteseconazole is obtained by chiral resolution. It is afforded in its pure enantiomeric form *via* resolution methodology by adding the racemic mixture of the fragment OTES-7 with di-*p*-toluoyl-*L*-tartaric acid (*L*-DPTTA) with the solvent mixture of isopropanol and acetonitrile. The yield of the overall product 91% and enantiomeric excess was 60–90% ee (Scheme 1).<sup>21</sup>

**2.1.2 Daridorexant (Quviviq™).** Daridorexant was developed by Idorsia Pharmaceuticals. It is an orexin receptor antagonist that is clinically used to treat insomnia in adult patients with difficulties of sleep concern.<sup>22,23</sup> The total synthesis of daridorexant is performed in 5 steps, starting from the commercially available chiral substrate 2-methyl-*L*-proline hydrochloride **DARI-1** (Scheme 2).<sup>24</sup> The amino group in 2-methyl-*L*-proline was protected with Boc<sub>2</sub>O and condensed with 6-chloro-2,3-diaminotoluene **DARI-3**, which furnishes amide **DARI-4**. The amide cyclizes intramolecularly at 100 °C to provide **DARI-5**, which is deprotected and further condensed with 5-methoxy-2-(2*H*-1,2,3-triazol-2-yl) benzoic acid **DARI-7** to give daridorexant (yield 63%) with enantiomeric excess of 90% ee. The chirality is installed in the molecule from the chiral proline derivative.

**2.1.3 Abrocitinib (Cibinqo™).** Abrocitinib (containing sulfonamide moiety) is a Janus kinase inhibitor improved by



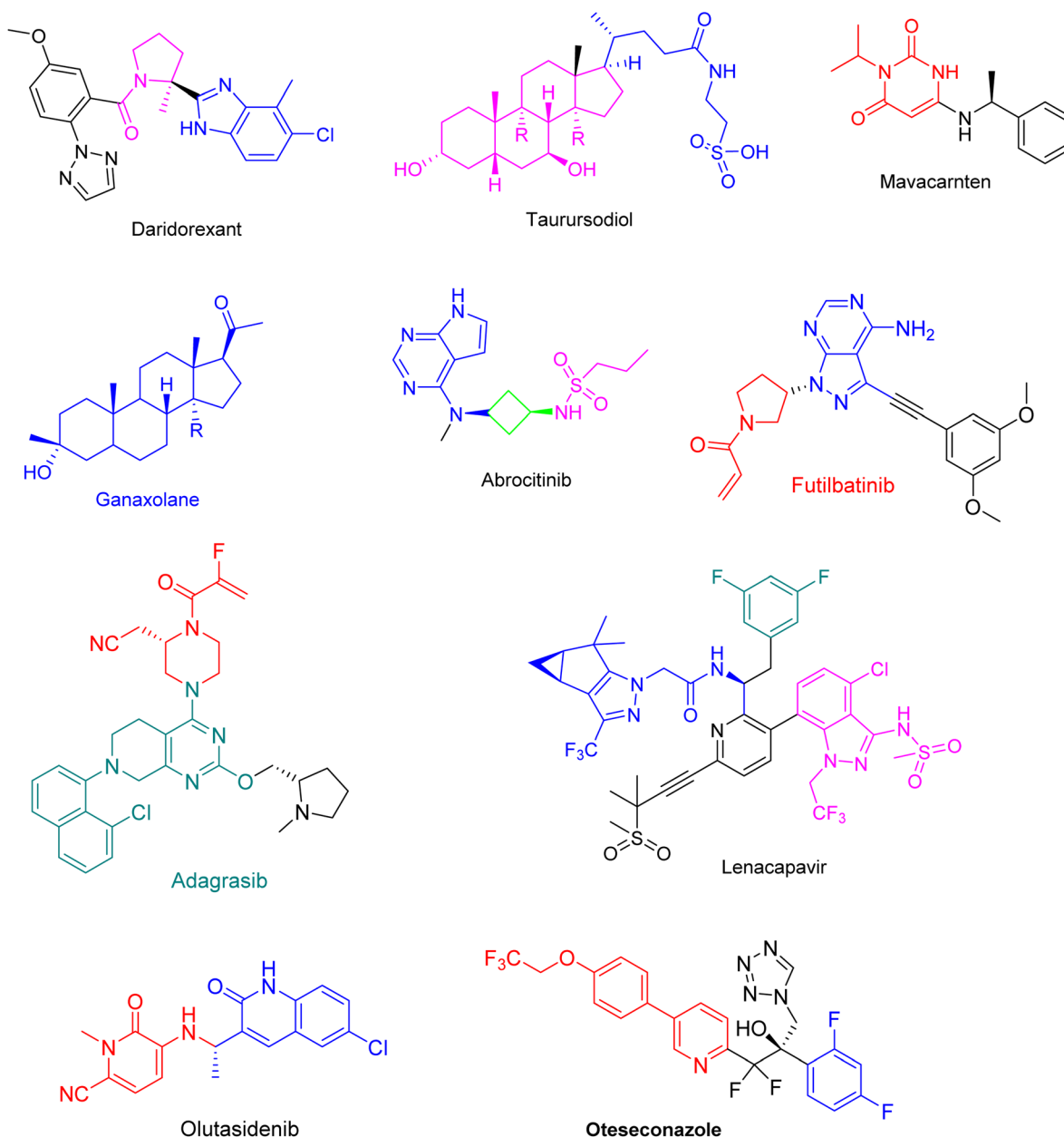


Fig. 5 Structure of chiral drugs approved by FDA in 2022.

Pfizer. It is used in the treatment of eczema (atopic dermatitis) in adult patients.<sup>25,26</sup> Curtius rearrangement of 3-oxocyclobutane-1-carboxylic acid **ABRO-1** with phenylmethanol **ABRO-2** gives intermediate **ABRO-3**, which is condensed with methylamine in acetic acid to give imine. The imine is stereoselectively reduced using  $\text{NaBH}_4$  to provide the chiral fragment **ABRO-4**. Nucleophilic aromatic substitution of pyrimidine derivative **ABRO-5** with **ABRO-4** followed by dechlorination and hydrolysis gives **ABRO-7**, which is sulfonated using propane-1-sulfonyl chloride to give abrocitinib with yield of 74% (99% ee). The single stereogenic center in abrocitinib is induced during the reduction step (Scheme 3).<sup>27</sup>

**2.1.4 Futilbatinib (Lytgobi™).** Futilbatinib (a fluorine and nitrogen aromatic heterocycle-rich drug molecule) developed by Taiho Pharmaceuticals is a permanent inhibitor of the fibroblast growth factor receptor (FGFR) used in the aid of intrahepatic cholangiocarcinoma.<sup>28</sup> The synthesis of futilbatinib can be done in 2 steps, starting from the chiral substrate **FUTI-1**, which undergoes Sonogashira coupling with *L*-ethynyl-3,5-dimethoxybenzene **FUTI-2** to give the chiral fragment **FUTI-3**, which upon the treatment with 3-chloropropionyl chloride **FUTI-4** furnishes futilbatinib (75% yield, 96.24% ee). The single chiral carbon in futilbatinib is obtained when the coupling reaction was conducted (Scheme 4).<sup>29</sup>



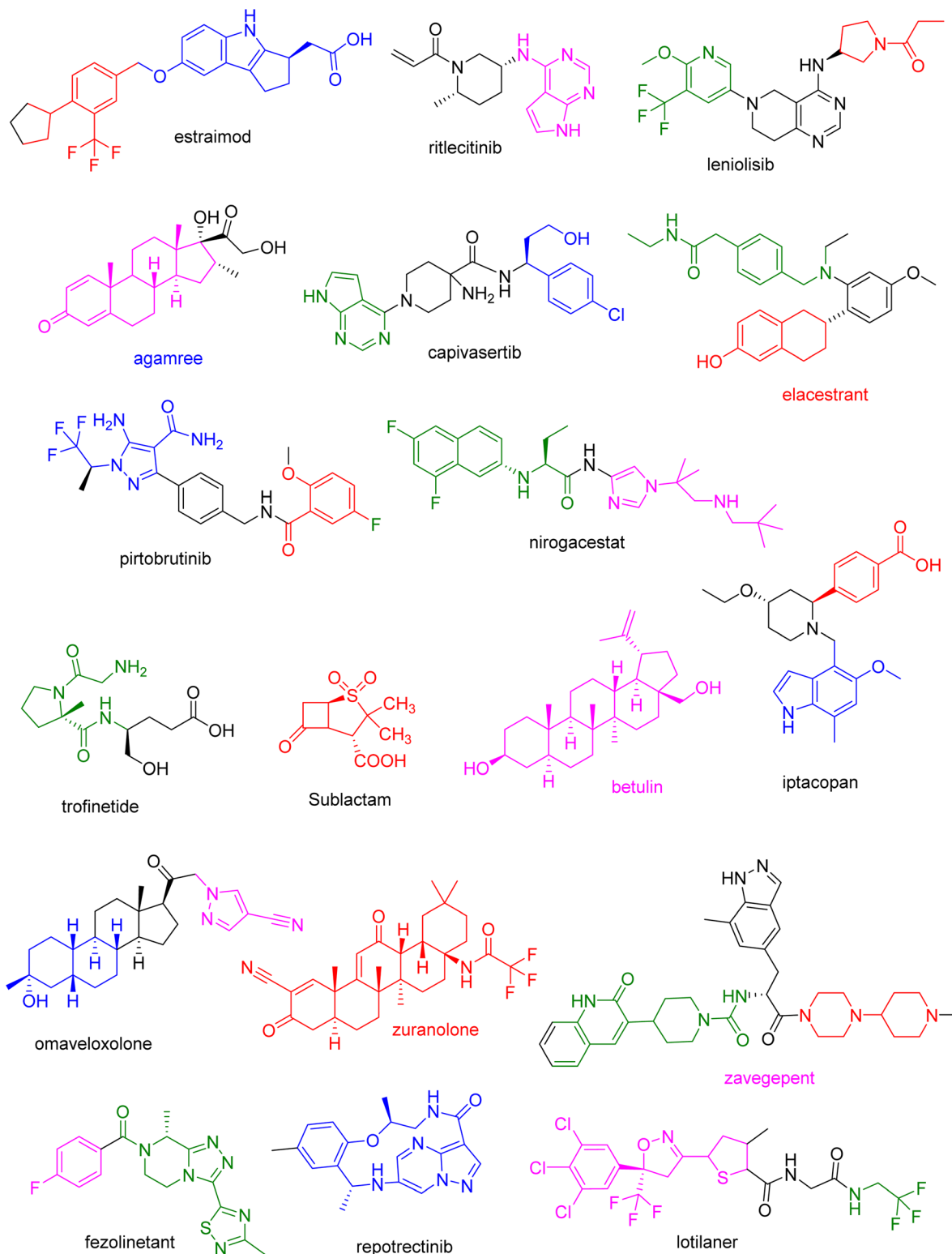


Fig. 6 Structure of chiral drugs approved by FDA in 2023.

**2.1.5 Adagrasib (Krazati™).** Adagrasib, developed by Mirati, is an inhibitor of KRAS that is applied for the treatment of metastatic or KRAS G12C-mutated locally modern non-small cell lung cancer in adults mostly one prior systemic.<sup>30,31</sup> The

total synthesis of adagrasib is carried out in 10 steps with a yield of 89%. There are two chiral centers in the adagrasib molecule. The first chiral center was introduced by Buchwald coupling (*S*)-(1-methylpyrrolidin-2-yl) methanol ADAG-4 (a proline-based



Table 2 List of chiral drugs approved by FDA in 2022

Medicine name	Active chemical	Therapeutic area	Indication/use
Vivjoa	Oteseconazole	Infections	To treat recurrent vulvovaginal candidiasis
Quviviq	Daridorexant	Central nervous system	To treat insomnia
Cibinqo	Abrocitinib	Dermatology	To treat atopic dermatitis
Lytgobi	Futibatinib	Cancer	To treat intrahepatic cholangiocarcinoma
Krazati	Adagrasib	Cancer	To treat non-small cell lung cancer
Sunlenca	Lenacapavir	Infections	To treat HIV-1 virus
Rezlidhia	Olutasidenib	Haematology	To treat relapsed or refractory acute myeloid leukemia
Camzyos	Mavacamten	Cardiology	To treat obstructive hypertrophic cardiomyopathy
Zalmy	Ganaxolone	Central nervous system	To treat seizures in people with CDD

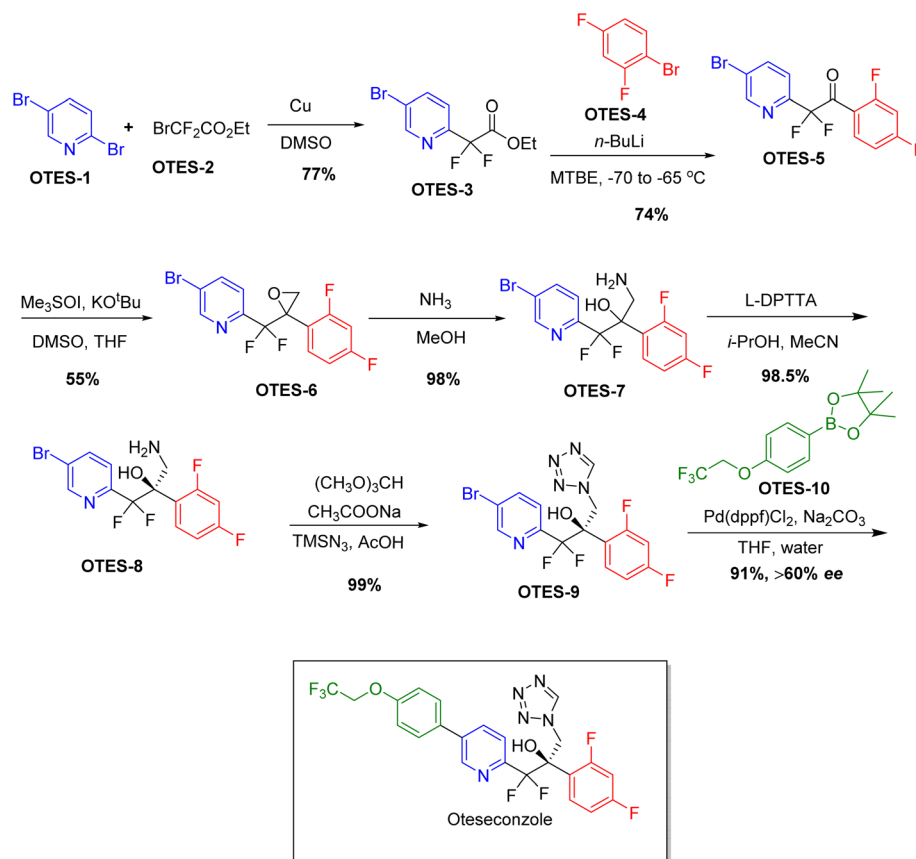
Table 3 List of chiral drugs approved by FDA in 2023

Medicine name	Active chemical	Therapeutic area	Indication/use
Xacduro	Sulbactam	Infections	To treat bacterial pneumonia
Veozah	Fezolinetant	Central nervous system	To treat vasomotor symptoms
Daybue	Trofinetide	Central nervous system	To treat rett syndrome
Truqap	Capivasertib	Cancer	To treat HR positive, HER2 negative breast cancer
Joenja	Leniolisib	Immunology	To treat APDS
Litfulo	Ritlecitinib	Dermatology	To treat alopecia areata
Fabhalta	Iptacopan	Immunology	To treat PNH
Orserdu	Elacestrant	Cancer	To treat breast cancer
Ogsiveo	Nirogacestat	Dermatology	To treat progressive systemic fibrosis
Jaypirca	Pirtobrutinib	Central nervous system	To alimant relapsed or refractory mantle cell
Zavzpret	Zavegepant	Nuerology	To treat migraines
Velsipity	Etrasimod	Gastroenterology	To alimant moderately to severely active ulcerative colitis in adults
Augtyro	Repotrectinib	Cancer	To treat ROS1-positive non-small cell lung cancer

Table 4 List of chiral drugs approved by FDA in 2024

Medicine name	Active chemical	Therapeutic area
Tryvio	Aprocitentan	To treat hypertension
Rezdiffra	Resmetirom	To treat noncirrhotic, non-alcoholic steatohepatitis with moderate to severe liver scarring
Tevimbra	Tislelizumab-jsgr	To alimant undetectable or metastatic esophageal squamous cell carcinoma
Letybo	letibotulinumtoxinA-wlbg	To temporarily improve the appearance of moderate-to-severe glabellar lines
Exblifep	Cefepime, enmetazobactam	To treat complicated urinary tract infections
Zelsuvmi	Berdazimer	To treat molluscum contagiosum
Lumisight	Pegulicianine	To treat optical imaging agent for the detection of cancerous tissue
Zevtera	Ceftobiprole	To treat definite bloodstream infections, bacterial skin and related to tissue infections, and community-acquired bacterial pneumonia
Voydeya	Danicopan	To treat extravascular hemolysis with paroxysmal nocturnal hemoglobinuria
Vafseo	Vadadustat	To treat anemia due to chronic kidney disease
Winrevair	Sotatercept-csrk	To treat pulmonary arterial hypertension
Duvyzat	Givinostat	To treat Duchenne muscular dystrophy in individuals aged 6 years and older
Iqirvo	Elafibranor	To treat primary biliary cholangitis in combination with ursodeoxycholic acid
Rytelo	Imetelstat	To treat low- to intermediate-1 risk myelodysplastic syndromes
Imdelltra	Tarlatamab-dlle	To treat extensive stage small cell lung cancer
Xolremdi	Mavorixafor	To treat WHIM syndrome (warts, hypogammaglobulinemia, infections and myelokathexis)
Ojemda	Tovorafenib	To treat relapsed or refractory pediatric low-grade glioma
Anktiva	Nogapendekin alfa inbakicept-pmln	To treat bladder cancer
Nemludio	Nemolizumab-ilto	To treat prurigo nodularis
Yorvipath	Palopegteriparatide	To treat hypoparathyroidism
Voranigo	Vorasidenib	To treat grade 2 astrocytoma or oligodendroglioma
Leqselvi	Deuruxolitinib	To treat severe alopecia areata
Kisunla	Donanemab-azbt	To treat Alzheimer's disease
Ohtuvayre	Ensifentrine	To treat chronic obstructive pulmonary disease
Piasky	Crovalimab-akkz	To treat paroxysmal nocturnal hemoglobinuria
Sofdra	Sofpironium	To treat primary axillary hyperhidrosis
Lazcluze	Lazertinib	To treat non-small cell lung cancer
Niktimvo	Axatilimab-csfr	To treat chronic graft-versus-host disease (cGVHD)
Livdelzi	Seladelpar	To treat primary biliary cholangitis (PBC)





Scheme 1 Synthesis of oteseconazole.

chiral amino alcohol) with **ADAG-3**. The second chiral center was introduced by coupling the chiral fragment **ADAG-11** with (*S*)-2-(piperazin-2-yl) acetonitrile **ADAG-12** to produce an intermediate **ADAG-13** with two chiral centers (Scheme 5).<sup>32,33</sup>

**2.1.6 Lenacapavir (Sunlenca™)**. Lenacapavir (a fluorine and nitrogen aromatic heterocycles-rich drug molecule) developed by Gilead Sciences is an antiretroviral for treating HIV. It is a first-line drug that blocks HIV-1 capsid protein and interfering with replication of HIV-1 virus.<sup>34,35</sup> The total synthesis of lenacapavir (yield 92%) is carried out in 12 steps. Chiral resolution of racemic **LENA-1** intermediate with (*R*)-2-hydroxy-2-phenylacetic acid **LENA-2** generates single enantiomer salt **LENA-3**. Sonogashira coupling of **LENA-3** and 3-methyl-3-(methylsulfonyl) but-1-yne **LENA-4** produces the chiral alkyne **LENA-5**, which on condensation with the carboxylic acid **LENA-6** under basic conditions to provide the chiral amide intermediate **LENA-7** with three stereocenter (Scheme 6).<sup>36</sup>

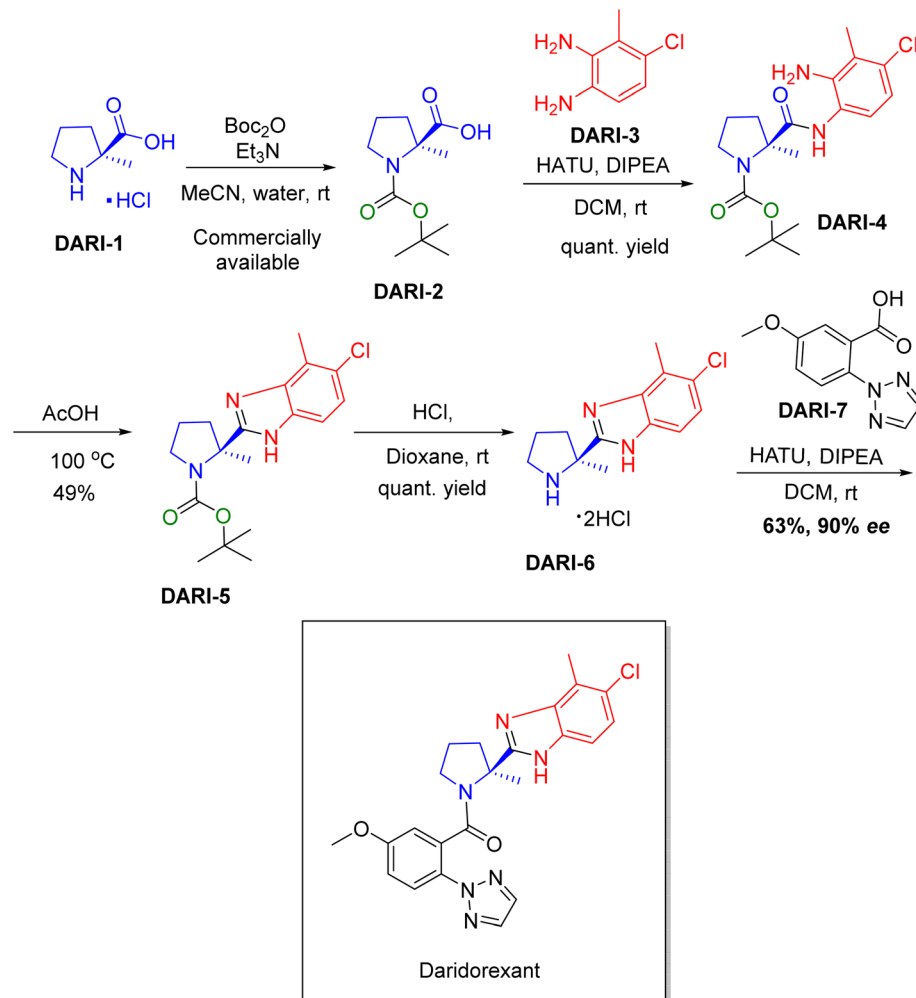
**2.1.7 Olutasidenib (Rezlidhia™)**. Rigel pharmaceuticals and forma therapeutics developed olutasidenib (a fluorine and nitrogen aromatic heterocyclic drug molecule), is a potential inhibitor of isocitrate dehydrogenase-1 (IDH1). It is used in the treatment of relapsed or refractory acute myeloid leukemia (AML) in adult patients with susceptible IDH1 mutation.<sup>37,38</sup> *N*-oxidation followed by acylation of 5-fluoropicolinonitrile **OLUT-1** gives acetate **OLUT-3**, which is hydrolysed and tautomerized

under basic conditions to provide pyridone **OLUT-4**. *N*-methylation with methyl iodide followed by condensation of **OLUT-4** with chiral amine **OLUT-6** affords olutasidenib with yield of 74% and 99% ee (Scheme 7). Chirality in olutasidenib is reproduced from the chiral fragment **OLUT-6** (Scheme 7).<sup>39</sup>

**2.1.8 Mavacamten (Camzyos™)**. MyoKardia, Inc. developed mavacamten (a fluorine and nitrogen aromatic heterocycle-rich drug molecule), an effective cardiac myosin inhibitor and also used for the treatment of obstructive hypertrophic cardiomyopathy (OHCM) in adult patients.<sup>40,41</sup> Condensation of isopropylamine **MAVA-1** with trimethylsilyl isocyanate **MAVA-2**, followed by the cyclization with dimethyl malonate, gives **MAVA-3**, and **MAVA-5**. In the end, the coupling reaction of **MAVA-5** with (*S*)- $\alpha$ -methylbenzylamine **MAVA-6** in dioxane at 90 °C furnishes expected product mavacamten (yield 69%) with a stereocenter transferred from the chiral amine unit (Scheme 8).<sup>42</sup>

**2.1.9 Ganaxolone (Ztalmy™)**. Developed by Marinus, ganaxolone is a steroid molecule for the treatment of seizures in people with cyclin-dependent kinase-like 5 deficiency disorder (CDD).<sup>43,44</sup> Pregnenolone **GANA-1**, a chiral starting material, on reduction followed by subsequent oxidation gives diketone **GANA-3**. Epoxidation of **GANA-3** followed by NaI-promoted ring-opening produces ganaxolone in good yield of 90% (Scheme 9).<sup>45</sup>





Scheme 2 Synthesis of daridorexant.

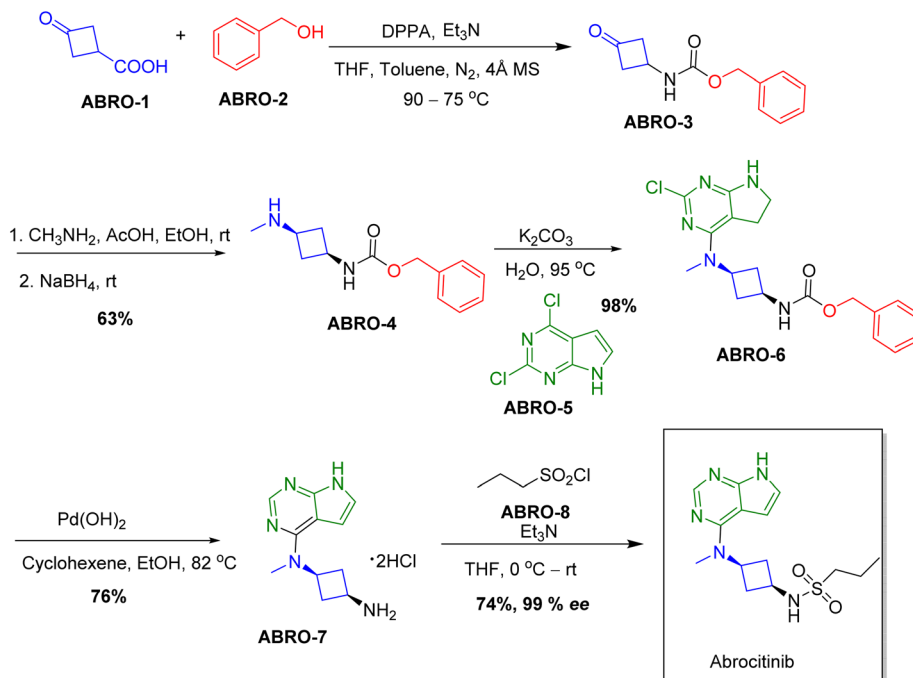
**2.1.10 Sulbactam/durlobactam (Xacduro™).** Xacduro was developed by Entasis Therapeutics, Inc. It is marketed for the treatment of bacterial pneumonia caused by the acinetobacter baumannii–calcoaceticus complex.<sup>46</sup> Xacduro consists of sulbactam and durlobactam. Sulbactam eliminates acinetobacter baumannii, while durlobactam protects Sulbactam from the enzymes produced by acinetobacter baumannii.<sup>47</sup> The total synthesis of sulbactam is conducted in 3 steps, starting from the commercially available chiral substrate 6-aminopenicilanic acid (6-APA) **SULB-1**. Sulbactam is obtained in 88% yield (Scheme 10).<sup>48</sup>

**2.1.11 Fezolinetant (Veoza™).** Fezolinetant, developed by Euroscreen Srl/Ogeda SA, which is applied for the treatment of moderate to severe vasomotor symptoms (hot flashes and night sweats) caused by menopause in women.<sup>49</sup> Fezolinetant was synthesized from chiral piperazinone **FEZO-1**, which is alkylated under buffered Meerwein conditions to give tetrahydropyrazine, which is further cyclized and followed by condensation with 4-fluorobenzoyl chloride **FEZO-3** to give the desired molecule with yield of 97% (Scheme 11).<sup>50</sup> The chiral

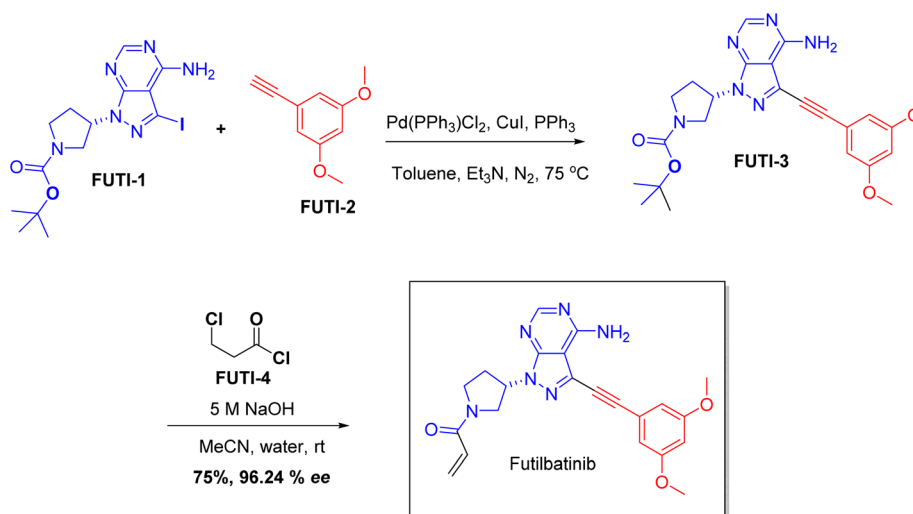
center in the drug molecule was reflected from the chiral starting material.

**2.1.12 Trofinetide (Daybue™).** Trofinetide, developed by the Walter Reed Army Institute of Research, a tripeptide also referred to as glycine-proline-glutamate (GPE), is used for the treatment of Rett syndrome, an X-linked neurodevelopmental method analysed by several cognitive, motor, and autonomic nervous system manifestations.<sup>51</sup> The total synthesis of trofinetide starts with the simple, commercially available (*S*)-2-methylpyrrolidine-2-carboxylic acid **TROF-1**. **TROF-1** was acylated and condensed with methanol to afford the corresponding methyl ester. The amino group in the proline was further reaction with (benzyloxy)carbonyl glycine **TROF-2** and hydrolyzed under alkaline protocol afforded acid **TROF-3**. Condensation of **TROF-3** with dibenzyl *L*-glutamate 4-methylbenzenesulfonate **TROF-4** results in new peptide bond formation. Deprotection of benzyl group in the amide **TROF-5** under palladium-carbon catalytic hydrogenation conditions gives trofinetide (yield 86%). Trofinetide has two chiral centers,





Scheme 3 Synthesis of abrocitinib.



Scheme 4 Synthesis of futibatib.

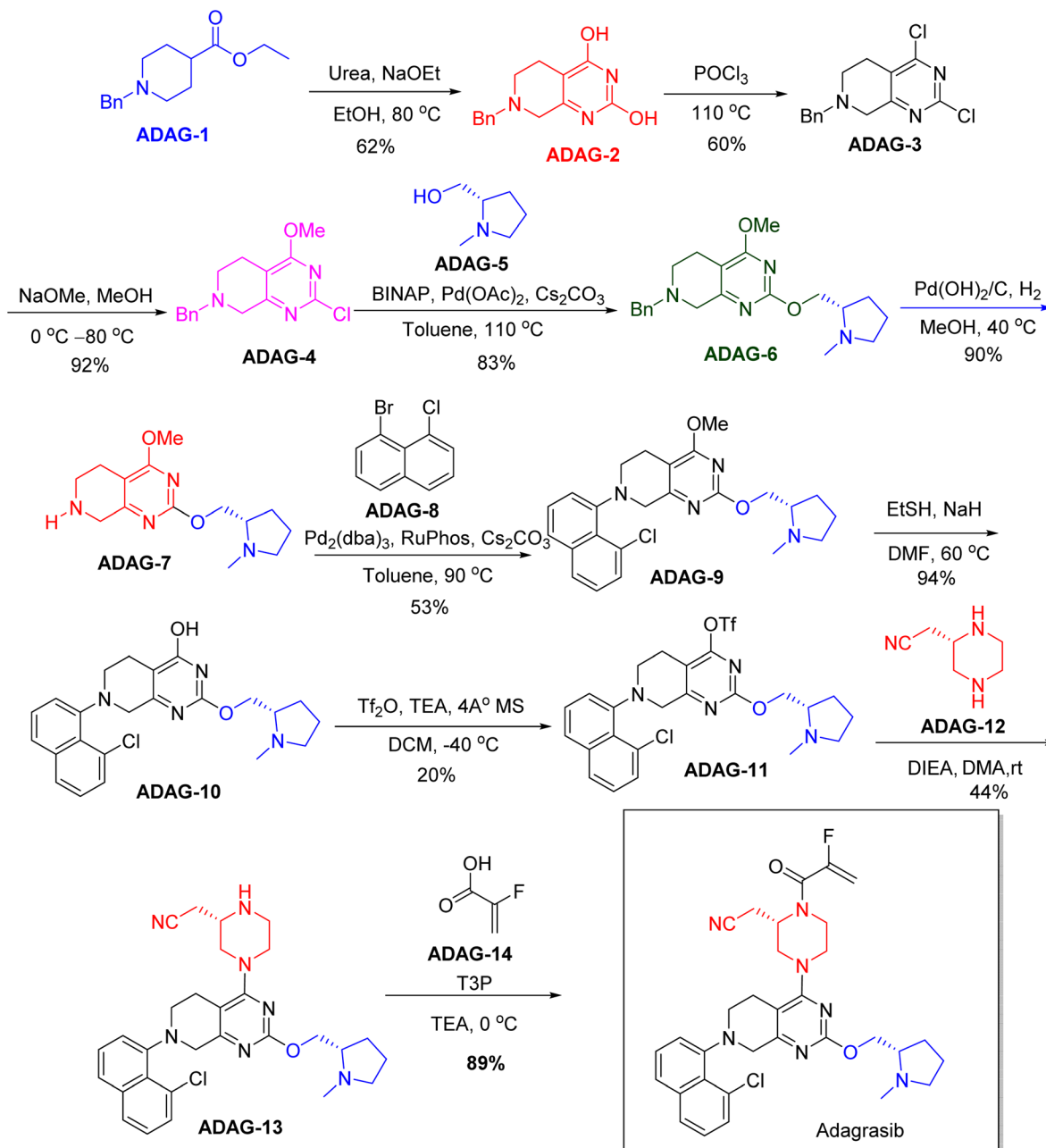
one from the proline molecule and the other from the glutamate derivate (Scheme 12).<sup>52</sup>

**2.1.13 Capivasertib (Truqap™).** Astra Zeneca Pharmaceutical Co. Ltd developed capivasertib, which is used in combination with fulvestrant (Faslodex™) to treat hormone receptor (HR) positive, human epidermal growth factor receptor-2-negative (HER2) breast cancer with metastatic disease in adult patients.<sup>53</sup> The protocol of synthesizing capivasertib is illustrated in Scheme 13.<sup>54</sup> The chiral amino acid **CAPI-1** was reduced to amino alcohol. Amino groups of the alcohol condense further with carboxylic acid **CAPI-2** to obtain amide

**CAPI-3**. Deprotection of **CAPI-3** in acidic medium gives the corresponding amine. Nucleophilic aromatic substitution of 4-chloropyrimidine **CAPI-4** with the chiral amine gives capivasertib with enantiomeric excess 100% ee. The stereocenter was introduced at the initial stage of synthesis by the chiral amino acid.

**2.1.14 Leniolisib (Joenja™).** Novartis Pharma AG developed leniolisib for the treatment of activated phosphoinositide 3-kinase delta syndrome (APDS), an immunodeficiency disorder that results from mutations in the gene responsible for encoding phosphatidylinositol-3-kinase.<sup>55,56</sup> Nucleophilic aromatic





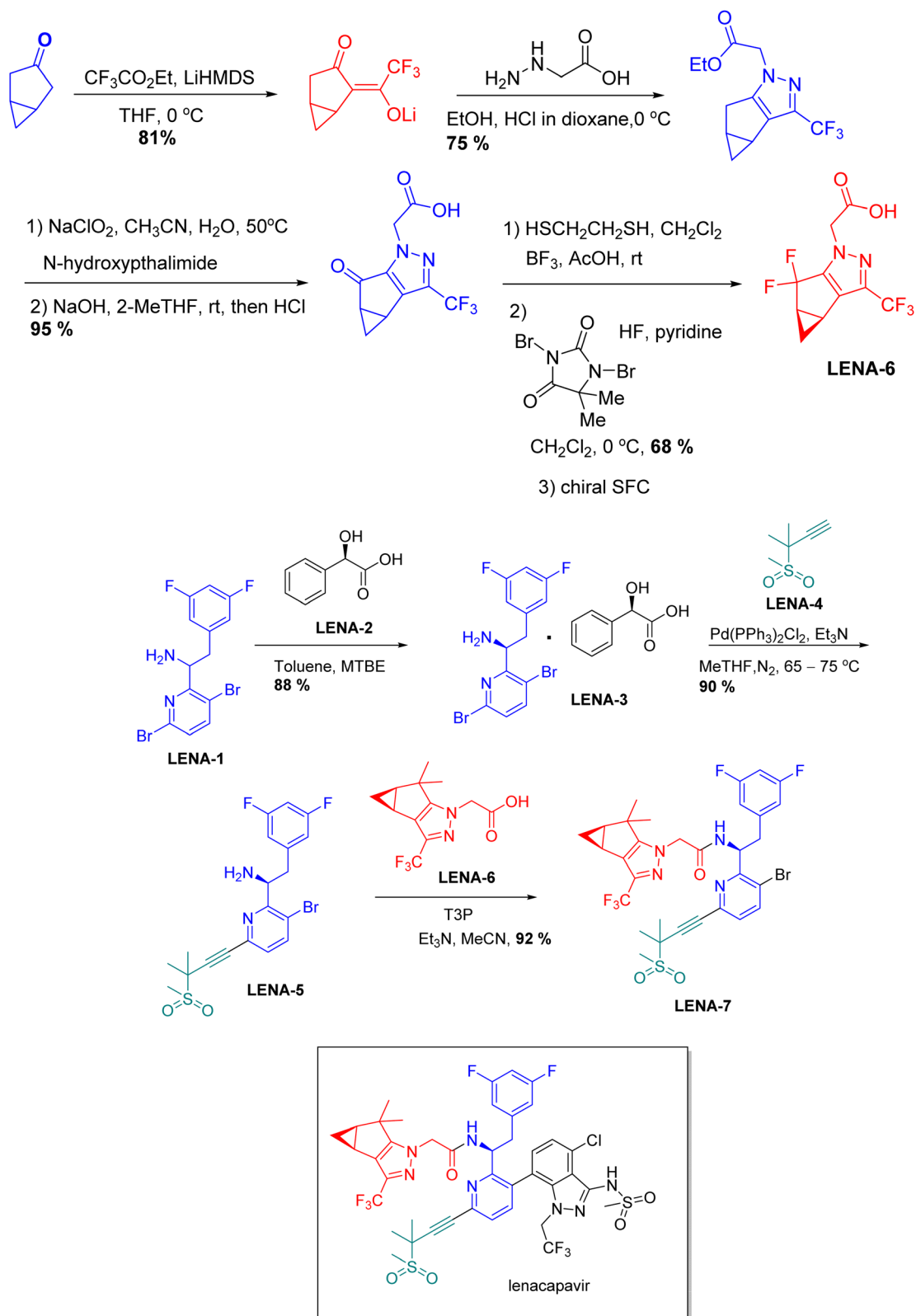
Scheme 5 Synthesis of adagrasib.

substitution of **LENI-2** with chiral *N*-Boc-(*S*)-aminopyrrolidine **LENI-1** and removal of benzyl protecting group under palladium hydroxide/carbon give **LENI-3**, which is coupled with 5-bromo-2-methoxy-3-(trifluoromethyl) pyridine **LENI-4** gives **LENI-5**. **LENI-5** was deprotected under acidic conditions and acylated to give leniolisib (76% yield, 95% ee) (Scheme 14).<sup>57</sup> The chirality is induced into the molecule from the chiral substrate.

**2.1.15 Ritlecitinib (Litfulo™)**. Ritlecitinib, produced by Pfizer, in the treatment of alopecia areata (severe hair loss). It is a potent kinase inhibitor, acting on Janus kinase and tyrosine kinase. The following scheme shows one of the methods to

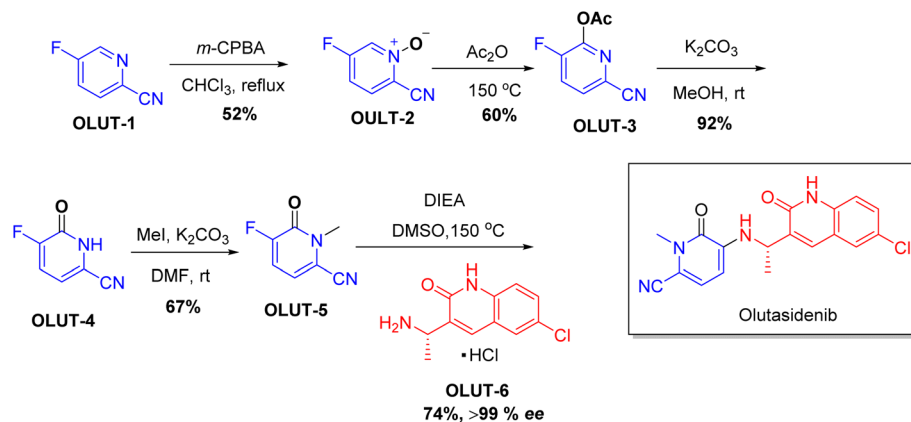
synthesize ritlecitinib.<sup>58,59</sup> Boc-protected 5-amino-2-methylpyridine **RITL-2** underwent hydrogenation to produce piperidine **RITL-3**, whose nitrogen is shielded using CbzCl. Now the diastereoisomeric mixture of **RITL-4** is subjected to Chiral SFC. Chiral SFC separates the mixture of diastereoisomers, to produce **RITL-5** (rac-cis). The Boc protecting group in **RITL-5** is removed under acidic conditions and further subjected to a nucleophilic aromatic substitution reaction with pyrimidine **RITL-6** to produce **RITL-7**. The Cbz protecting group was removed from **RITL-7** and reaction of amidation with acryloyl chloride. Chiral SFC is employed again to obtain the *L*-isomer of



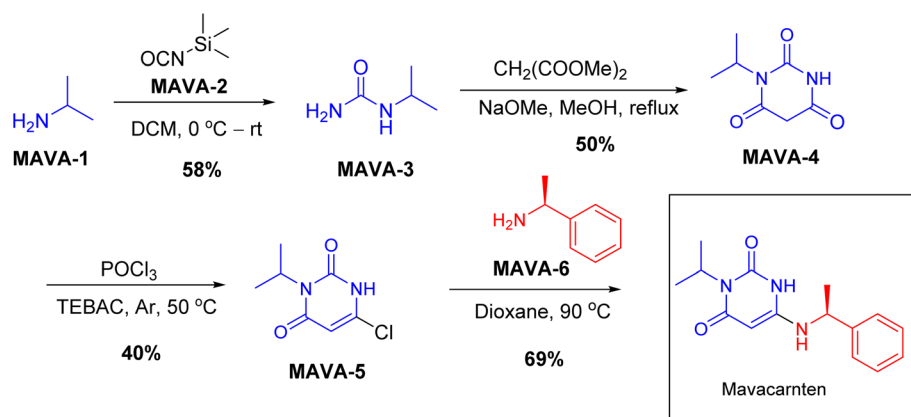


Scheme 6 Synthesis of lenacapavir.

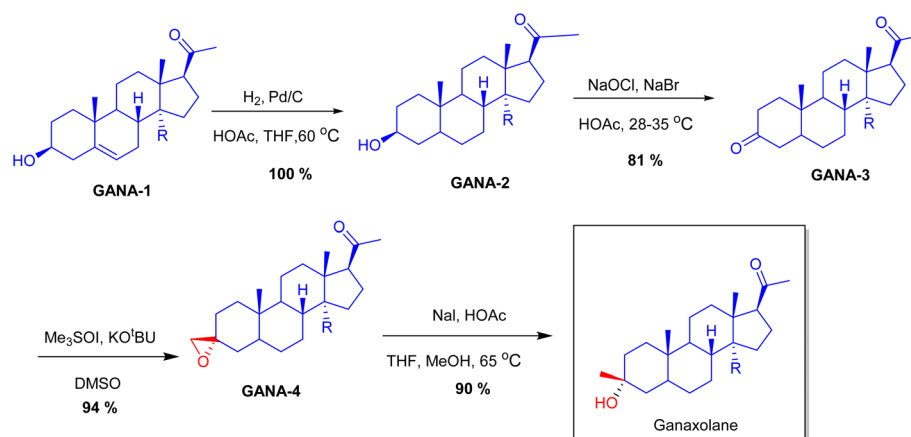




Scheme 7 Synthesis of olutasidenib.

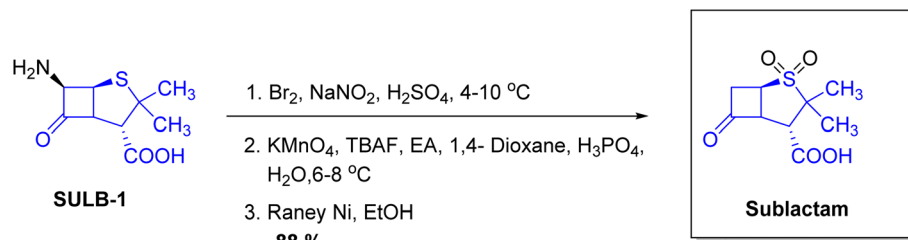


Scheme 8 Synthesis of mavacamten.

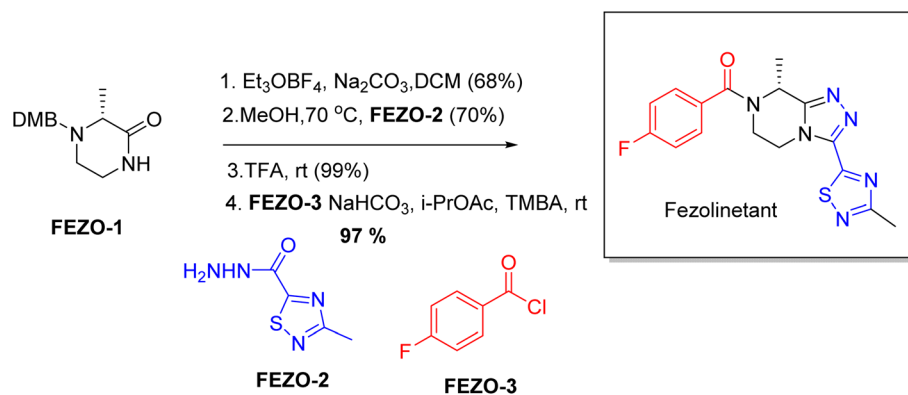


Scheme 9 Synthesis of ganaxolone.

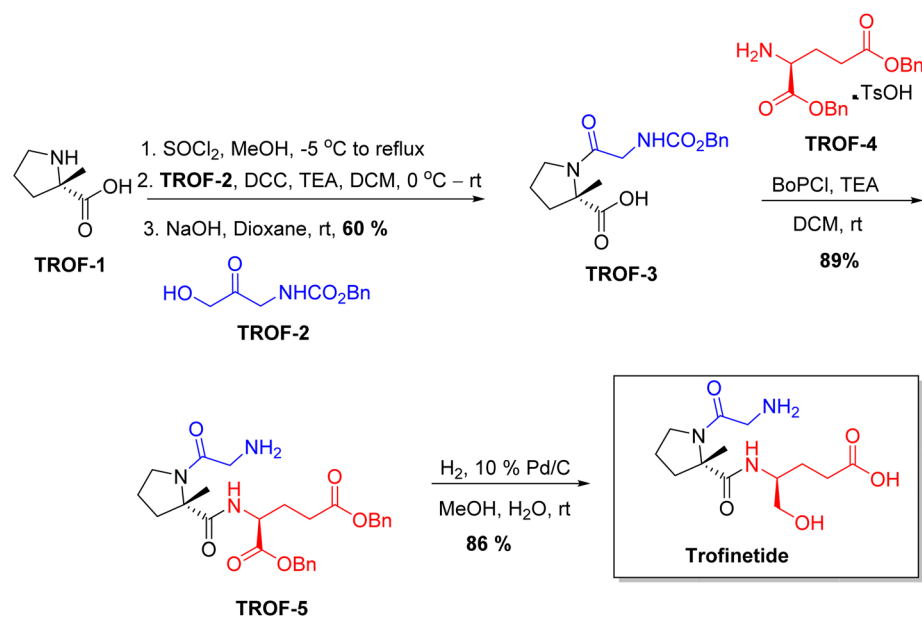




Scheme 10 Synthesis of sulbactam.



Scheme 11 Synthesis of fezolinetant.



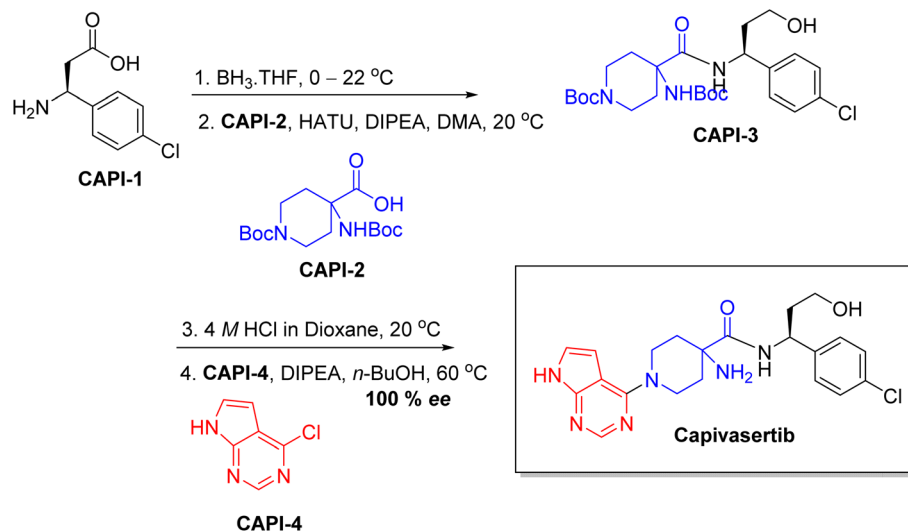
Scheme 12 Synthesis of trofinetide.

ritlecitinib with low yield of 17% and enantiomeric excess of 99.98% ee (Scheme 15).<sup>60</sup>

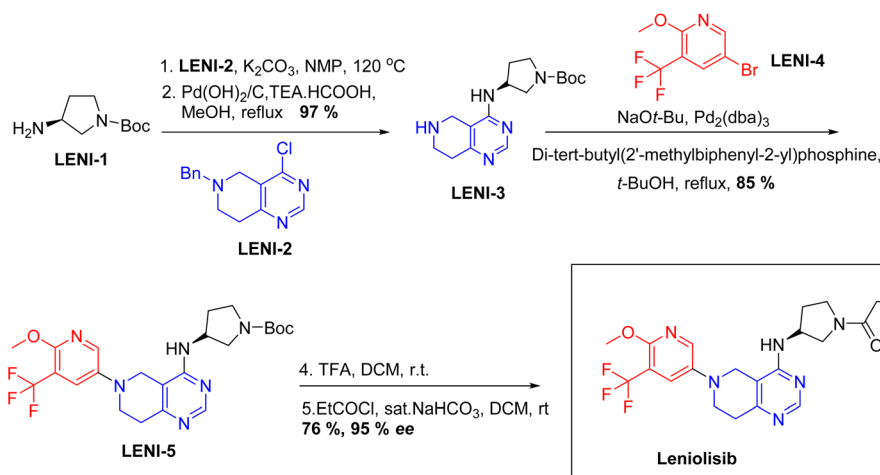
**2.1.16 Iptacopan (Fabhalta™).** Novartis AG of Switzerland developed iptacopan, a small-molecule complement factor B inhibitor, which is used for the treatment of paroxysmal nocturnal hemoglobinuria (PNH).<sup>61,62</sup> The total synthesis of

iptacopan is a 12-step process that begins with the reaction of 4-bromobenzonitrile **IPTA-1** with 4-methoxypyridine **IPTA-2**. The key step in the asymmetric synthesis of iptacopan is the chiral resolution of intermediate **IPTA-3** to produce chiral fragment **IPTA-4**, which was condensed with **IPTA-5** to obtain **IPTA-6**. Ester hydrolysis followed by *N*-deprotection of **IPTA-6** under





Scheme 13 Synthesis of capivasertib.



Scheme 14 Synthesis of leniolisib.

alkaline conditions produces iptacopan (38% yield, 99% ee) (Scheme 16).<sup>63</sup>

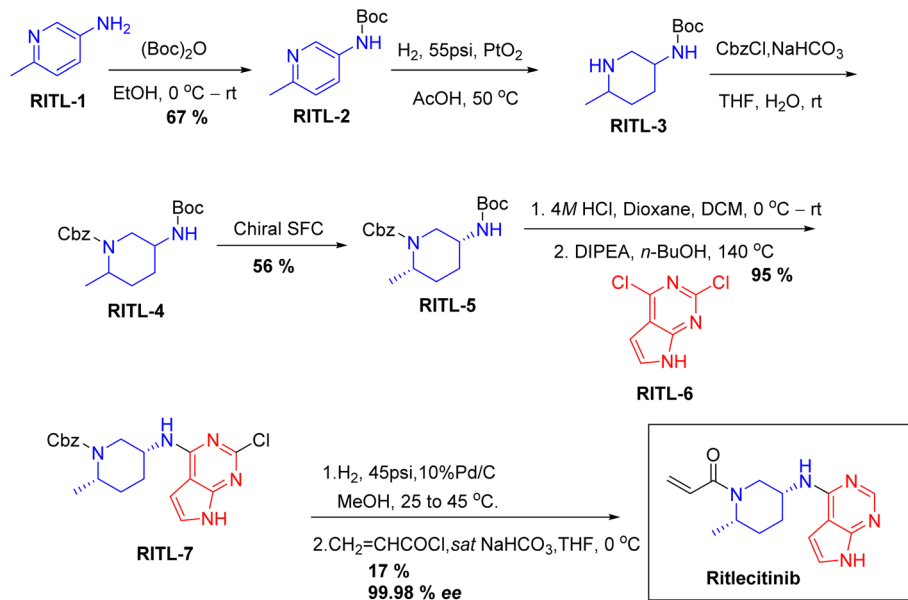
**2.1.17 Elacestrant (Orserdu™).** Elacestrant created by Eisai Co., Ltd is a selective estrogen receptor degrader (SERD) that is approved for the treatment of breast cancer.<sup>64,65</sup> The synthesis of elacestrant is a 15-step process started with demethylation of ester **ELAC-1** (Scheme 17).<sup>66</sup> Elacestrant is a drug molecule with a single chiral center with enantiomeric excess of 99% ee. The chiral center is introduced by resolution of the ester fragment **ELAC-2** using a chiral chromatographic column.

**2.1.18 Nirogacestat (Ogsiveo™).** Nirogacestat (which contains a difluorophenyl moiety) was developed by Pfizer Inc. and is a selective, noncompetitive inhibitor of  $\gamma$ -secretase which is exploited under adult patients with progressive systemic fibrosis.<sup>67</sup> The synthesis of nirogacestat begins with the reduction of the ester part of **NIRO-1** to give aldehyde, which is

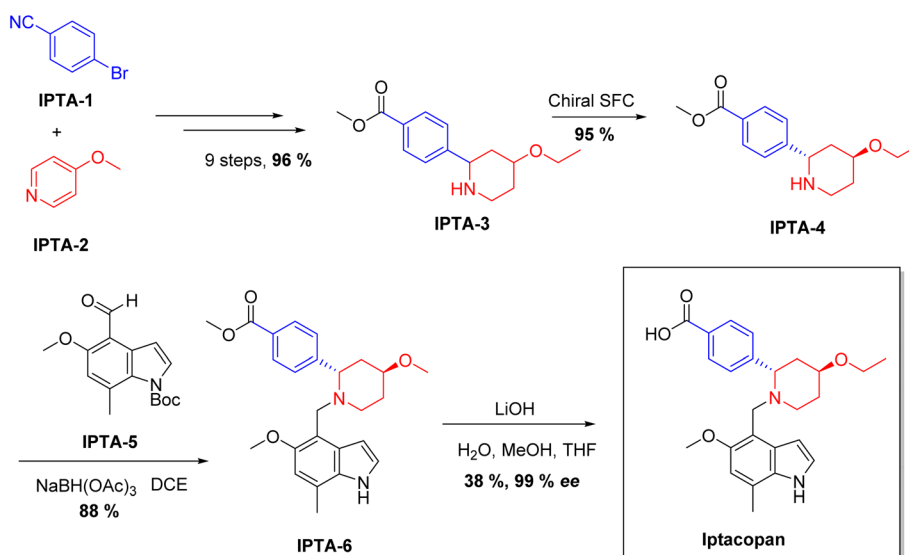
condensed further with 2,2-dimethylpropan-1-amine **NIRO-2** to afford amine **NIRO-3**. The reduction of the nitro group of **NIRO-3** gave amine **NIRO-4**, which was subjected to condensation with chiral carboxylic acid **NIRO-5** to give amide nirogacestat (Scheme 18).<sup>68</sup> The single chiral center is introduced during the amide coupling reaction.

**2.1.19 Pirtobrutinib (Jaypirca™).** Pirtobrutinib (which contains the CF<sub>3</sub> group and F-phenyl moiety) developed by Eli Lilly is Bruton's tyrosine kinase (BTK) inhibitor to treat relapsed or refractory mantle cell lymphoma (MCL) in adult patients.<sup>69</sup> In the asymmetric synthesis of pirtobrutinib, the chirality is achieved by cyclization of **PIRT-1** with chiral fragment **PIRT-2** in the presence of TEA to furnish pyrazole **PIRT-3**, which was later hydrolyzed in the presence of methanesulfonic acid (MsOH) to give pirtobrutinib in good yield 84% (Scheme 19).<sup>70</sup>

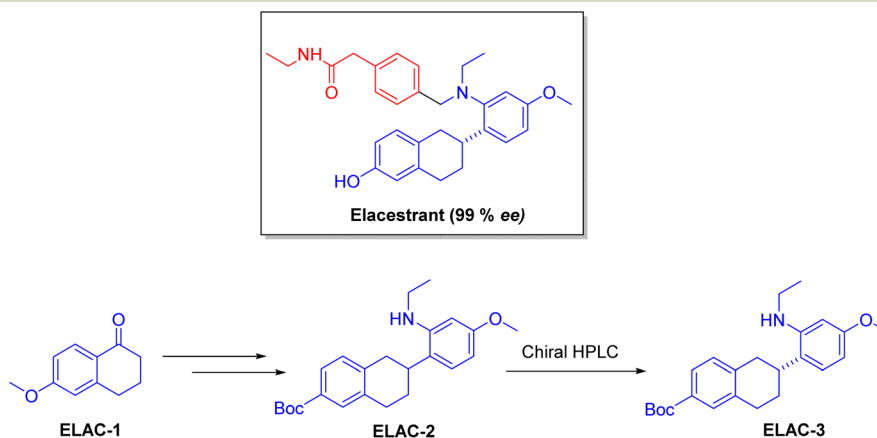




Scheme 15 Synthesis of ritlecitinib.

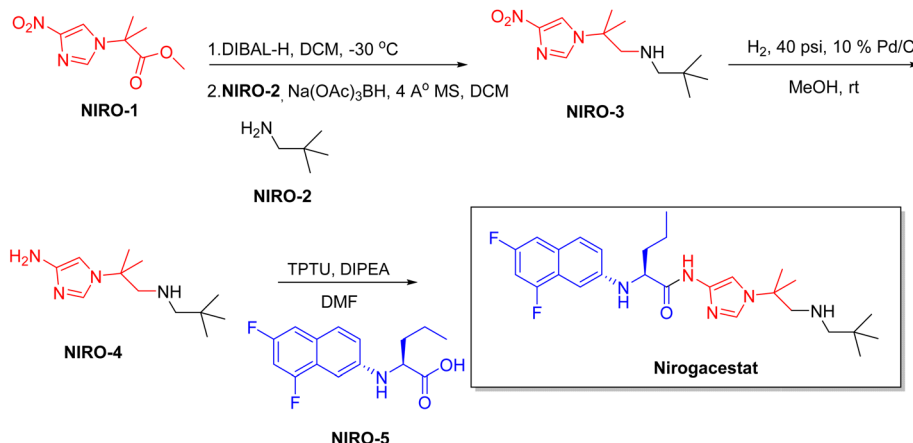


Scheme 16 Synthesis of iptacopan.

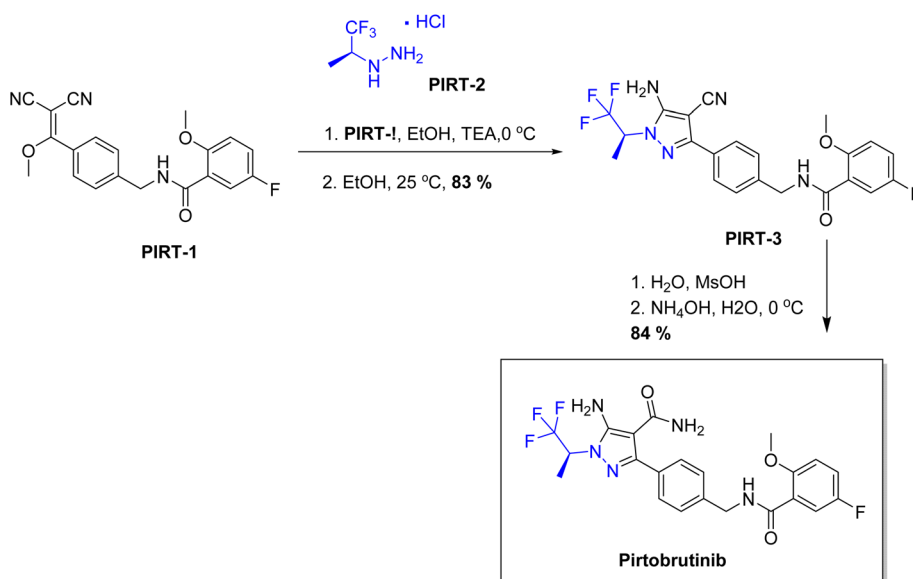


Scheme 17 Synthesis of elacestrant.



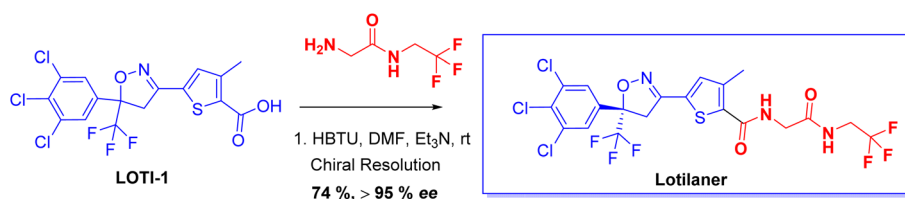


Scheme 18 Synthesis of nirogacestat.



Scheme 19 Synthesis of pirtobrutinib.

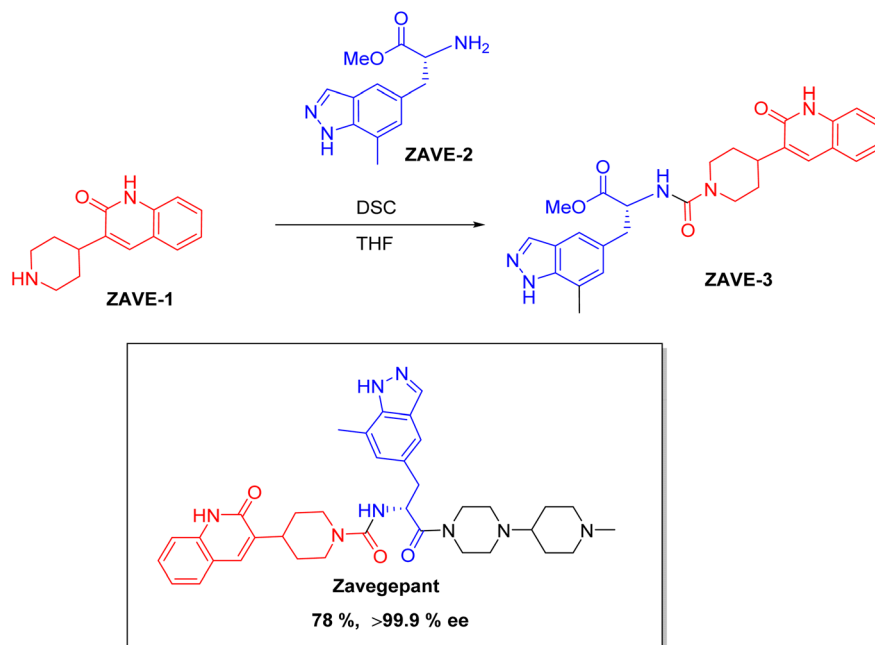
**2.1.20 Lotilaner (Xdemvy™).** Tarsus Pharmaceuticals, Inc. developed lotilaner in the treatment of Demodex blepharitis (inflammation of the eyelid) caused by tiny parasitic mites living in the hair follicles.<sup>71</sup> Chiral chromatographic separation of racemic intermediate **LOTI-1** gives the chiral lotilaner in a three-step process (yield 74% and 95% ee) (Scheme 20).<sup>72</sup>



Scheme 20 Synthesis of lotilaner.

**2.1.21 Zavegepant (Zavzpret™).** Bristol Myers Squibb Coworkers developed zavegepant, which is a calcitonin gene-related peptide receptor antagonist in the treatment of acute treatment of migraines.<sup>73,74</sup> A convenient method for the syntheses of zavegepant was disclosed in 2013 which is an 8-step process. Chirality is induced during the coupling reaction of **ZAVE-1** and **ZAVE-2** with *N,N'*-succinimidyl carbonate (DSC),





Scheme 21 Synthesis of zavegepant.

where **ZAVE-2** is transformed into the chiral urea derivative. Zavegepant (yield 78% and 99.9% ee) is synthesized in consecutive path from the intermediate derivative, ZAVE-3 (Scheme 21)<sup>75</sup>

### 3 Conclusion

The fundamental pillar of drug discovery and development is chirality evidenced by the fact that the majority of clinically employed drugs are chiral. It has been clear that the individual enantiomers are clinically more potent and can have considerable advantages in safety and efficacy compared to racemates. Since single enantiomer outperform racemates, this leads to the development of single isomer as drugs. The past ten years (2013–2023) have not seen a complete decline in the approval of racemic drugs. But some of the novel racemates that the FDA and/or EMA approved during this period were either analogues of well-known medications or had been marketed for several decades abroad. The undefined stereocenter that is involved in therapeutic activity is absent from all four of the remaining cases. There are no longer any novel medications on the market with unknown stereocenters that are therapeutically significant. This research highlights how crucial stereoselective synthetic procedures and characterization methods are in the context of modern pharmaceutical manufacture. However, it's important to consider the prospect of selling innovative drugs as racemates.

Asymmetric synthesis serves a way to induce chirality in the drug molecule. The technological advancement in asymmetric synthesis and analytical separation techniques encourage the synthesis of chiral drugs in a single enantiomeric form. Over the last ten years, the traditional chiral swap method has vanished. In general, this is regarded as an excellent progression because

there is no proof that the patient has benefited from it. Combining chiral swapping with drug repurposing has become popular.<sup>76,77</sup> A limitation/challenges of these FDA approve molecules: (1) chiral medicines serve a significant role in modern medicine, however getting pure enantiomers from racemic combinations might offer difficulties. (2) This significant search approach recognizes that axial chirality caused by atropisomerism has the potential to be missed, particularly, Class II atropisomers. The important Class III atropisomers are anticipated to be easily detected, whereas Class I compounds are not considered chiral. In addition to offering various benefits, this combination strategy circumvents the drawbacks of the traditional chiral switch approach. As of right now, this method has only been used to sell two pharmaceuticals. By using this strategy more extensively, it may be possible to create medicinally useful drugs more quickly.

### Abbreviation

AML	Acute myeloid leukemia
6-APA	6-Aminopenicilanic acid
APDS	Activated phosphoinositide 3-kinase $\delta$ syndrome
BINAP	2-Diphenylphosphinosnaphthyl
Boc	<i>t</i> -Butyloxy carbonyl
BTK	Bruton's tyrosine kinase
Cbz	Benzylloxycarbonyl
CDD	Cyclin-dependent kinase-like 5 deficiency disorder
DCM	Dichloro methane
DIBAL-H	Diisobutylaluminium hydride
DIPEA	<i>N,N</i> -diisopropylethylamine
DMA	Dimethylacetamide



DMF	<i>N,N</i> -dimethyl formamide
DPPA	Diphenylphosphoryl azide
DSC	<i>N,N'</i> -succinimidyl carbonate
FDA	U.S. Food and Drug Administration
FGFR	Fibroblast growth factor receptor
GPE	Glycine–proline–glutamate
HATU	Hexafluorophosphate azabenzotriazole tetramethyl uranium
HER2	Human epidermal growth factor receptor 2
HIV	Human immunodeficiency virus
HR	Hormone receptor
IDH1	Isocitrate dehydrogenase-1
MCL	Mantle cell lymphoma
MsOH	Methanesulfonic acid
MTBE	Methyl <i>t</i> -butyl ether
OHCM	Obstructive hypertrophic cardiomyopathy
PI3K $\delta$	Phosphatidylinositol-3-kinase $\delta$
TBAF	Tetrabutylammonium fluoride
TBTU	<i>O</i> -(benzotriazol-1-yl)- <i>N,N,N',N'</i> -tetramethyluronium tetrafluoroborate
TEA	Triethylamine
TEMPO	2,2,6,6-Tetramethylperidinoxy
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
SERD	Selective estrogen receptor degrader

## Data availability

The data used to support the findings of the study are included within the article.

## Author contributions

Narmatha Senkuttuvan: writing – review & editing for synthesis. Boopathi Komarasamy: writing – review & editing for synthesis. Rajavenkatesh Krishnamoorthy: writing – review for literature analysis. Shuvajyoti Sarkar: writing – review & editing for synthesis. Sivasankar Dhanasekaran: writing – review for literature analysis. A. Parthiban: supervision – conceptualization.

## Conflicts of interest

The authors declare that there are no conflicts of interests.

## Acknowledgements

We thank Prof. USN Murty, Director of the National Institute of Pharmaceutical Education and Research Guwahati (NIPER-G) for excellent support. We thank Dr Gayathri K, Postdoctoral fellow University of Iowa for valuable discussions.

## References

- 1 Food and Drug Administration, *Development of New Stereoisomeric Drugs*, Rockville, MD, 1992.
- 2 A. Calcaterra and I. D'Acquarica, *J. Pharm. Biomed. Anal.*, 2018, **147**, 323–340.

- 3 I. Agranat, S. R. Wainshtein and E. Z. Zusman, *Nat. Rev. Drug Discovery*, 2012, **11**, 972–973.
- 4 S. T. Toenjes and J. L. Gustafson, *Future Med. Chem.*, 2018, **10**, 409–422.
- 5 M. Ishikawa and Y. Hashimoto, *J. Med. Chem.*, 2011, **54**, 1539–1554.
- 6 F. Lovering, *MedChemComm*, 2013, **4**, 515–519.
- 7 I. P. Silvestri and P. J. J. Colbon, *ACS Med. Chem. Lett.*, 2021, **12**(8), 1220–1229.
- 8 R. U. McVicker and N. M. O'Boyle, *J. Med. Chem.*, 2024, **67**, 2305–2320.
- 9 L. A. Nguyen, H. He and C. Pham-Huy, *Int. J. Biomed. Sci.*, 2006, **2**, 85–100.
- 10 R. Tamatam and D. Shin, *Pharmaceuticals*, 2023, **16**, 339.
- 11 *New Drugs at FDA: CDER's New Molecular Entities and New Therapeutic Biological Products*, U. S. Food and Drug Administration (FDA), 2023, available online: <https://www.fda.gov/drugs/development-approval-processdrugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-bi>.
- 12 J. Y. Zhang, Y. T. Wang, L. Sun, S. Q. Wang and Z. Y. Chen, *Mol. Biomed.*, 2023, **4**, 26.
- 13 Y. T. Wang, P. C. Yang, Y. F. Zhang and J. F. Sun, *Eur. J. Med. Chem.*, 2024, **265**, 116124.
- 14 P. L. Feldman, D. K. Jung, I. Kaldor, G. J. Pacofsky, J. A. Stafford and J. H. Tidwell, WO2000069836, 2000.
- 15 D. Yamashita, D. Gotchev, P. Pitis, X. T. Chen, G. Liu and C. C. K. Yuan, WO2012129495, 2012.
- 16 C. Zhang and J. Chakma, WO2016109361, 2016.
- 17 Y. El-Kattan and Y. S. Babu, US20200140389, 2020.
- 18 I. Ohsawa, D. Honda, Y. Suzuki, T. Fukuda, K. Kohga, E. Morita, S. Moriwaki, O. Ishikawa, Y. Sasaki and M. Tago, *Allergy*, 2021, **76**, 1789–1799.
- 19 S. M. Hoy, *Drugs*, 2022, **82**, 1017–1023.
- 20 J. D. Sobel, *Am. J. Obstet. Gynecol.*, 2016, **214**, 15–21.
- 21 W. J. Hoekstra, C. M. Yates, M. Behnke, A. Alimardanov, S. A. David, and D. F. Fry, WO2015143172A1, 2015.
- 22 A. Markham, *Drugs*, 2022, **82**, 601–607.
- 23 A. K. Morin, C. I. Jarvis and A. M. Lynch, *Pharmacotherapy*, 2007, **27**, 89–110.
- 24 C. Boss, C. Brotschi, M. Gude, B. Heidmann, T. Sifferlen, and M. Von Raumer, WO2015083071, 2015.
- 25 E. Niculet, C. Bobeica, I. A. Stefanopol, A. M. Pelin, A. Nechifor and C. Onisor, *Ther. Clin. Risk Manage.*, 2022, **18**, 399–407.
- 26 D. Y. Leung, M. Boguniewicz, M. D. Howell, I. Nomura and Q. A. Hamid, *J. Clin. Invest.*, 2004, **113**, 651–657.
- 27 X. Lu, Z. Zhong and X. Zhang, WO2021218948A1, 2021.
- 28 Y. Y. Syed, *Drugs*, 2022, **82**, 1737–1743.
- 29 M. Kondo, WO2020096042A1, 2020.
- 30 S. Dhillon, *Drugs*, 2023, **83**, 275–285.
- 31 E. O'Sullivan, A. Keogh, B. Henderson, S. P. Finn, S. G. Gray and K. Gately, *Cancers*, 2023, **15**, 1635.
- 32 J. B. Fell, J. P. Fischer, B. R. Baer, J. F. Blake, K. Bouhana and D. M. Briere, *J. Med. Chem.*, 2020, **63**, 6679–6693.



- 33 N. A. Margot, V. Naik, L. VanderVeen, O. Anoshchenko, R. Singh R and H. Dvory-Sobol, *J. Infect. Dis.*, 2022, **226**, 1985–1991.
- 34 T. Vishwanatha, N. R. Panguluri and V. V. Sureshbabu, *Synthesis*, 2013, **45**, 1569–1601.
- 35 H. Dvory-Sobol, N. Shaik, C. Callebaut and M. S. Rhee, *Curr. Opin. HIV AIDS*, 2022, **17**, 15–21.
- 36 K. M. Allan, A. L. Batten, G. Brizgys, S. Dhar, I. J. Dooze and A. Goldberg, WO2019035973A1, 2019.
- 37 L. F. Newell and R. J. Cook, *Br. Med. J.*, 2021, **375**, n2026.
- 38 Olutasidenib (Rezlidhia) for acute myeloid leukemia, *Med. Lett. Drugs Ther.*, 2023, **65**, e58–e59.
- 39 J. A. Caravella, J. Lin, R. B. Diebold, A. M. Campbell, A. Ericsson and G. Gustafson, *J. Med. Chem.*, 2020, **63**, 1612–1623.
- 40 S. J. Keam, *Drugs*, 2022, **82**, 1127–1135.
- 41 N. Lakdawala, S. Saberi, S. Day, J. Ingles, C. Semsarian, I. Olivotto, C. Ho, J. Fine, Y. Xu, M. Sutton, J. Xie and Y. Wang, *J. Card. Failure*, 2022, **28**, S37–S38.
- 42 J. Oslob, R. Anderson, D. Aubele, M. Evanchik, J. C. Fox and B. Kane, WO2014205223A1, 2014.
- 43 V. Nohria and E. Giller, Ganaxolone, *Neurotherapeutics*, 2007, **4**, 102–105.
- 44 H. E. Olson, S. T. Demarest, E. M. Pestana-Knight, L. C. Swanson, S. Iqbal and D. Lal, *Pediatr. Neurol.*, 2019, **97**, 18–25.
- 45 D. S. Reddy, WO2019209850A1, 2019.
- 46 S. J. Keam, *Drugs*, 2023, **83**, 1245–1252.
- 47 A. El-Ghali, A. J. Kunz Coyne, K. Caniff, C. Bleick and M. J. Rybak, *Pharmacotherapy*, 2023, **43**, 502–513.
- 48 Z. M. Song, W. Liu, J. Yang and Y. Sun, *Chin. J. Med. Chem.*, 2004, **14**, 180–181.
- 49 A. Lee, *Drugs*, 2023, **83**, 1137–1141.
- 50 H. R. Hoveyda, G. L. Fraser, G. Dutheil, M. El Bousmaqui, J. Korac, F. Lenoir, A. Lapin and S. Noel, *ACS Med. Chem. Lett.*, 2015, **6**, 736–740.
- 51 S. J. Keam, *Drugs*, 2023, **83**, 819–824.
- 52 D. Gluckman, G. B. Thomas, J. Guan, M. Draganow, A. K. Anand, N. K. De Rosbo, F. Sieg and M. A. Brimble, US20070298009, 2007.
- 53 B. R. Davies, H. Greenwood, P. Dudley, C. Crafter, D. H. Yu, J. Zhang, J. Li, B. Gao, Q. Ji, J. Maynard, S. A. Ricketts, D. Cross, S. Cosulich, C. C. Chresta, K. Page, J. Yates, C. Lane, R. Watson, R. Luke, D. Ogilvie and M. Pass, *Mol. Cancer Ther.*, 2012, **11**, 873–887.
- 54 P. D. Gluckman, G. B. Thomas, J. Guan, M. Draganow, A. K. Anand, N. K. De Rosbo, F. Sieg and M. A. Brimble, US20070298009, 2007.
- 55 A. Parthiban and P. Makam, *RSC Adv.*, 2022, **12**, 29253–29290.
- 56 S. J. Woodhead, M. Frederickson, C. Hamlett, A. J. Woodhead, M. L. Verdonk, H. F. Sore, D. W. Walker, P. Blurton, I. Collins, K. M. Cheung, J. Caldwell, T. F. Da Fonseca McHardy, R. W. A. Luke, Z. S. Matusiak, A. Leach and J. J. Morris, US20100093748A1, 2010.
- 57 S. Duggan and Z. T. Al-Salama, *Drugs*, 2023, **83**, 943–948.
- 58 V. K. Rao, S. Webster, V. Dalm, A. Šediva, P. M. van Hagen, S. Holland, S. D. Rosenzweig, A. D. Christ, B. Sloth, M. Cabanski, A. D. Joshi, S. de Buck, J. Doucet, D. Guerini, C. Kalis, I. Pylvaenäinen, N. Soldermann, A. Kashyap, G. Uzel, M. J. Lenardo, D. D. Patel, C. L. Lucas and C. Burkhart, *Blood*, 2017, **130**, 2307–2316.
- 59 K. Hoegenauer, N. Soldermann, F. Zecri, R. S. Strang, N. Graveleau, R. M. Wolf, N. G. Cooke, A. B. Smith, G. J. Hollingworth, J. Blanz, S. Gutmann, G. Rummel, A. Littlewood-Evans and C. Burkhart, *ACS Med. Chem. Lett.*, 2017, **8**, 975–980.
- 60 H. A. Blair, *Drugs*, 2023, **83**, 1315–1321.
- 61 J. B. Telliez, M. Dowty, L. Wang, J. Jussif, T. Lin, L. Li, E. Moy, P. Balbo, W. Li, Y. Zhao, K. Crouse, C. Dickinson, P. Symanowicz, M. Hegen, M. E. Banker, F. Vincent, R. Unwalla, S. Liang, A. M. Gilbert, M. F. Brown, M. Hayward, J. Montgomery, X. Yang, J. Bauman, J. I. Trujillo, A. Casimiro-Garcia, F. F. Vajdos, L. Leung, K. F. Geoghegan, A. Quazi, D. Xuan, L. Jones, E. Hett, K. Wright, J. D. Clark and A. Thorarensen, *ACS Chem. Biol.*, 2016, **11**, 3442–3451.
- 62 A. Thorarensen, M. E. Dowty, M. E. Banker, B. Juba, J. Jussif, T. Lin, F. Vincent, R. M. Czerwinski, A. Casimiro-Garcia, R. Unwalla, J. I. Trujillo, S. Liang, P. Balbo, Y. Che, A. M. Gilbert, M. F. Brown, M. Hayward, J. Montgomery, L. Leung, X. Yang, S. Soucy, M. Hegen, J. Coe, J. Langille, F. Vajdos, J. Chrencik and J. B. Telliez, *J. Med. Chem.*, 2017, **60**, 1971–1993.
- 63 A. D. James, K. Kulmatycki, B. Poller, A. A. Romeo, J. J. Van Lier, K. Klein and D. Pearson, *Drug Metab. Dispos.*, 2023, **51**, 873–883.
- 64 D. V. Rizk, B. H. Rovin, H. Zhang, N. Kashihara, B. Maes, H. Trimarchi, V. Perkovic, M. Meier, D. Kollins, O. Papachristofi, A. Charney and J. Barratt, *Kidney Int. Rep.*, 2023, **8**, 968–979.
- 65 N. Mainolfi, T. Ehara, R. G. Karki, K. Anderson, A. Mac Sweeney, S. M. Liao, U. A. Argikar, K. Jendza, C. Zhang, J. Powers, D. W. Klosowski, M. Crowley, T. Kawanami, J. Ding, M. April, C. Forster, M. Serrano-Wu, M. Capparelli, R. Ramqaj, C. Solovay, F. Cumin, T. M. Smith, L. Ferrara, W. Lee, D. Long, M. Prentiss, A. De Erkenez, L. Yang, F. Liu, H. Sellner, F. Sirockin, E. Valeur, P. Erbel, D. Ostermeier, P. Ramage, B. Gerhartz, A. Schubart, S. Flohr, N. Gradoux, R. Feifel, B. Vogg, C. Wiesmann, J. Maibaum, J. Eder, R. Sedrani, R. A. Harrison, M. Mogi, B. D. Jaffee and C. M. Adams, *J. Med. Chem.*, 2020, **63**, 5697–5722.
- 66 S. M. Hoy, *Drugs*, 2023, **83**, 555–561.
- 67 S. Hamaoka, N. Kitazawa, K. Nara, A. Sasaki, A. Kamada and T. Okabe, US20120004315A1, 2012.
- 68 P. Wei, M. Walls, M. Qiu, R. Ding, R. H. Denlinger, A. Wong, K. Tsaparikos, J. P. Jani, N. Hosea, M. Sands, S. Randolph and T. Smeal, *Mol. Cancer Ther.*, 2010, **9**, 1618–1628.
- 69 M. A. Brodney, D. D. Auperin, S. L. Becker, B. S. Bronk, T. M. Brown, K. J. Coffman, J. E. Finley, C. D. Hicks, M. J. Karmilowicz, T. A. Lanz, D. Liston, X. Liu, B. A. Martin, R. B. Nelson, C. E. Nolan, C. E. Oborski,



- C. P. Parker, K. E. Richter, N. Pozdnyakov, B. G. Sahagan, J. B. Schachter, S. A. Sokolowski, B. Tate, D. E. Wood, K. M. Wood, J. W. Van Deusen and L. Zhang, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 2637–2640.
- 70 E. B. Gomez, M. S. Rosendahal, S. M. Rothenberg, S. W. Andrews and B. J. Brandhuber, *Blood*, 2019, **134**, 4644.
- 71 J. L. Jensen, A. R. Mato, C. Pena, L. E. Roeker and C. C. Coombs, *Ther. Adv. Hematol.*, 2022, **13**, 20406207221101697.
- 72 A. D. A. Jose, E. Charles, F. Jared, F. Scott and M. Nicholas, WO2022056100A1, 2022.
- 73 S. Dhillon, *Drugs*, 2023, **83**, 825–831.
- 74 D. Moreno-Ajona, A. Perez-Rodríguez and P. J. Goadsby, *Gepants, Curr. Opin. Neurol.*, 2020, **33**, 309–315.
- 75 P. V. Chaturvedula, S. E. Mercer, S. S. Pin, G. Thalody, C. Xu, C. M. Conway, D. Keavy, L. Signor, G. H. Cantor, N. Mathias, P. Moench, R. Denton, R. Macci, R. Schartman, V. Whiterock, C. Davis, J. E. Macor and G. M. Dubowchik, *Bioorg. Med. Chem. Lett.*, 2013, **23**, 3157–3161.
- 76 I. D'Acquarica and I. Agranat, *ACS Pharmacol. Transl. Sci.*, 2023, **6**, 201–219.
- 77 S. Ali and J. Zhou, *Eur. J. Med. Chem.*, 2023, **256**, 115476.

