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INVITED REVIEW

Tailor-made amino acid-derived pharmaceuticals approved by the FDA in 2019

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Abstract

Amino acids (AAs) are among a handful of paramount classes of compounds innately involved in the origin and evolution of all known life-forms. Along with basic scientific explorations, the major goal of medicinal chemistry research in the area of tailor-made AAs is the development of more selective and potent pharmaceuticals. The growing acceptance of peptides and peptidomimetics as drugs clearly indicates that AA-based molecules become the most successful structural motif in the modern drug design. In fact, among 24 small-molecule drugs approved by FDA in 2019, 13 of them contain a residue of AA or di-amines or amino-alcohols, which are commonly considered to be derived from the parent AAs. In the present review article, we profile 13 new tailor-made AA-derived pharmaceuticals introduced to the market in 2019. Where it is possible, we will discuss the development form drug-candidates, total synthesis, with emphasis on the core-AA, therapeutic area, and the mode of biological activity.

Keywords Tailor-made amino acids · Drug design · Modern pharmaceuticals and medicinal formulations · Asymmetric synthesis · Blockbuster drugs

Introduction

Amino acids (AAs), in various arrangements, like α-, β-, γ-, and others, are ubiquitous in nature, playing a pivotal role in the emergence of live and biological evolution. Since the discovery of asparagine in 1806 (Vauquelin and Robiquet

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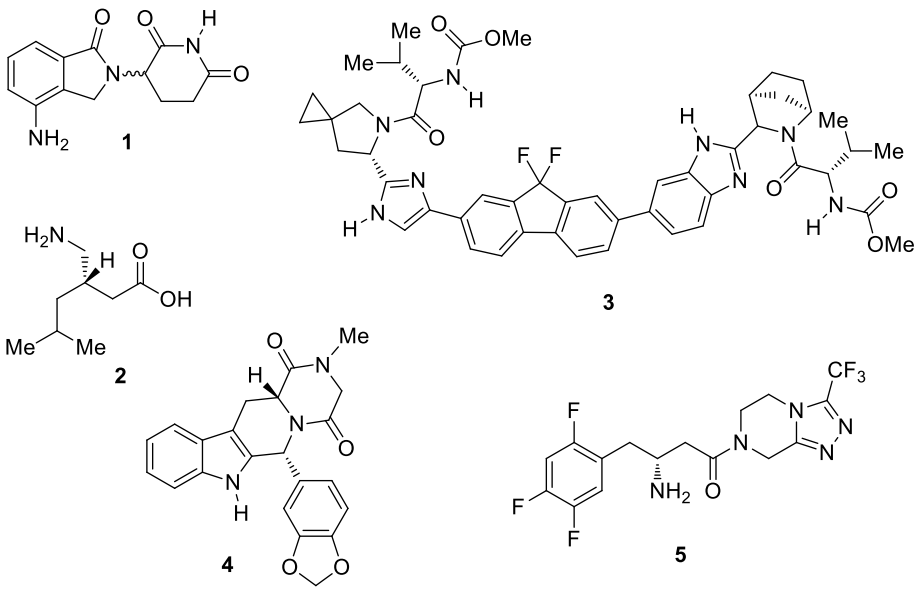
1806), over thousands of various types of amino acids, including halogen and even fluorine-containing derivatives, were isolated from natural sources (Vickery et al. 1931; Kukhar and Soloshonok 1994; Soloshonok and Izawa 2009). Due to the adequate structural and functional complexity, some natural and tailor-made AAs (Soloshonok et al. 1999a) can be used as medicine in their own right. For example, there are a range of approved drugs that consist of only an amino acid mimicking the effects of (*S*)-glutamic acid, the major excitatory neurotransmitter in the central nervous system (CNS) (Watkins and Olverman 1987). On the other end of the molecular spectrum of AAs applications are peptides. Since the discovery and understanding the physiological role of peptide hormones such as vasopressin, oxytocin, and insulin, growing acceptance of peptides and peptidomimetics as drugs has enabled major advances in pharmacology, biology, and chemistry (Weiland et al. 1991; Kastin et al. 2013; Lau et al. 2018). Nevertheless, the major area of application of AAs in modern drug discovery is the relatively small-molecule pharmaceuticals in which tailor-made AA plays a crucial part of the structural design. For example, AA residues are featured prominently in such all-time blockbuster drugs as lenalidomide **1** (Scheme 1) (Tageja 2011), pregabalin **2** (Frampton 2014), ledipasvir **3** (Keating 2015), cialis **4** (Borthwick 2012), and sitagliptin **5** (Matveyenko et al. 2009; Zhou et al. 2014), to mention just a few.

Considering the structural trends of newly approved pharmaceuticals, one can notice a gradually increasing number of drugs containing tailor-made AAs. Along with fluorination (Mei et al. 2019a, 2020; Zhu et al. 2018; Kukhar et al. 2009; Aceña et al. 2013; Mikami et al. 2011; Sorochinsky and Soloshonok 2010), the introduction of AA residues seems to have a profound effect on the successful drug design. There are a few general indications supporting this supposition. First of all, inclusion of an AA residue in drug-candidates usually improves functional and structural complexity by providing two orthogonal functionalities and a stereogenic center. These factors bode well for the success rate of compounds moving through the discovery phase to approval. Of particular significance is that promiscuity and off-target toxicity are known to be reduced with the increasing number of stereogenic centers and overall structural complexity, underscoring pharmaceutical potential of AA-based compounds.

Chemistry practitioners pay keen attention to the records pertinent to the new pharmaceutical drugs, particular aspects of their structural design and therapeutic areas. Keeping up with the rapid pace of developments in the area of AA-based pharmaceuticals, we decided to initiate a series of review articles specifically devoted to the subject of newly FDA-approved drugs derived from various types of tailor-made amino acids. Underscoring our initiative, we can mention that among 24 small-molecule drugs approved by FDA in 2019, 13 of them, a slightly more than 50%, contain a residue of AA or di-amines or amino-alcohols, which are commonly considered to be derived from the parent AAs. We, in the present review article, profile 13 new tailor-made AAs-derived pharmaceuticals introduced to the market in 2019. Where it is possible, we will discuss the development form drug-candidates, total synthesis, with emphasis on the core-AA, therapeutic area, and the mode of biological activity. Our experience in the area of pharmaceuticals and tailor-made AAs allows us to expect that such review updates will be welcomed by the multidisciplinary research community including synthetic, medicinal, and pharmaceutic chemists form both academy and industry.



Scheme 1 Structures of tailor-made amino acid-derived blockbuster drugs

Asymmetric synthesis of tailor-made AAs: general aspects

The synthesis of AAs is a well-developed field offering a great variety of methodological approaches (Soloshonok and Sorochinsky 2010; Kim et al. 2011; Wang et al. 2011; Popkov and De Spiegeleer 2012; So et al. 2012; D'Arrigo et al. 2012a, b; Periasamy et al. 2013; Bera and Namboothiri 2014; Metz and Kozlowski 2015; He et al. 2016; Soloshonok 2002; Han et al. 2011b; Kuwano et al. 1998; Mita et al. 2014; Molinaro et al. 2015; Zhang et al. 2020; Merkens et al. 2020). Nevertheless, from the standpoint of practicality, there still is a critical need for the development of new and advanced synthetic methods appropriate for large-scale manufacture of tailor-made AAs of high chemical and enantiomeric purity. Application of Schiff bases of glycine derivatives (Fig. 1) represents one of the most general and well-explored approaches for the synthesis of AAs.

Achiral compound **6**, simply derived from benzophenone and glycine ester, was introduced by the Stork group in 1976 (Stork et al. 1976). This discovery and prolific chemistry of Schiff base **6** have inspired the development of various chiral derivatives, for example **7** (Yamada et al. 1976) and **8** (Belokon et al. 1983, 1985a, b). In particular, the proline-derived Ni(II) complex **8** has been highly appreciated as a versatile nucleophilic glycine equivalent, featuring ready availability, high C−H acidity, and recyclability of the chiral auxiliary (Sorochinsky et al. 2013a, b; Aceña et al. 2014; Wang et al. 2017). The glycine moiety in Ni(II) complex **8** can be transformed into a desired side chain using various general reactions, such as alkyl halide alkylations (Tang et al. 2000; Soloshonok et al. 2001b), dialkylations (Ellis et al. 2003a, 2003b), secondary alkyl halide alkylations (Soloshonok et al. 2001a), bisalkylations (Taylor et al. 2004), aldol (Soloshonok et al. 1996, 1993), Mannich (Kawamura et al. 2015; Soloshonok et al. 1997b), and Michael (Soloshonok et al. 1999b, 2000a, 2000b) addition reactions. Multiple step processes, as in addition cyclization, leading to pyroglutamic acids (Soloshonok et al. 1997a, 2000c), α-substituted thalidomide (Yamada et al. 2006), and derivatives of 1-amino-2-vinylcyclopropane-1-carboxylic acid (Sato et al. 2016; Kawashima et al. 2016) can also be conveniently performed. Furthermore, this Ni(II) complex approach showed particular promise for the direct kinetic resolution of unprotected α-AAs (Takeda et al. 2014; Soloshonok et al. 2009; Nian et al. 2015). Using the modular design of chiral ligands (Soloshonok et al. 2005; Ellis et al. 2006), a new modification of proline-derived complex **9** was successfully introduced. It was found that the presence of the *p*- and *m*-Cl atoms on the *N*-benzyl group and the *m*-chlorine atom on the *o*-aminobenzophenone moiety and in complex **9** provides for the essential parallel displaced-type of π interactions between the aromatic rings, governing the stereochemical outcome of the reactions on the glycine moiety (Nian et al. 2017). As a result of these aromatic interactions, the synthesis of the target amino acids can be performed with excellent levels of diastereoselectivity (> 98%) rendering Ni(II) complex as a practically useful chiral nucleophilic glycine equivalent. Synthesis of Ni(II) complex **9** has been recently optimized for a kilogram scale (Romoff et al. 2017; Romoff 2020) and used for large-scale preparation of several CF_3-containing acids of pharmaceutical interest (Yin et al. 2019; Mei et al. 2019b, c, d; Han et al. 2019a).

While the Ni(II) complexes of AAs Schiff bases are currently the leading methodology, other methods are still being explored for more efficient synthesis of tailor-made AAs (Nagato et al. 2020; Mkrtchyan et al. 2020; Cativiela et al. 2020; Melnykov et al. 2019; Han et al. 2019c; Mahindra et al. 2019; Verhoork et al. 2019; Shahzad et al. 2019).

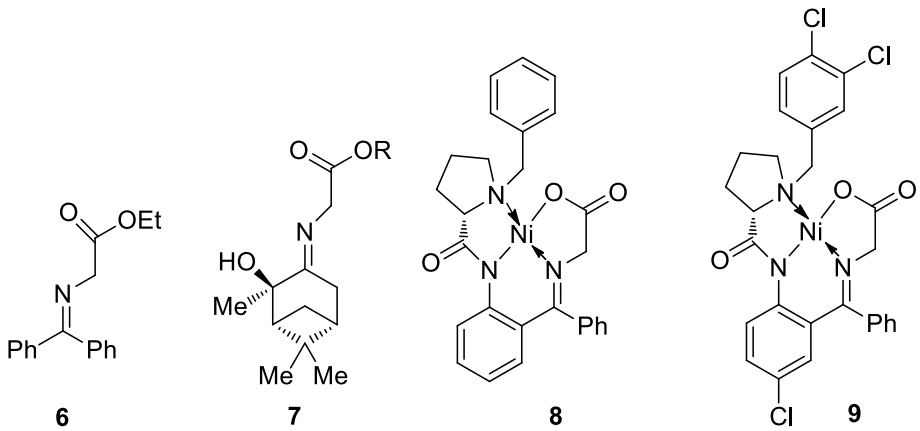


Fig. 1 Schiff bases of glycine derivatives **6**–**9**

Alpelisib (Piqray™)

Alpelisib (**11**), also named as NVP-BYL719 was discovered by Novartis as a new α-specific phosphatidylinositol-3-kinase (PI3K) inhibitor (Fig. 2). It contains a key 2-aminothiazole scaffold, which has been demonstrated as a useful structural template for the development of inhibitors showing isoform selectivity. Specifically, introducing an (*S*)-pyrrolidine carboxamide moiety derived from proline (**10**) into the template via a urea linkage leads to an inhibitor of PIK3CA subtype and suppresses the mutant subunit. The crystal of the complex of PI3Kα and alpelisib (**11**) was successfully obtained and used for the determination of the binding model. The crystal structure indicated clearly all the interactions of alpelisib with ATP-binding pocket of the apo structure in PI3Kα[89].

Novartis also conducted the structure–activity study about inhibition of p110α, p110β, p110δ, and p110γ activity. IC_{50} value for the compound **12** bearing (*S*)-pyrrolidine-2-carboxamide was 0.014, 4.4, 0.33, and 0.43 μM, respectively. The increased IC_{50} value was observed when pyrrolidine unit was induced. In particular, almost fivefold of IC_{50} (p110α) (0.62 μM) was found for compound **13** (Fig. 3) (Furet et al. 2013). In 2015, Novartis further improved structures by variation from 5-(pyridyl-4-yl)thiazol-2-amino bicycles key skeleton to 4*H*-thiazolo[5′,4′:4,5]pyrano[2,3-*c*]pyridine-2-amino tricyclic scaffold. The results disclose that the tricyclic compound showed similar biochemical efficacy, selectivity, and cell activity compared with the acyclic alpelisib (**11**). However, the significantly improved solubility in aqueous buffer was observed (Gerspacher et al. 2015). In January 2016, Novartis and radius Health launched the global clinical cooperation to conduct preclinical trials to investigate the effect of alpelisib (**11**) combined with elacestrant (RAD 1901). In May 2019, alpelisib (Piqray™) (**11**) was approved by FDA for treatment of HR-positive, HER2-negative, PIK3CA-mutated advanced, or metastatic breast cancer (Markham et al. 2019a; Kirstein et al. 2019; Wang et al. 2015).

The synthesis of alpelisib (**11**) was patented by Novartis in 2010 (Caravatti et al. 2010), and then, they reported an improved process in 2012, which started from 1-(4-methylpyridin-2-yl)ethenone (**14**) (Scheme 2) (Erb et al. 2012). Ketone **14** was converted into trifluoromethylated silyl enol ether **15** by reacting with $TMSCF_3$ in the presence of NaOAc in dimethyl sulfoxide (DMSO). Deprotection of silyl enol ether **15** resulted in alcohol **16**, which was protected by methanesulfonyl group to give the intermediate **17**. Then, the treatment of intermediate **17** by $AlMe_3$ at room temperature provided the key pyridine intermediate **18**. Subsequently, the intermediate **18** was treated with LDA, followed by reaction with Weinreb amide affording the pyridinyl ketone **19**. Cyclization reaction of ketone **19** with thiourea in the presence of NBS at 40 °C provided the 2-aminothiazole intermediate **20**, which underwent the protection reaction by phenyl chloroformate resulting in intermediate **21**. Finally, the substitution reaction of intermediate **21** by (*S*)-pyrrolidine-2-carboxamide (**22**) in THF/H_2O at 60 °C gave alpelisib (**11**).

Erdafitinib (Balversa™)

Erdafitinib (**24**), also named JNJ-42756493, is an effective small-molecule selective inhibitor of pan-fibroblast growth factor receptor (FGFR) kinase, which was discovered by the collaboration between Astex Pharmaceuticals and Janssen in 2008 (Fig. 4) (Markham 2019b; Stuyckens et al. 2018). Erdafitinib (**24**) has been proved to be an effective inhibitor of FGFR1, FGFR2, FGFR3, and FGFR4 (IC_{50} value = 1.2, 2.5, 3, and 5.7 nmol/L, respectively), but its inhibitory effect on vascular endothelial growth factor receptor (VEGFR) 2 kinase is weak (IC_{50} = 36.8 nmol/L). Erdafitinib (**24**) also showed dose-dependent antitumor activities in a variety of preclinical studies using xenogeneic mouse models (Perera et al. 2017).

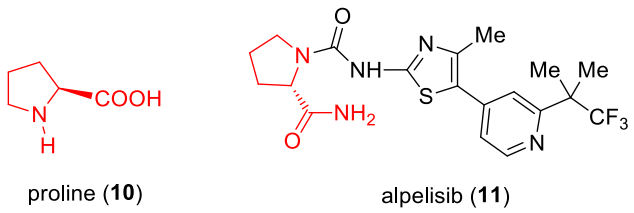
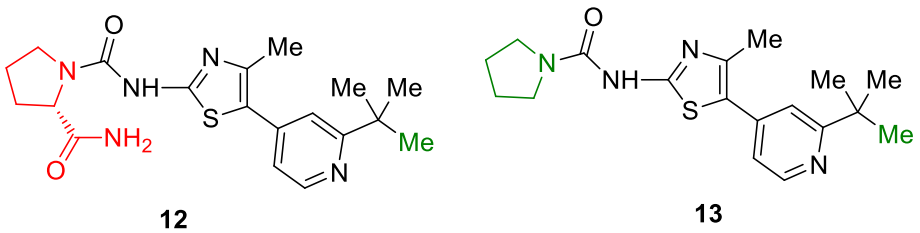
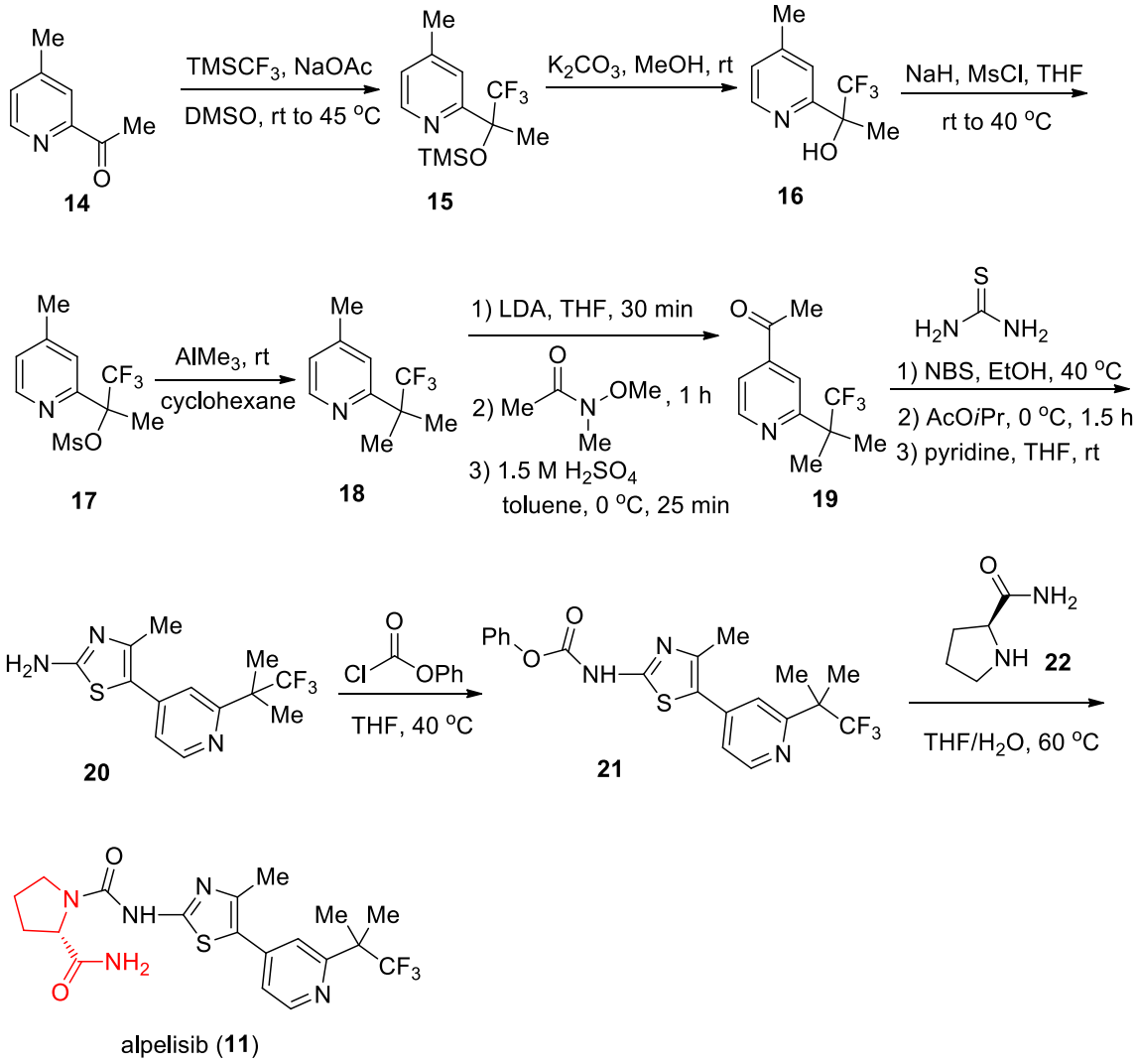


Fig. 2 Chemical structure of alpelisib (**11**)

Fig. 3 Chemical structures of PI3K inhibitors **12** and **13**





Scheme 2 Synthesis of alpelisib (**11**)

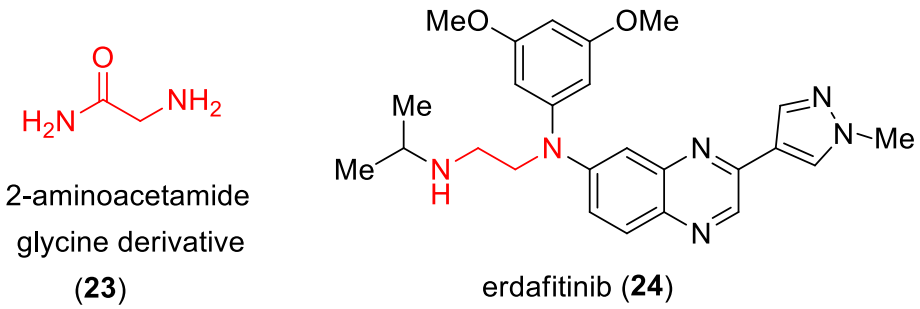


Fig. 4 Chemical structure of erdafitinib (**24**)

Erdafitinib (**24**) contains a quinoxaline and pyrazole bicyclic unit, and a 1,3-diamine moiety, which could be derived from 2-aminoacetamide (glycine derivative, **23**) (Fig. 4). In 2011, Astex pharmaceuticals patented their SAR studies of this type of quinoxaline derivatives. The results showed that the glycine-derived moiety was important for their bioactivities. Variation from this moiety to ethyl (**25**, pIC_{50} value = 8.53, 8.11, 8.73, 7.92 for FGFR1, FGFR2, FGFR3, and FGFR4, respectively), to methyl (**26**, pIC_{50} value = 8.36, 7.91, 8.66, 7.76 for FGFR1, FGFR2, FGFR3, and FGFR4, respectively), and to methoxylethyl (**27**, pIC_{50} value = 8.27, 7.93, 8.47, 7.55 for FGFR1, FGFR2, FGFR3, and FGFR4,

respectively), the increased IC_{50} values were found (Fig. 5) (Saxty et al. 2011). The binding between drug enzymes has been disclosed by the X-ray crystal structure of erdafitinib-FGFR1 complex. It can be found a hydrogen bond between *N*1 of quinoxaline and A564 (the third hinge residue), as well as a hydrogen bond between dimethoxyphenyl oxygen with N–H moiety of FGFR1 DFG-D641. Also, there exist hydrophobic interaction between erdafitinib (**24**) and five spinal residues (RS2/3, CS6/7/8), three shell residues (Sh1/2/3), KLIFS-3, and AVK514 (Roskoski 2020; Murray et al. 2019).

Erdafitinib (**24**) has been approved for use in patients with urothelial cancer who are susceptible to FGFR3 or FGFR2 gene alterations. It showed tolerance and preliminary clinical activity in advanced solid tumors with FGFR pathway genomic changes (Bahleda 2019). In April 2019, erdafitinib (Balversa™) received its approval in USA by FDA for the treatment of locally advanced or metastatic urothelial carcinoma (Markham 2019b).

In 2011, Astex Pharmaceuticals patented their SAR studies of this type of quinoxaline derivatives, and developed the method for the synthesis of erdafitinib (**24**) (Saxty et al. 2011). Suzuki coupling reaction between 2-chloro-6-nitroquinoxaline (**28**) and boric ester **29** gave the nitro intermediate **30**, which was reduced to amine **31** in the presence of Raney Ni. Then, the dimethoxylphenyl moiety was introduced to the amine **31** via the Pd-catalyzed coupling reaction with 74% yield. Subsequently, deprotonation by NaH in DMF, followed by a substitution reaction with (2-bromoethoxy)(*tert*-butyl)dimethylsilane (**33**) afforded the intermediate **34** in 95% yield. Deprotection of **34** by TBAF at room temperature gave the alcohol **35**, which was protected by methanesulfonyl again to generate intermediate **36**. Finally, substitution reaction between isopropylamine and intermediate **36** at 90 °C for 3 h furnished erdafitinib (**24**) (Scheme 3).

In this patent, an alternative synthetic method to erdafitinib (**24**) also been developed, which started from intermediate **32** via the direct substitution reaction with *N*-(2-chloroethyl) propan-2-amine salt (**37**) with the use of a base and phase transfer catalyst (Scheme 4).

Darolutamide (Nubeqa™)

Darolutamide (**39**), also named ODM-201, is a novel structurally distinct non-steroidal androgen receptor (AR) antagonist and shows excellent antitumor activity and satisfactory safety in phase studies. It was discovered by Finnish pharmaceutical company Orion Corporation as a treatment for castration-resistant prostate cancer (CRPC) (Fig. 6) (Moilanen et al. 2015; Fizazi et al. 2014; Ferroni et al. 2017).

Darolutamide (**39**) is a (*S*)-2-aminopropanamide (**38**) derived compound including a mixture (1:1) of diastereomers featuring (*R/S*)-ethyl-5-(1-hydroxyethyl)-1*H*-pyrazole-3-carboxylate moiety (**39a** and **39b**). The inhibitory activity of darolutamide (**39**) relies significantly on the carboxylate structural unit, which was disclosed by the SAR studies on in vitro antiproliferative activities. When the hydroxylethyl group on 1*H*-pyrazole moiety was removed (**40**), the activity against VCaP cells almost disappeared. The same result was found when 1*H*-pyrazole moiety was replaced by phenyl group (**41**). With further modification focused on the position of amide group, the antiproliferative activities of compounds **42** decreased dramatically by reversing the position of amine and carbonyl groups (IC_{50} (VCaP) > 30 μM) (Fig. 7) (Yu et al. 2019).

In June 2014, Finnish pharmaceutical company Orion Corporation collaborated with Bayer for the development of darolutamide (**39**). Based on the positive results in the phase III androgen receptor inhibiting agent for metastatic-free

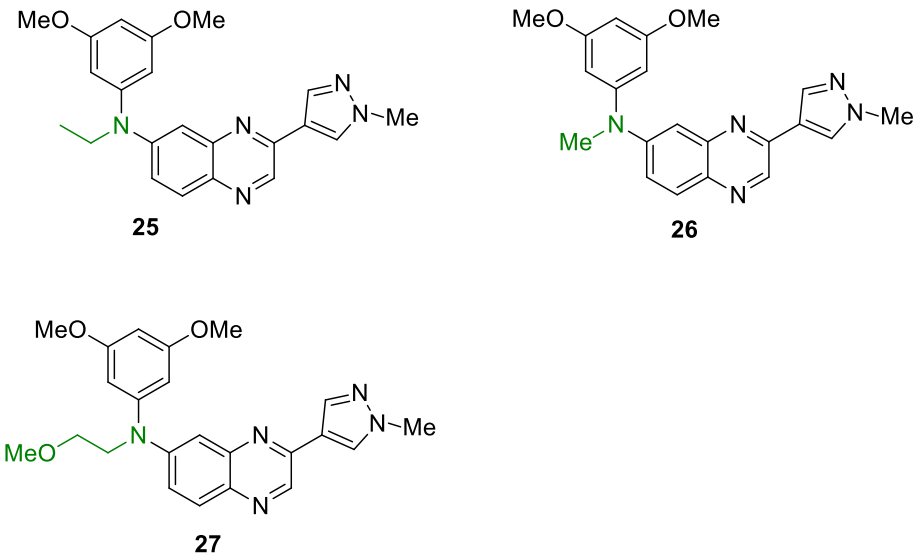
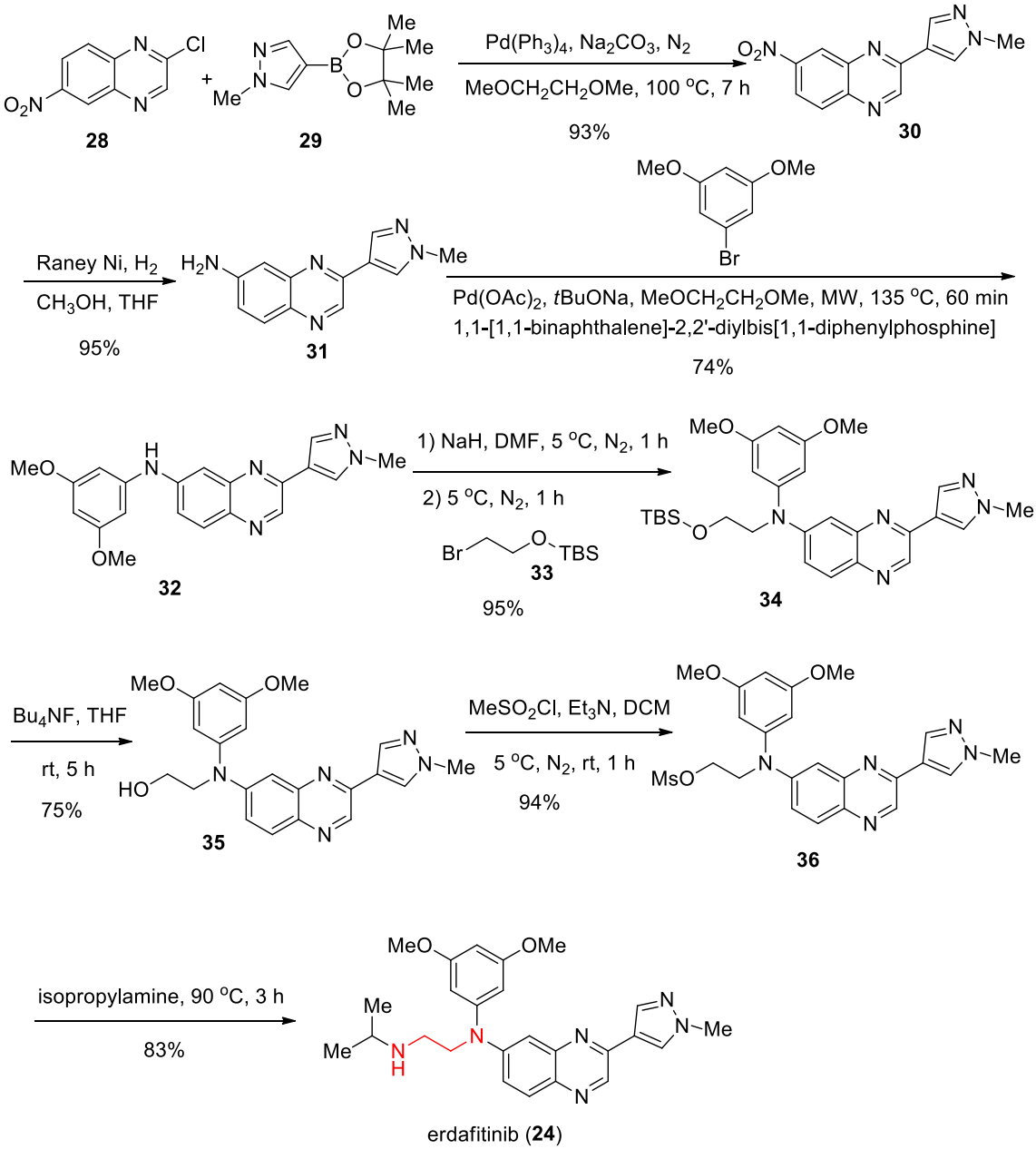


Fig. 5 Chemical structure of FGFR inhibitors



Scheme 3 Synthesis of erdafitinib (**24**)

Scheme 4 An alternative way to erdafitinib (**24**)

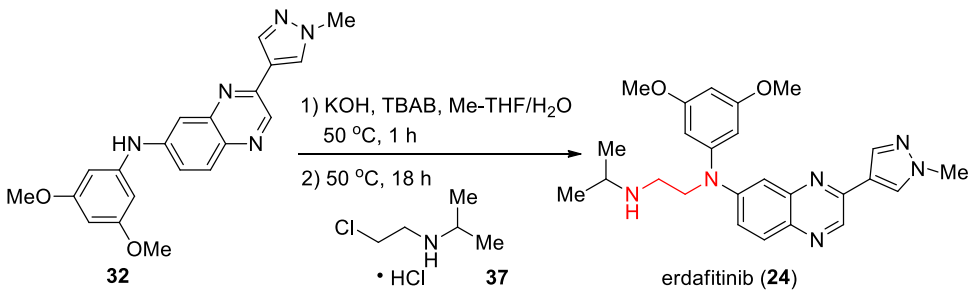
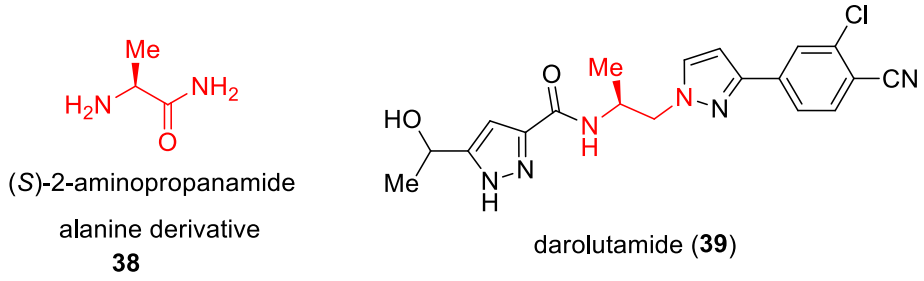


Fig. 6 Structure of darolutamide (**39**)



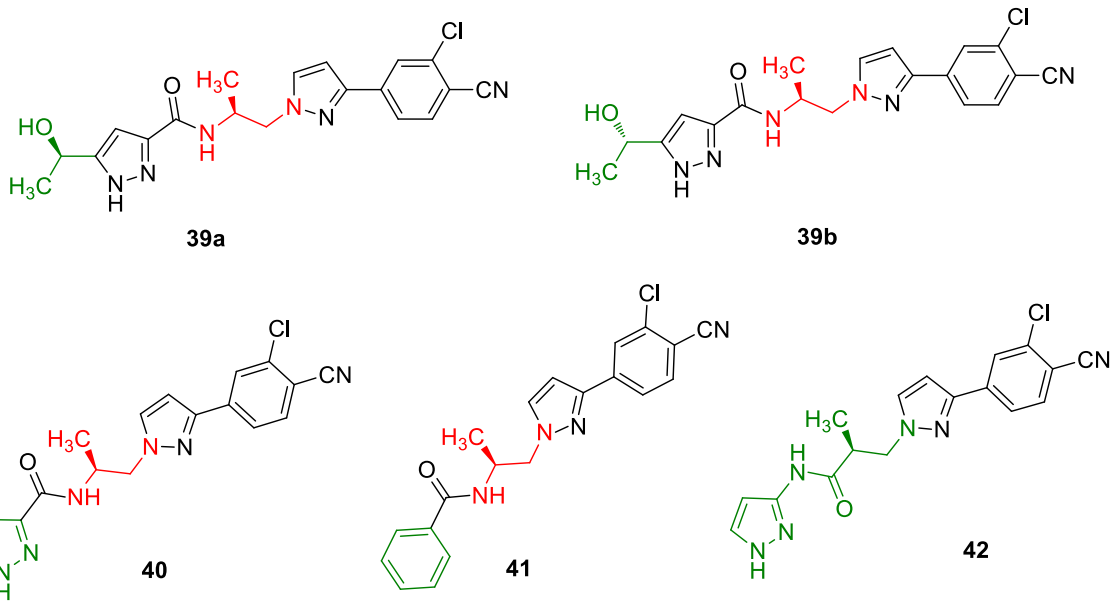
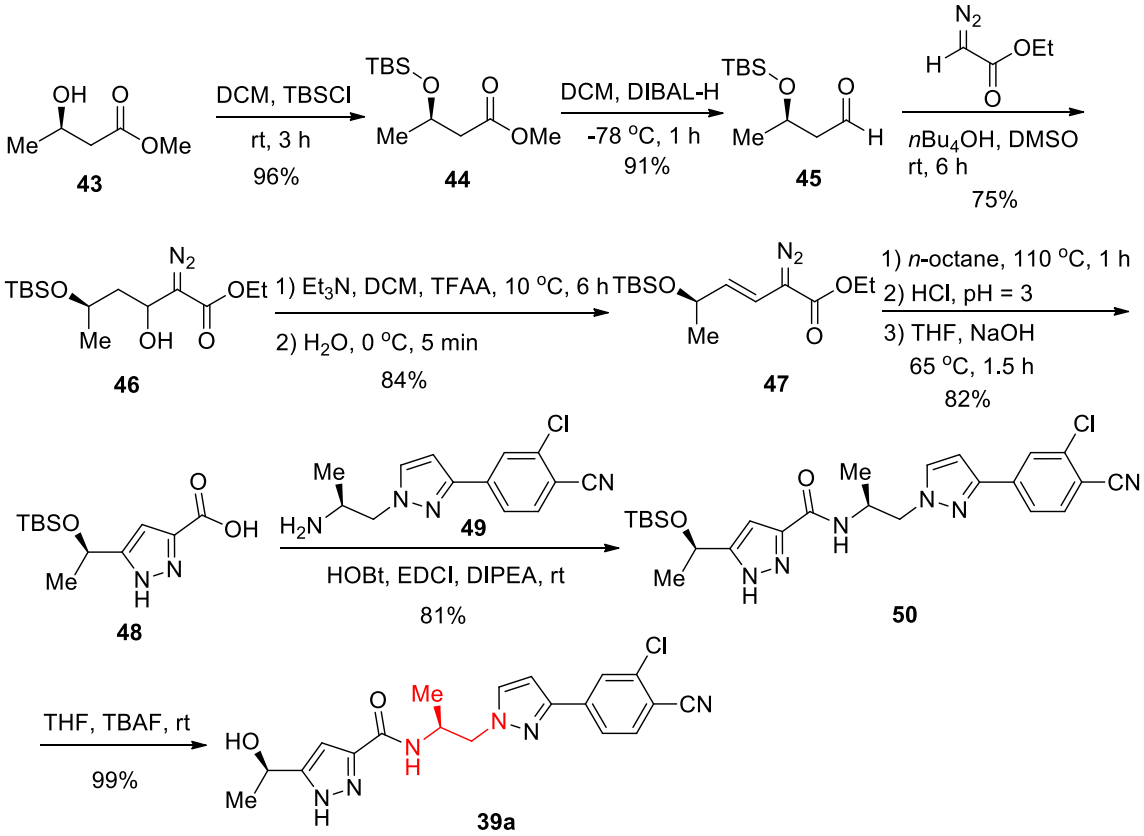


Fig. 7 Structures of compounds in SAR studies

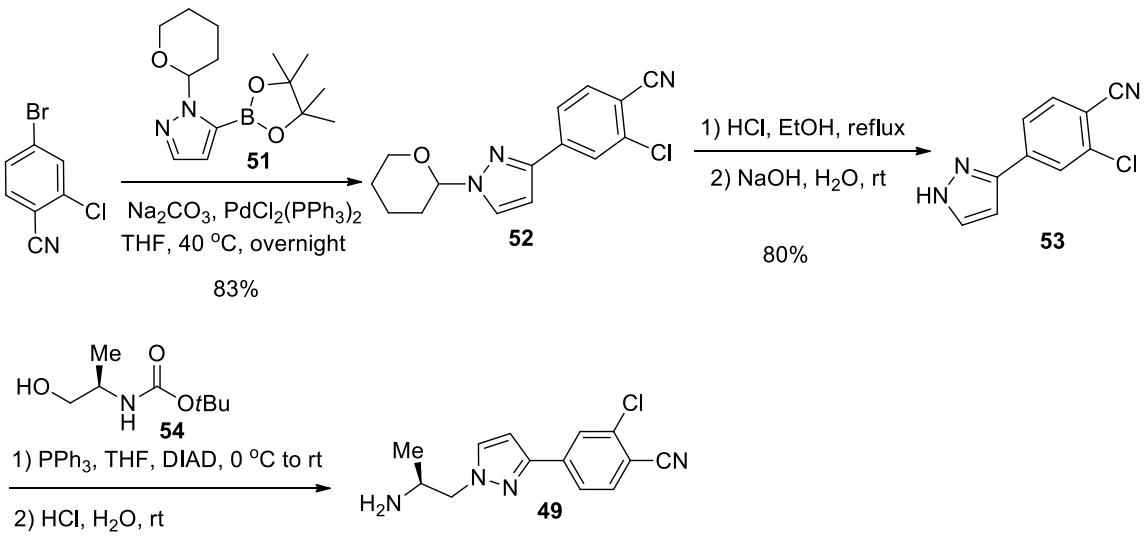
survival (ARAMIS) trial, darolutamide received its approval in the USA for the treatment of men with non-metastatic castration-resistant prostate cancer in July of 2019 (Markham and Duggan 2019d).

Orion Corporation in 2016 developed a method for the preparation of darolutamide diastereomers via a key enzymes (KREDs)-promoted reduction with poor yield (Törmäkangas and Heikkinen 2016). Then, a new synthetic method for compound **39a** was developed with the commercially available enantiopure (*R*)-methyl 3-hydroxybutanoate (**43**) as starting material (Scheme 5) (Pan et al. 2017). Compound **39b** could be prepared via the same synthetic method. Protection of hydroxyl group of **43** by *tert*-butyldimethylsilyl chloride (TBSCl) afforded **44** in 96% yield. DIBAL-H reduction of **44** gave the corresponding aldehyde **45** in 91% yield, which was converted into diazo intermediate **46** via the reaction with ethyl diazoacetate in the presence of tetrabutylammonium hydroxide (TBAOH) at room temperature. Subsequently, the combination of $(CF_3CO)_2O$ and Et_3N in CH_2Cl_2 was employed for the dehydration reaction of **46,** resulting in the vinyl 4-diazo carbonyl compound **47** in 84% yield. Then, **47** was dispensed in *n*-octane and heated to 110 °C for 1 h giving rise to pyrazole intermediate via an intramolecular 1,3-dipolar cycloaddition, which was directly hydrolyzed with 10% NaOH in THF to form the acid **48** in 82% yield. The coupling reaction between **48** and **49** with the use of 1-hydroxybenzotriazole (HOBt) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI) gave the corresponding product **50** in 81% yield. Further treatment by tetrabutylammonium fluoride (TBAF) with the removal of TBS group in **50** finished the synthesis of target compound **39a** in 99% yield.

The synthesis of amine intermediate **49** is shown in Scheme 6, which started from the commercially available 4-bromo-2-chlorobenzonitrile (Yu et al. 2019). Pd-catalyzed Suzuki coupling reaction of 4-bromo-2-chlorobenzonitrile with boric ester **51** at 40 °C gave the intermediate **52**, which underwent the deprotection reaction under acidic conditions affording the intermediate **53**. Finally, condensation reaction between **53** and (*R*)-*tert*-butyl-1-hydroxypropan-2-yl carbamate (**54**) in the presence of diisopropyl azodiformate (DIAD) gave the desired amine **49**.

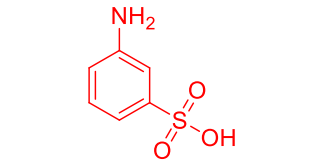


Scheme 5 Synthesis of **39a**

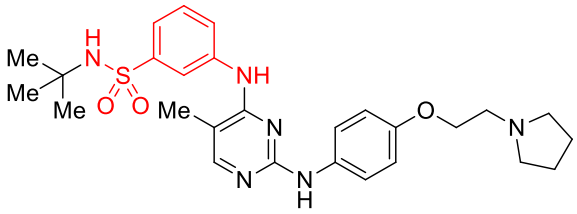


Scheme 6 Synthesis of intermediate **49**

Fig. 8 Chemical structure of fedratinib (**56**)



3-aminobenzenesulfonic acid (**55**)

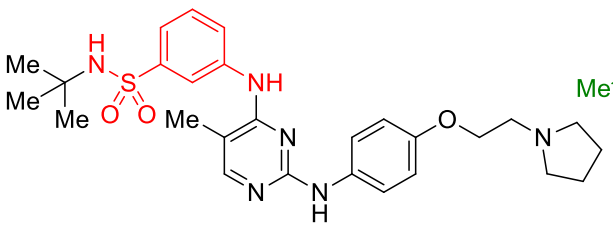


fedratinib (**56**)

Fedratinib (Inrebic™)

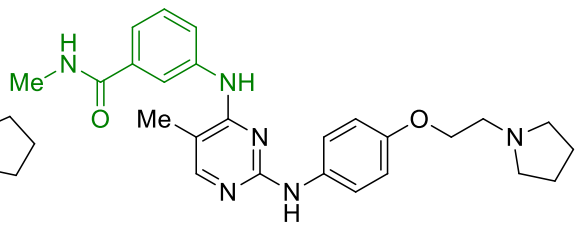
Fedratinib (**56**), also named as TG101348, was originally developed by TargeGen as a kinase inhibitor with good activities against the wild type and mutationally activated JAK2 and FMS-like tyrosine kinase 3 (Fig. 8). In particular, fedratinib (**56**) showed a highly selective inhibiting JAK2 activity comparing with effect on TYK2, JAK1, and JAK3, with the in vitro IC_{50} values of 3 nM, 150 nM, 100 nM, and 1000 nM, respectively (Werning et al. 2008; Malerich et al. 2010). In August of 2019, febratinib (Inrebic™) developed by Celgene Corporation received its first global approval in the USA to treat adult patients with intermediate-2 or high-risk primary or secondary myelofibrosis (Blalr 2019). It should be mentioned that inhibition of thiamine transporters with fedratinib was also reported, and fedratinib could inhibit the uptake of thiamine into Caco-2 cells with IC_{50} value of 0.940 μM, and into THTR-2 with IC_{50} value of 1.36 μM (Giacomini et al. 2017).

Fedratinib (**56**) contains a key 2,4-diamino-pyrimidine structural core, and a systematic variation of the substituents and side chains was carried out based on the 2,4-diamino-pyrimidine core by TargeGen in 2007 (Fig. 8) (Cao et al. 2007; Tefferi 2012). In particular, fedratinib (**56**) also features an amino acid analog, 3-aminobenzenesulfonamide (**55**) moiety on the pyrimidine ring. Actually, amino sulfonic acids and their derivatives widely exist in the natural products, and have been used in the design of peptidomimetics and drug discovery (Grygorenko et al. 2018; Frankel and Moses 1960). The SAR studies disclosed that the IC_{50} of fedratinib (**56**) for JAK2 kinase was 12.5 nM. Changing the 3-aminobenzenesulfonamide moiety into benzamide



fedratinib (**56**)

JAK2 IC_{50} = 12.5 nM



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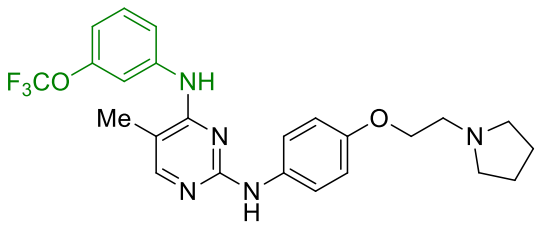
JAK2 IC_{50} = 257 nM



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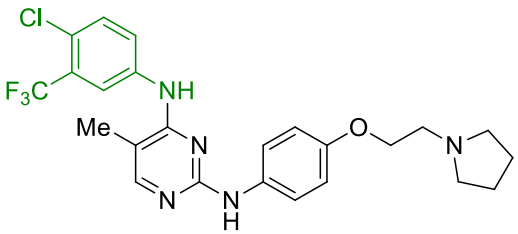
JAK2 IC_{50} = 20.7 nM



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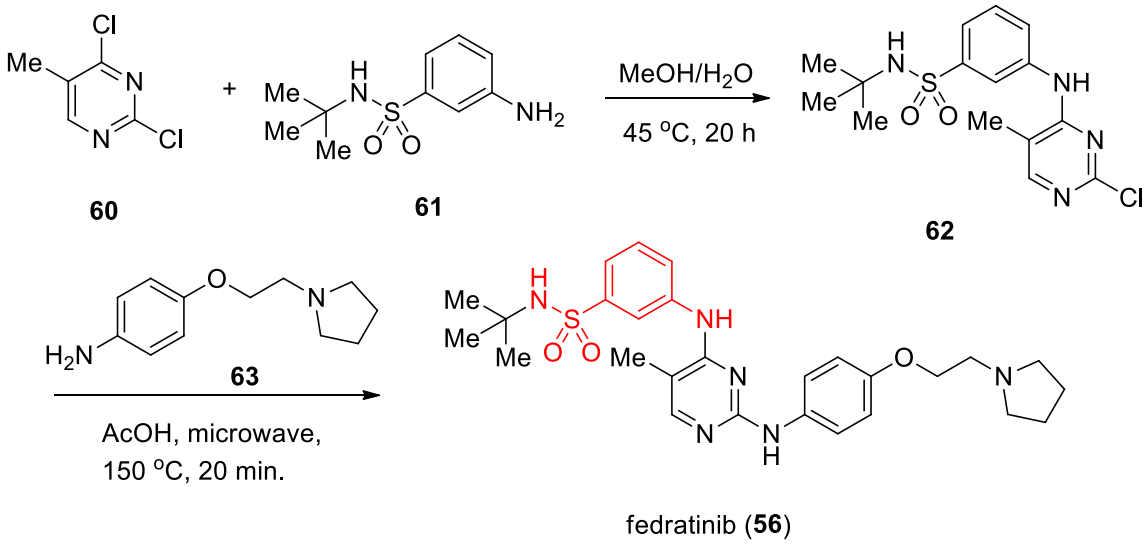
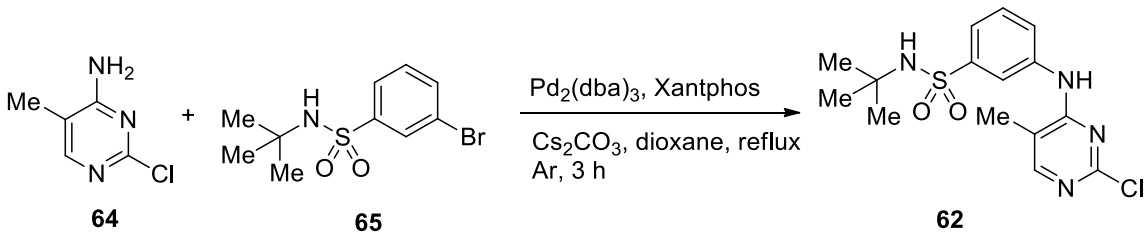
JAK2 IC_{50} = 23.4 nM

Fig. 9 Chemical structure of kinase inhibitors



Scheme 7 Synthesis of fedratinib (**56**)



Scheme 8 Improved synthetic method for the preparation of intermediate **62**

(**57**) resulted in dramatically decreased activity with IC_{50} of 257 nM. Other substituents, like phenyl group (**58** and **59**), led to increased IC_{50} values (20.7 nM and 23.4 nM respectively) (Fig. 9).

The synthesis of fedratinib (**56**) was patented by TargeGen, Inc. in 2007 (Cao et al. 2007), which started from the substitution reaction of 2,4-dichloro-5-methylpyrlmidin (**60**) and *N*-*tert*-butyl-3-(2-chloro-5-methyl-pyrimidin-4-ylamino)-benzenesulfon amide (**61**) (Scheme 7). The substitution reaction of compound **60** by amine **61** in methanol/water at 45 °C for 20 h provided the key intermediate N-tert-Butyl-3-(2-chloro-5-methyl-pyrimidin-4-ylamino)-benzenesulfon amide (**62**) in 79% yield. Then, the second substitution reaction between intermediate **62** and 4-(2-pyrrolidin-1-yl-ethoxy)-phenylamine (**63**) in the acetic acid under microwave initiation conditions at 150 °C for 20 min afforded the corresponding fedratinib (**56**) in 27% yield. In 2012, they developed another way for the preparation of the key intermediate **62** via the Pd-catalyzed coupling reaction of 2-chloro-5-methylpyrimidin-4-amine (**64**) and 3-bromo-*N*-(*tert*-butyl)benzenesulfonamide (**65**) with an improved yield (98%) (Scheme 8) (Tefferi 2012).

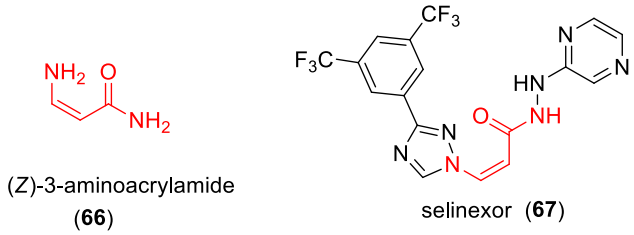


Fig. 10 Chemical structure selinexor (**67**)

Selinexor (Xpovio™)

Selinexor (**67**), also named as KPT-330, is an oral selective inhibitor of nuclear export (SINE) with a favorable toxicity profile and proved to have preclinical and clinical activity against a broad range of solid tumors and hematological malignancies (Fig. 10). Selinexor (**67**) is also an oral, small-molecule inhibitor of Exportin-1 (XPO1), which was developed by Karyopharm Therapeutics for the treatment of cancer (Syed 2019). Selinexor (**67**) showed good

cytotoxicity in a wide scope of myeloid leukemia cell lines with less than 0.5 μM of IC50 values (Taylor et al. 2018). In the phase II study, the combination of selinexor (**67**) and dexamethasone showed synergistic anticancer activity with a 21% overall response rate (ORR) in in patients with heavily pretreated, refractory myeloma with limited therapeutic options (Vogl et al. 2018). In July 2019, selinexor (Xpovio™) received its first global approval in USA and was used to treat adults with relapsed or refractory multiple myeloma (Syed 2019).

On the other hand, in phase I study of selinexor (**67**), the combination of selinexor with fludarabine and cytarabine was used in pediatric patients with relapsed or refractory leukemia. A promising response was observed and XPO1 target inhibition was demonstrated in all patients who received selinxor at more than 40 mg/m^2 (Alexander et al. 2016). Selinexor (**67**) was also found to affect normal immune homeostasis, in particular with the greatest effect on CD8 T cells, which possibly allowed the development of selinexor in antitumor immunity (Tyler et al. 2017).

Selinexor (**67**) contains a substituted 1,2,4-triazole core, a (*Z*)-3-aminoacrylamide (**66**) moiety, and a 2-hydrazinylpyrazine unit (Fig. 10). In particular, the (*Z*)-3-aminoacrylamide moiety was important for the biochemical activity via the SAR studies. IC_{50} values on Rev for the compounds **67**, **68,** and **69** were all less than 1 μM, while the IC_{50} value for the compound **70** featuring a (*E*)-3-aminoacrylamide moiety could not be tested (Fig. 11) (Sandanayaka et al. 2013).

Selinexor was accessed as showed in Scheme 9 (Sandanayaka et al. 2013), which was developed by Karyopharm Therapeutics in 2013 with 3,5-bis(trifluoromethyl) benzonitrile (**71**) as the starting reagent. Benzonitrile **71** reacted with NaSH in the presence of $MgCl_2$ at room temperature for 3 h generating 3,4-bis(trifluoromethyl)benzothioamide (**72**) in 90% yield. Then, benzothioamide **72** was treated by hydrazine hydrate in DMF at room temperature for 1 h, followed by refluxing with HCOOH at 90 °C for 3 h, affording 3-(3,5-bis(trifluoromethyl)phenyl)-1H-1,2,4-triazole (**73**) as a yellow solid in 75% yield. Subsequently, triazole **73** underwent the substitution reaction with (*Z*)-isopropyl 3-idooacrylate (**74**) by the use of 1,4-diazabicyclo[2.2.2] octane;triethylenediamine (DABCO) as a base**,** affording the ester intermediate **75** in 61% yield, which was converted into acid **76** in the presence of LiOH at room temperature with excellent yield (94%). Finally, condensation reaction between carboxylic acid **76** and 2-hydrazinopyridine (**77**) in the presence of propylphosphonic anhydride (T3P) (50% in EtOAc) and DIPEA achieved the synthesis to give selinexor (**67**) in 48% yield.

In 2017, an improved synthetic method for the preparation of selinexor (**67**) was developed (Scheme 10), which could avoid the generation of (*E*)-isomer impurity. The intermediate **78** containing iodoethene moiety was used in the substitution reaction with intermediate **73**, affording the desired selinexor (**67**) in 50% yield (Chen et al. 2017).

Entrectinib (Rozlytrek™)

Entrectinib (RXDX-101) (**80**), developed by Nerviano Medical Sciences, was designed for selectively inhibiting pan-tropomyosin receptor kinases (pan-TRK), *c-ros* oncogene 1 kinase (ROS1), and anaplastic lymphoma kinase (ALK) (Fig. 12). It was got its first global approval in June 2019, and then was approved by the FDA in August 2019 for the treatment of ROS1-positive metastatic non-small cell lung

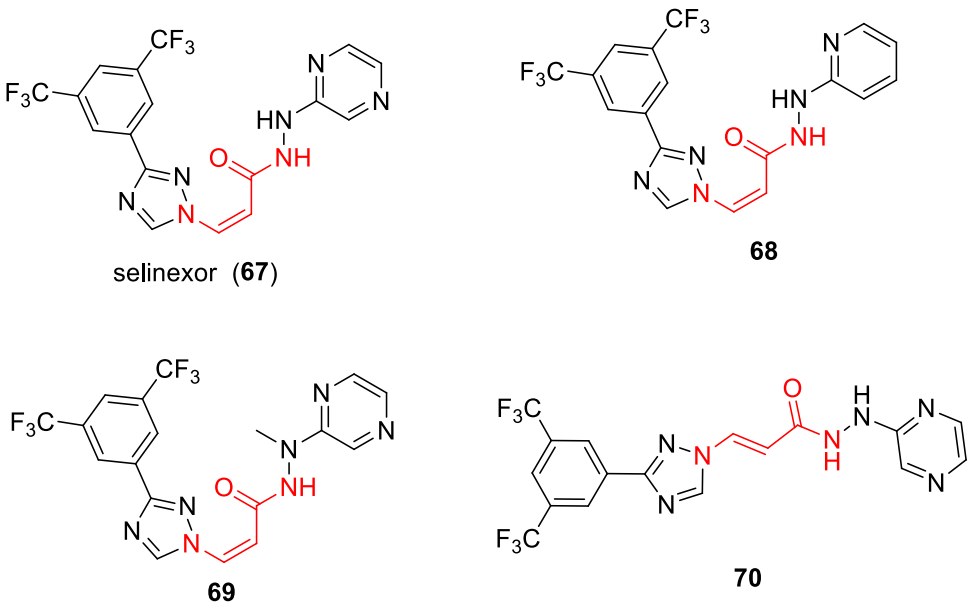
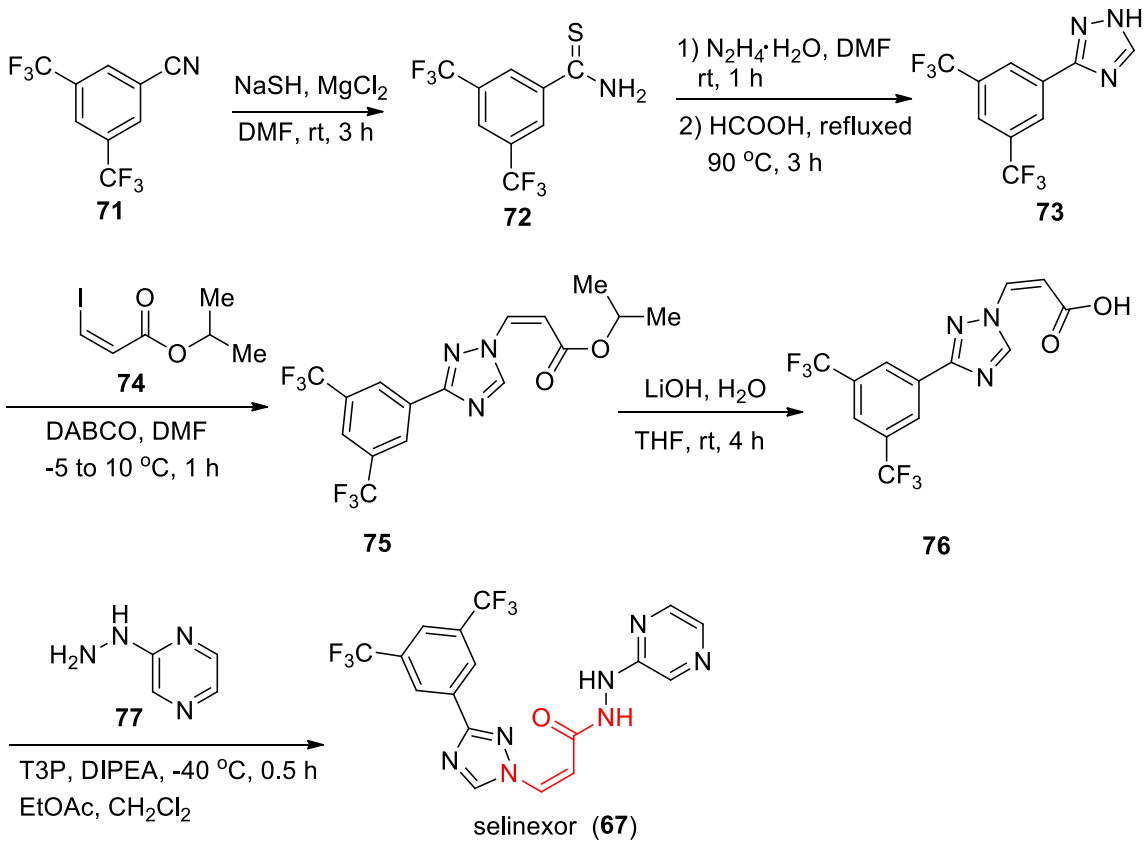
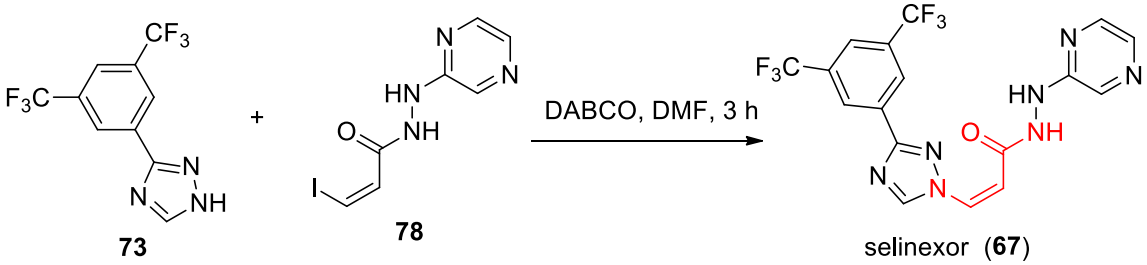


Fig. 11 Chemical structure selinexor (**67**) and related nuclear transport modulators (**68–70**)

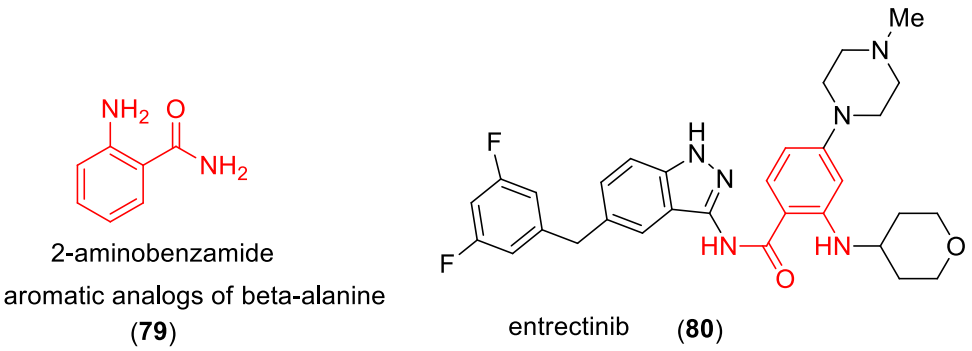


Scheme 9 Synthesis of selinexor (**67**)



Scheme 10 An alternative synthetic method for selinexor (**67**)

Fig. 12 The chemical structure of entrectinib (**80**)



cancer and neurotrophic tyrosine receptor kinase (NTRK) gene fusion-positive solid tumors (Al-Salama et al. 2019a).

Entrectinib features an indazole moiety and an aromatic analog of β-alanine, 2-aminobenzamide (**79**) structural unit (Fig. 12). In particular, the nitrogen atom of the amino group is important for binding with hinge (Shirahashi et al. 2019). Nerviano Medical Sciences carried out thorough SAR studies starting from a promising 3-amino-5-substituted indazole compound (**81**), which showed a good biochemical potency (IC_{50} = 0.073 μM) against ALK and moderate antiproliferative activity against ALK-positive Karpass-299 cell line (IC_{50} = 0.253 μM) (Menichincheri et al. 2016). Then, they performed the optimization studies via variation of the substitution at 2-position on aromatic ring A. Introduction of an unsubstituted amino group (**82**) led almost no obviously improved potency (ALK IC_{50} = 0.067 μM) comparing with compound **81**. They found that the existence of a mono-substituted amino most probably occupied the adenosine triphosphate (ATP) sugar pocket region and displaced the water molecule via the analysis of the complex structure of the ALK kinase in complex with the PHA-E429. Also, mono-substituted amino substituents at this position were able to stabilize the bioactive conformation through intramolecular hydrogen bonding (Menichincheri et al. 2016). Further optimization of the substituent on the nitrogen atom at ring A led to the discovery of **80** (Fig. 13) with good biochemical potencies with IC_{50} values of 0.012 μM on ALK, 0.122 μM on IGF1R, 0.007 μM on the kinases ROS1, 0.001 μM on TRKA, and 0.031 μM on Karpas-299, respectively (Menichincheri et al. 2016). In addition to stable regression in ALK-dependent ALCL and NSCLC, the novel CAD-ALK-dependent colorectal cancer could also be well suppressed by **80** (Amatu et al. 2015).

The synthetic method developed by Nerviano Medical Sciences for the preparation of entrectinib (**80**) is shown in Scheme 11, which used 3-cyano-4-fluorophenylboronic acid (**84**) as the starting material. First, Suzuki coupling reaction between 3-cyano-4-fluorophenylboronic acid (**84**) and 3,5-difluorobenzyl bromide (**85**) with $Pd(PPh_3)_4$ as a catalyst in the presence of K_3PO_4 provided the desired coupling diarylmethane product **86** at 100 °C under argon atmosphere. Then, the cyano group was converted into free amino group via the treatment of hydrazine hydrate in *n*-butanol at 120 °C, and the corresponding 3-aminoindazole **87** was obtained. On the other hand, treatment of acid **88** in dry dichloromethane by oxalyl chloride at room temperature for 2 h gave the acyl chloride **89**, which was used directly for the reaction with 3-aminoindazole **87** without purification. After stirring at − 20 °C for 4 h, the amide **90** was obtained. Finally, deprotection of amide **90** in the presence of triethylamine at 65 °C for 2 h afforded entrectinib (**80**) (Menichincheri et al. 2016; Lombardi et al. 2009).

Zanubrutinib (Brukinsa™)

Zanubrutinib (BGB-3111) (**92**), discovered and developed by BeiGene Company, was a potently and specifically irreversible BTK (Bruton's tyrosine kinase) inhibitor targeting B-cell malignancies (Guo et al. 2019). Zanubrutinib (**92**) showed excellent selective activity against BTK, and with only a minimal inhibitory effect on other kinases such as ITK, JAK3, EGFR, and Src family kinases, comparing with other known irreversible BTK inhibitors in the clinic (Guo et al. 2019; Pan et al. 2007; Byrd et al. 2016; Walter et al. 2016; Evans et al. 2013; Watterson et al. 2019). For

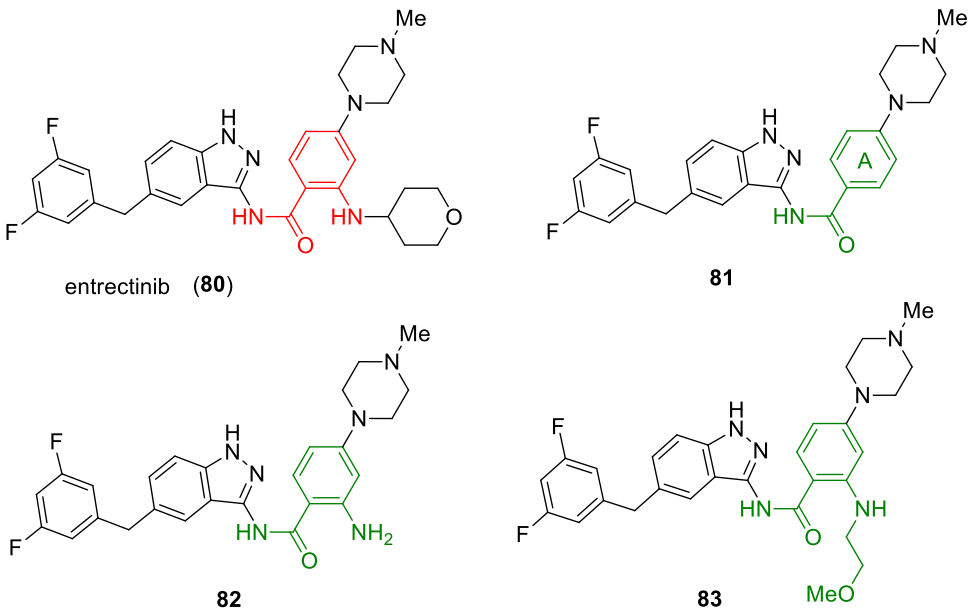
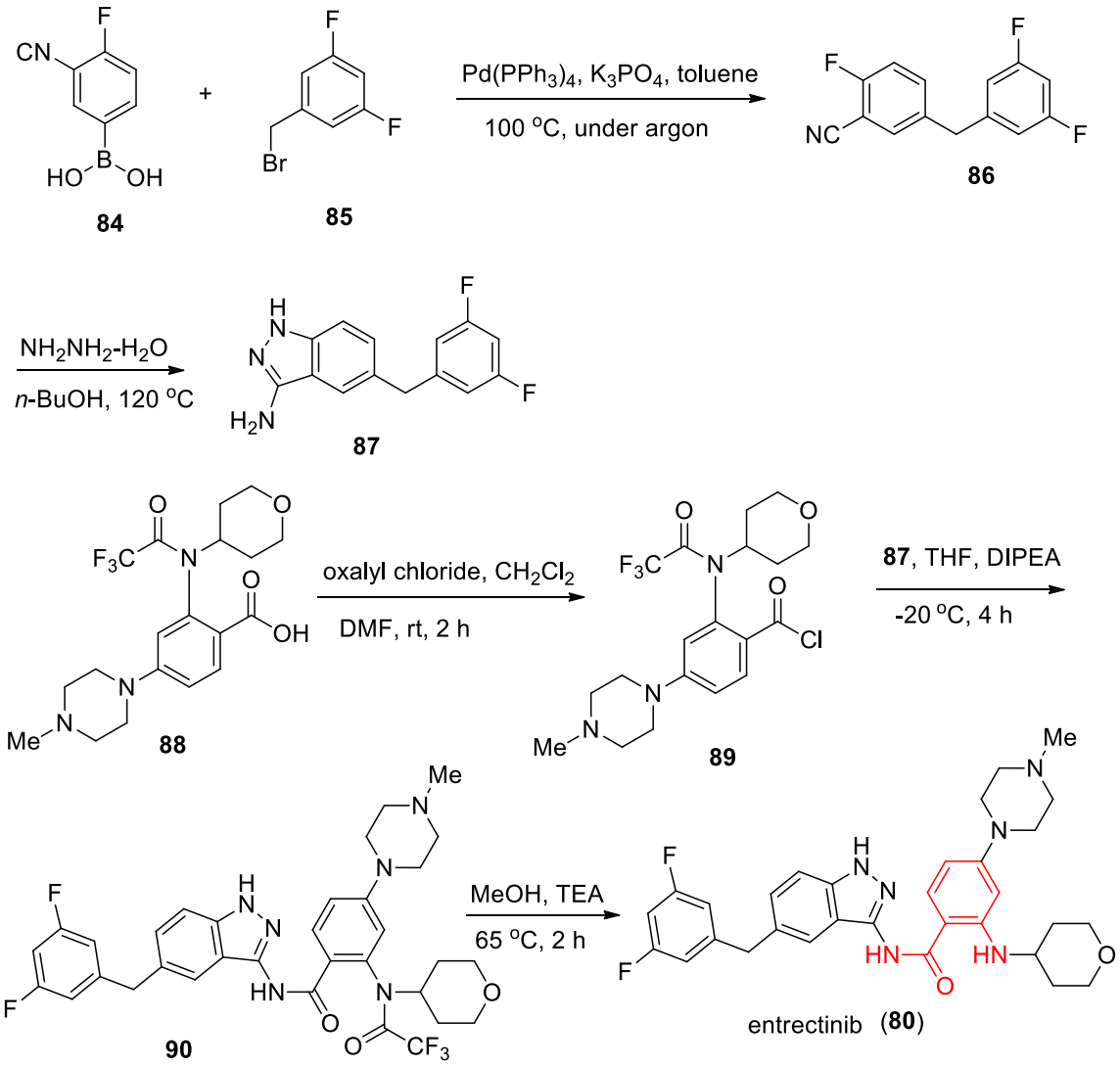


Fig. 13 The discovery of entrectinib (**80**)



Scheme 11 Synthesis of entrectinib (**80**)

examples, the IC_{50} value of zanubrutinib (**92**) against BTK is 0.30 nM, and showed 187-fold against ITK (IC_{50} = 56 nM), 1933-fold against JAK3 (IC_{50} = 580 nM), and 1800-fold against HER2 (IC_{50} = 530 nM), respectively. On the contrary, the first clinically effective covalent BTK inhibitor, ibrutinib (**93**), demonstrated dramatically lower selectivities among BTK, ITK, JAK3, and HER2 with IC_{50} values of 0.18 nM, 3.0 nM, 10.0 nM, and 19.0 nM respectively. The same trend was also found in the inhibitory activity of zanubrutinib (**92**) and ibrutinib (**93**) in cells (Fig. 14) (Honigberg et al. 2010). In November 2019, zanubrutinib (**92**) got its first approval by FDA for the treatment of in adult patients with mantle cell lymphoma (MCL) (Syed 2020).

Zanubrutinib (**92**) is a derivative of 5-amino-1*H*-pyrazole-4-carboxamide (**91**) featuring an (*S*) configuration carbon center (Fig. 14). BeiGene did the SAR studies based on the 5-amino-1*H*-pyrazole-4-carboxamide core structure with variations on the aliphatic amide moiety and the substitutions on the phenyl ring. It was found that the (*S*) absolute configuration is very important for the biological activity, as the compound **94** with (*R*) absolute configuration showed 36-fold BTK IC_{50} value (11 nM) comparing with zanubrutinib (**92**) (0.3 nM). Introduction of an azetidine (**95**), instead of a piperidine, displaced no improvement (IC_{50} = 0.58 nM). In particular, the obviously increased IC_{50} values were observed when a gem-methyl group (**96**) or a cyclopropyl group (**97**) was inserted with IC_{50} values of 3.5 nM and 41 nM, respectively (Fig. 15) (Guo et al. 2019).

The synthesis of zanubrutinib (**92**) developed by BeiGene is shown in Scheme 12 (Guo et al. 2019; Guo 2014). The synthesis started from the generation of 4-phenoxybenzoyl chloride (**98**) by the reaction between 4-phenoxybenzoic acid and $SOCl_2$ under reflux. Then, condensation reaction between 4-phenoxybenzoyl chloride (**98**) and malononitrile

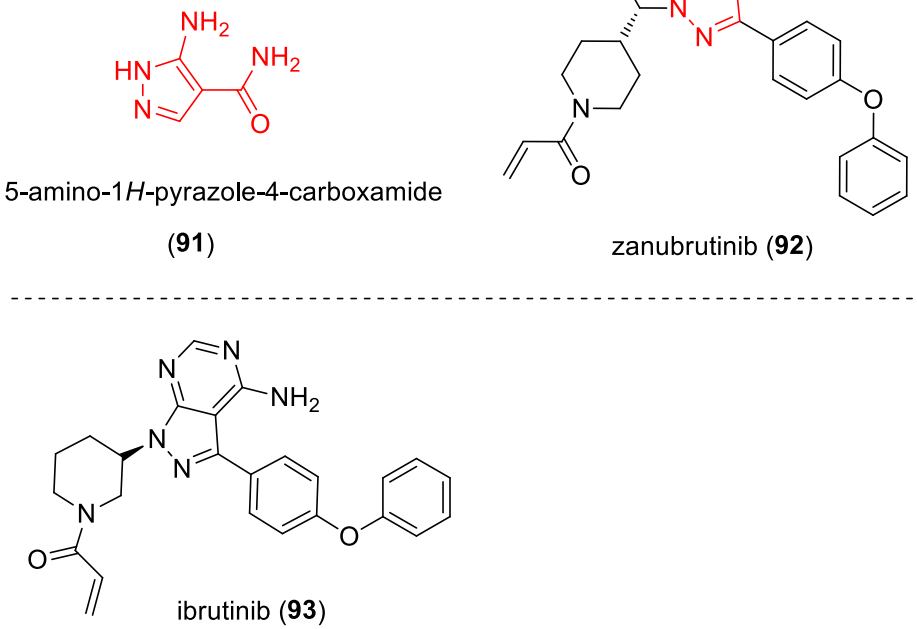


Fig. 14 Structures of zanubrutinib (**92**) and ibrutinib (**93**)

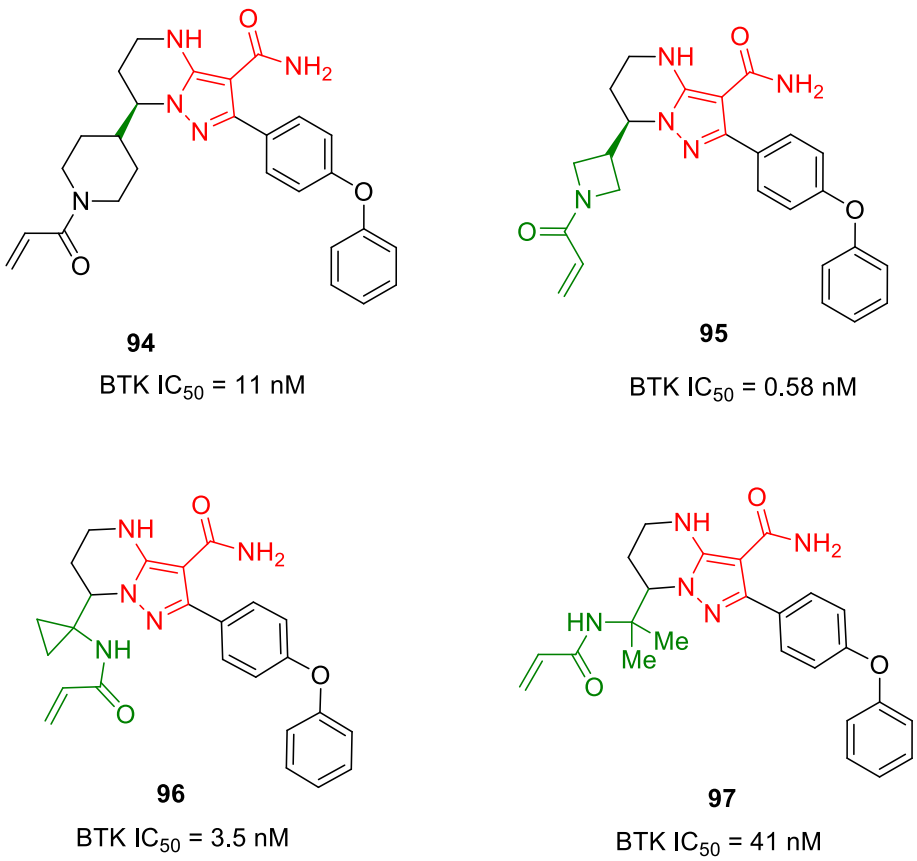
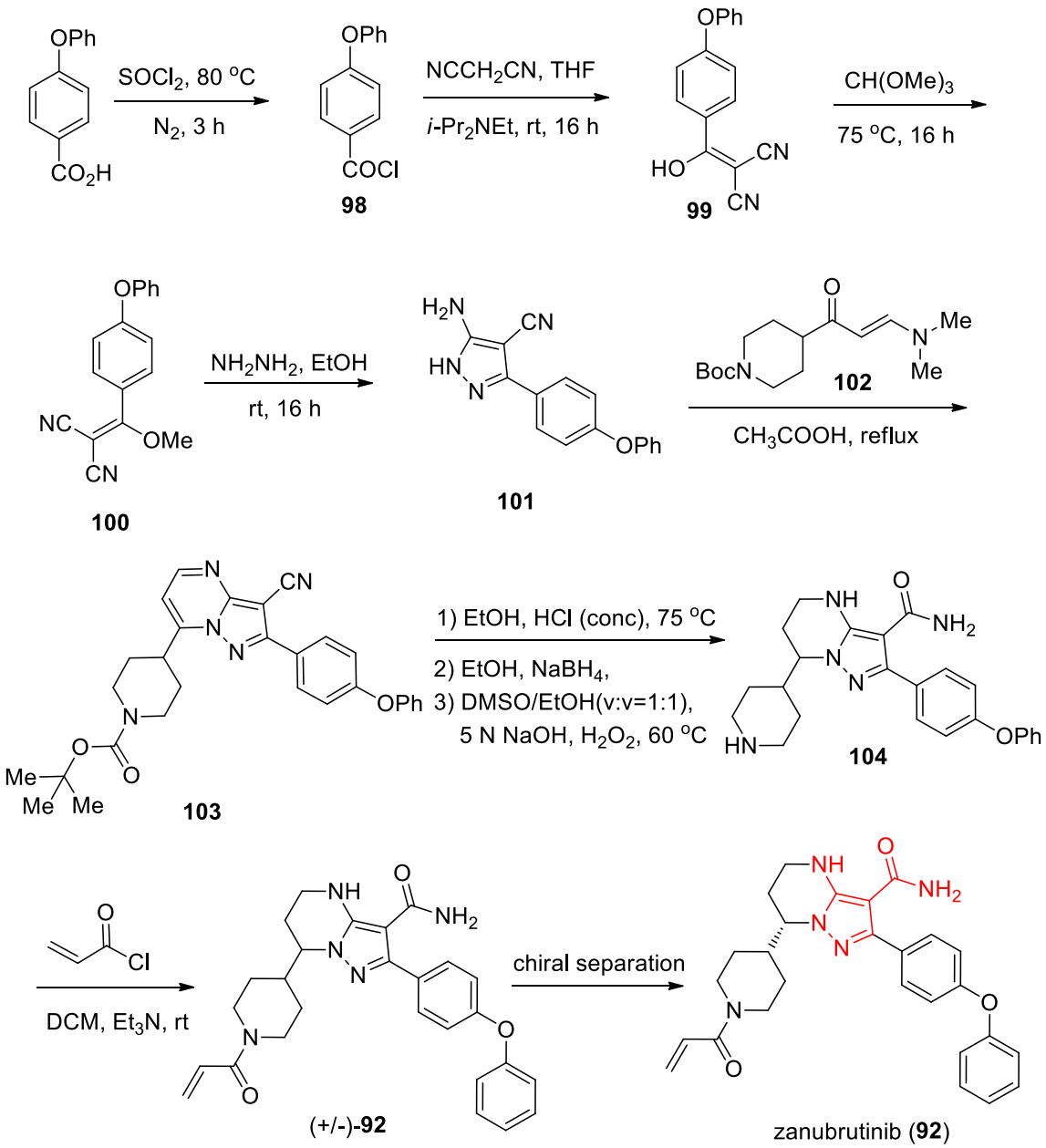


Fig. 15 Chemical structures of BTK inhibitors **94–97**



Scheme 12 Synthesis of zanubrutinib (**92**)

in the presence of DIPEA afforded the intermediate **99**, which was converted into the methylation compound **100** via refluxing with trimethoxymethane at 75 °C for 16 h. Cyclization reaction of intermediate **100** with hydrazine hydrate in ethanol at room temperature afforded 5-amino-3-phenyl-1*H*-pyrazole-4-carbonitrile (**101**). Subsequently, intermediate **101** was subjected to an intermolecular cyclization with 3-dimethylamino-2-propen-1-one **102** affording the intermediate **103** bearing pyrazolopyrimidine core. After removal of the Boc-protecting group, the pyrimidine ring of **103** was reduced using $NaBH_4$, and the resulting intermediate was hydrolyzed by H_2O_2 in the presence of NaOH to generate the amide **104**. Acryloylation of **104** in the presence of triethylamine resulted in the racemic **92**, which was further separated by chiral HPLC to deliver final pure enantiomer of zanubrutinib (**92**).

Ubrogepant (Ulbrelvy™)

Ubrogepant (Ubrelvy™) (**107**), also known as MK-1602, is an oral small-molecule drug developed by Allergan under license from Merck (Fig. 16) (Dodick et al. 2019). It is highly selective human calcitonin gene-related peptide receptor

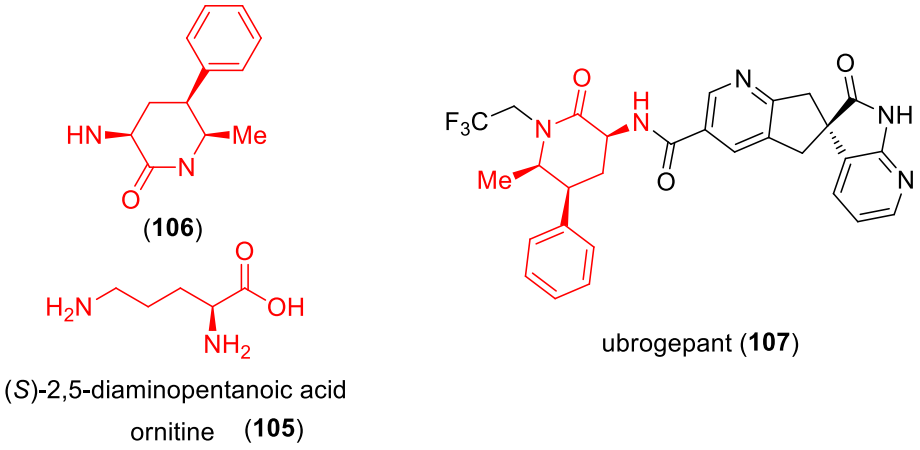


Fig. 16 Chemical Structure of ubrogepant (**107**)

(CGRP) antagonist for the acute treatment of migraine. In functional assays, ubrogepant exhibited similar high-affinity binding for native CGRP receptors (Ki = 0.067 nM) and for cloned human and rhesus monkey CGRP receptors (Ki = 0.070 and 0.079 nM at respective cloned receptors). Ubrogepant also has potent inhibition of the human α-CGRP-stimulated cyclic AMP response in human CGRP receptor-expressing HEK293 cells (IC_{50} 0.08 nM). Furthermore, the results in vivo studies of ubrogepant showed that ubrogepant produced concentration-dependent inhibition of capsaicin-induced dermal vasodilation (CIDV) (EC_{50} of 3.2 and 2.6 nM in rhesus monkeys and humans, respectively) (Moore et al. 2020). Clinical study showed that ubrogepant significantly reduced pain and other bothersome symptoms (Dodick et al. 2019).

Ubrogepant (**107**) was patented by Merck in 2013 (Bell et al. 2013). It contains a piperidinone carboxamide azaindane core structure and an ornitine (**105**) derived 3-aminopiperidin-2-one moiety (**106**) (Fig. 16). The SAR studies showed that variation of substitutions on lactam ring resulted in increased K_i values. In particular, 25-fold Ki value (1.7 nM) was found when 3-aminopiperidin-2-one moiety was replaced by 3-aminoazepan-2-one (**110**) (Fig. 17). In August 2015, it was licensed to Allergan for the development and marketing worldwide. In December 2019, it was approval in USA by FDA for the acute treatment of migraine with or without aura in adults (Scott 2020).

The synthesis of ubrogepant (**107**) involves two key fragments lactam **111** and a spiro acid **112**. In 2017, the Yasuda group reported a new and highly economical synthetic route for the synthesis of ubrogepant (**107**) by simple amide formation reaction between corresponding amino lactam **111** and spiro acid **112** (Scheme 13) (Yasuda et al. 2017). The synthesis of enantiopure lactam **111** started from the alkylation of phenylacetone **114** with alkene **113**. The asymmetric transamination of **115** was carried out by dynamic kinetic transamination (DK-TA) using enzyme ATA-426 to form lactam **116** bearing two stereocenters at

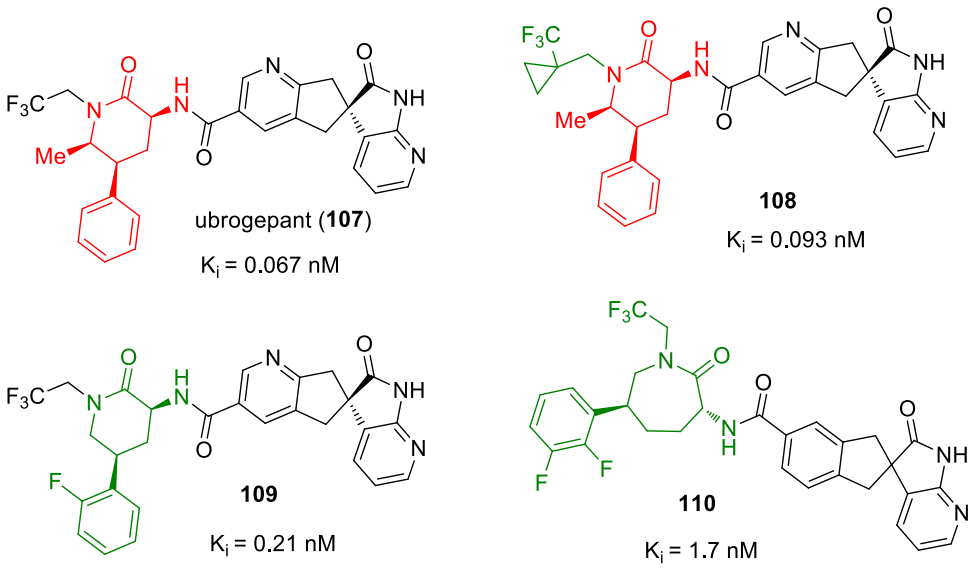
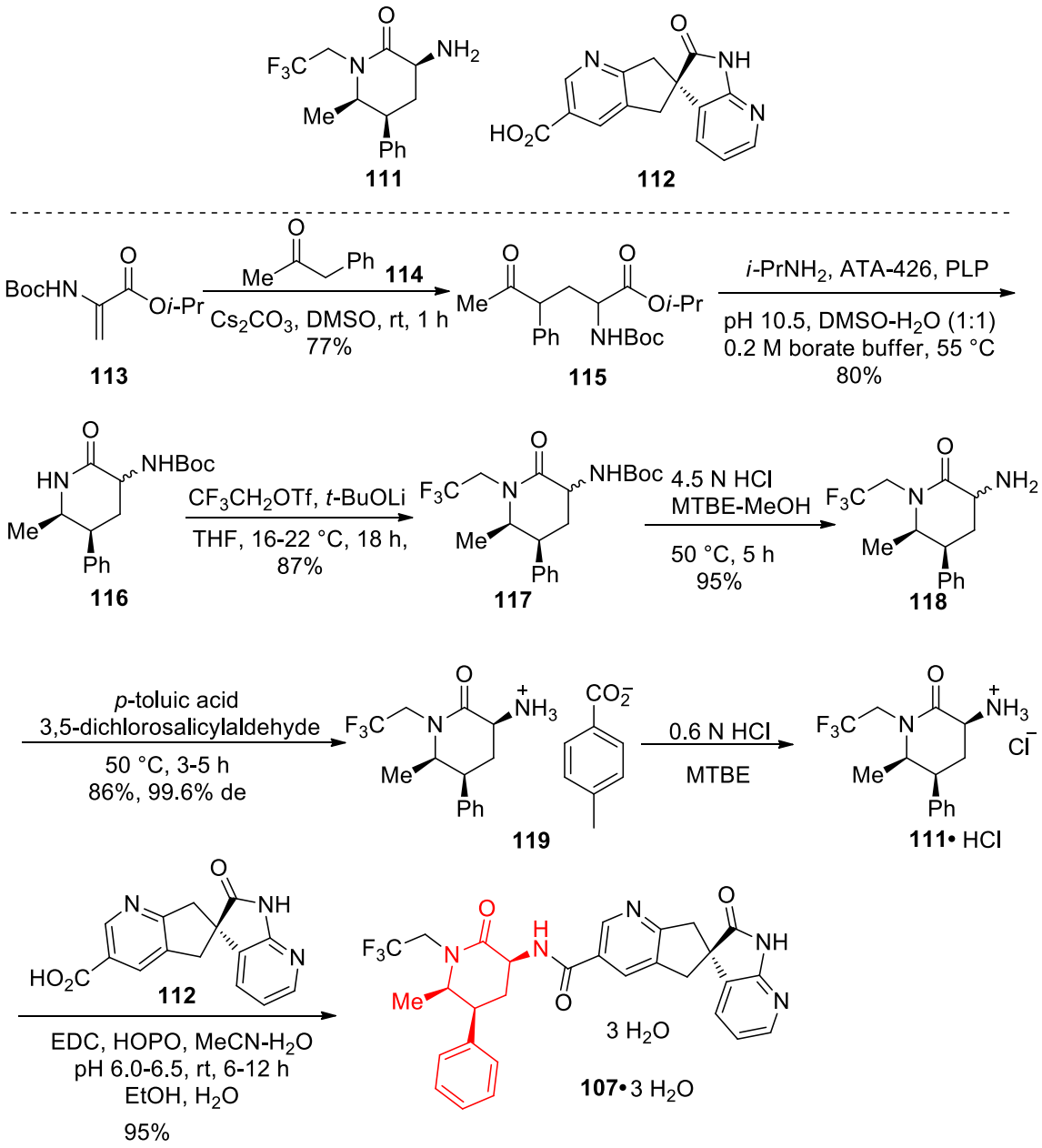


Fig. 17 Chemical Structures of ubrogepant (**107**) and related CGRP receptor antagonists

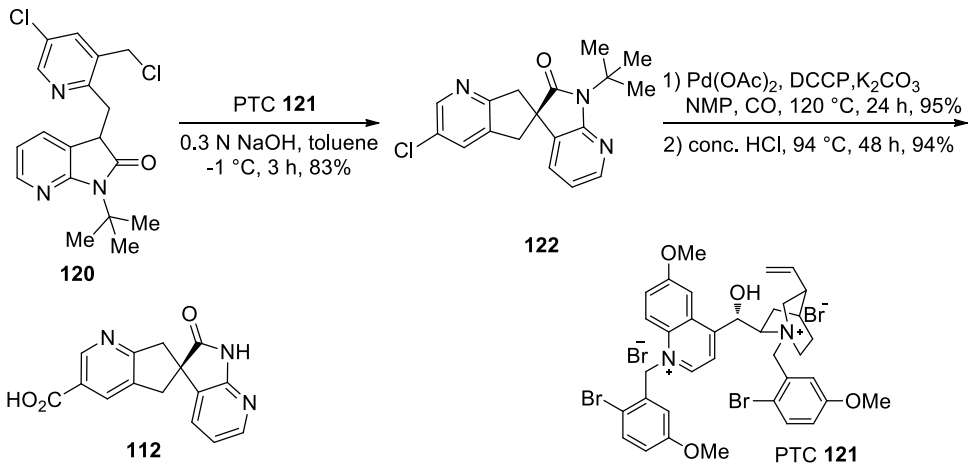


Scheme 13 Synthesis of ubrogepant (**107**)

C5 and C6 (syn/anti > 60:1). The product **116** was isolated as a crystalline 3:2 (*β*:*α*) diastereomeric mixture at the C3 position. A slightly excess *t*-BuOLi and triflate were used to give *N*-alkylation product **117** in a high yield followed by de-Boc to get **118**. Compound **118** was treated with TsOH in the presence of 1 mol % of 3,5-dichlorosalicylaldehyde at 50 °C, crystals precipitated as the pure *β*-isomer of the *p*-toluic acid salt **119** in 86% yield and with a 99.6% de. The stereochemistry at C3 center in **119** was set by a crystallization-induced diastereoselective transformation (CIDT). After a salt break of **119**, the HCl salt of optically pure lactam **111** in the aqueous layer was directly used to react with **112** using EDC as a coupling reagent in the presence of a catalytic amount of 2-pyridinol-1-oxide (HOPO). Ubrogepant (**107**) was formed without epimerization at the α-carbon center of the newly formed amide bond and isolated as a trihydrate in a 95% yield in excellent optical and chemical purities.

The synthesis of acid intermediate **112** is shown in Scheme 14. The spirocyclization of **120** proceeded under basic conditions in the presence of phase transfer catalyst (PTC) **121** gave optical purity **122** in 99.5% ee after crystallization (Xiang et al. 2014). The carbonylation of **122** under the condition exemplified by the Buchwald group gave the

Scheme 14 Synthesis of intermediate **112**



intermediate acid followed by the removal of *t*-Bu group to give compound **112**.

Lumateperone (Caplyta™)

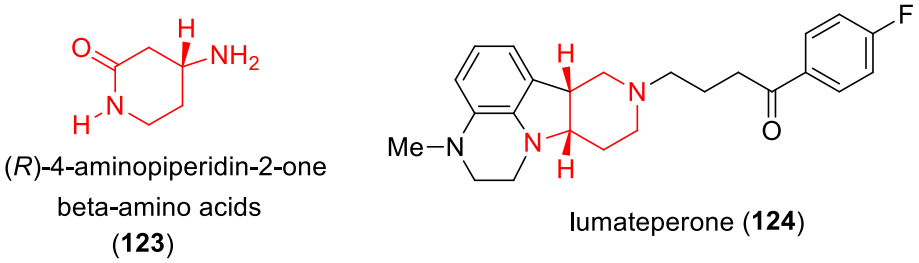
Lumateperone (Caplyta™) (**124**), also known as ITI-007 or ITI-722, is a new oral drug developed by Intra-Cellular Therapies under a license from Bristol-Myers Squibb for the treatment of schizophrenia and other neuropsychiatric and neurological disorders (Fig. 18) (Blair 2020). Lumateperone acts synergistically through multiple systems (serotonergic, dopaminergic, and glutamatergic), thus representing a unique approach for the therapeutic management of a range of neuropsychiatric disorders (Vanover et al. 2019). It possesses a potent antagonistic activity at serotonin 5-hydroxytryptamine 2A (5-HT_{2A}, Ki = 0.54 nM) receptors, and also binds to dopamine D_2 receptors (Ki 32 nM), dopamine D_1 receptors (Ki = 52 nM), and serotonin transporters (SERT, Ki = 62 nM) (Davis et al. 2015; Correll et al. 2020). Preclinical studies demonstrated that lumateperone indirectly modulates glutamatergic phosphoprotein with D_1-dependent augmentation of both NMDA and AMPA activities through the mammalian target of rapamycin (mTOR) pathway, which indicates that it may have potent and quick antidepressant effects (Krogmann et al. 2019; Kumar and Kuhad 2018). The previous results of schizophrenia efficacy studies found robust improvements in depressive as well as psychotic symptoms for those patients with comorbid depression. In various clinical trials to date, the safety profile of lumateperone was found to be similar to that of placebo.

In December 2019, lumateperone received its first global approval in USA for the treatment of schizophrenia in adults. The drug is also under clinical development for bipolar depression, behavioral disorders associated with dementia and Alzheimer's disease, sleep maintenance insomnia, and major depressive disorders. Preclinical development of a long-acting injectable formulation of lumateperone for schizophrenia is also underway in the USA (Blair 2020).

Lumateperone molecule has a (*R*)-4-aminopiperidin-2-one (**123**)-derived quinoxaline-containing tetracyclic core and a side chain (Fig. 18). The quinoxaline core generally exhibits better physicochemical and pharmacological properties, and, consequently, has better in *vivo* efficacy than compounds **125**–**128** with other polycyclic cores (Fig. 19) (Robichaud et al. 2003; Li et al. 2014).

The Bristol-Myers Squibb filed a patent application in 2003 on the synthesis of lumateperone (**124**) (Robichaud et al. 2003). In 2014, the Li group reported two routes for the synthesis of lumateperone (**124**) (Li et al. 2014). In the first route, starting material 3,4-dihydroquinoxalin-2(*1H*)-one **129** was treated with $NaNO_2$ and AcOH to give **130** which was then reduced with Zn to afford **131** (Scheme 15). Fisher-indole cyclization of **131** with ethyl

Fig. 18 Chemical structure of lumateperone (**124**)



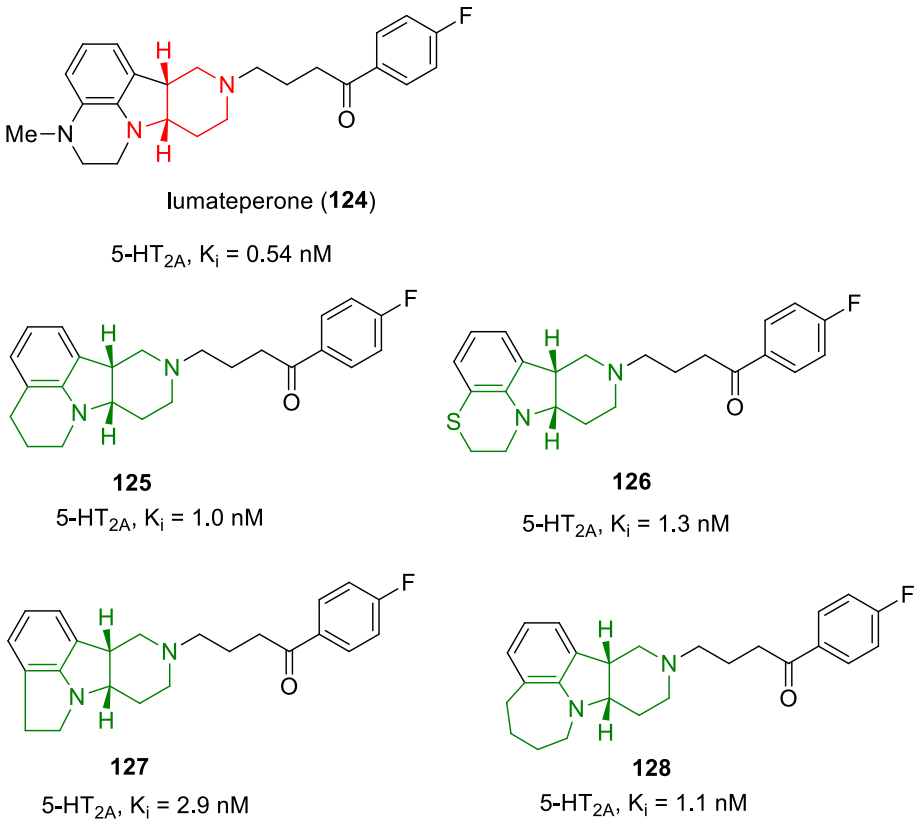


Fig. 19 SAR studies with variations of tetracyclic key unit

4-oxopiperidine-1-carboxylate **132** was used for one-step construction of the tetracyclic core of **133**. *Cis*-reduction of **133** with $NaBH_3CN$ in TFA afforded indoline (*cis*)-**134** which reacted with MeI and NaH to afford *N*-methylation product **135**. Compound **137** was produced through the selective carbonyl reduction of **135** with BH_3 followed by deprotection of **136** with KOH in *n*-butanol. The *p*-fluoro butyrophenone side chain was introduced by *N*-alkylation under basic conditions to give the racemic (*cis*)-**139** which was resolved by chiral chromatograph to afford the (6b*R*,10a*S*)-**124**.

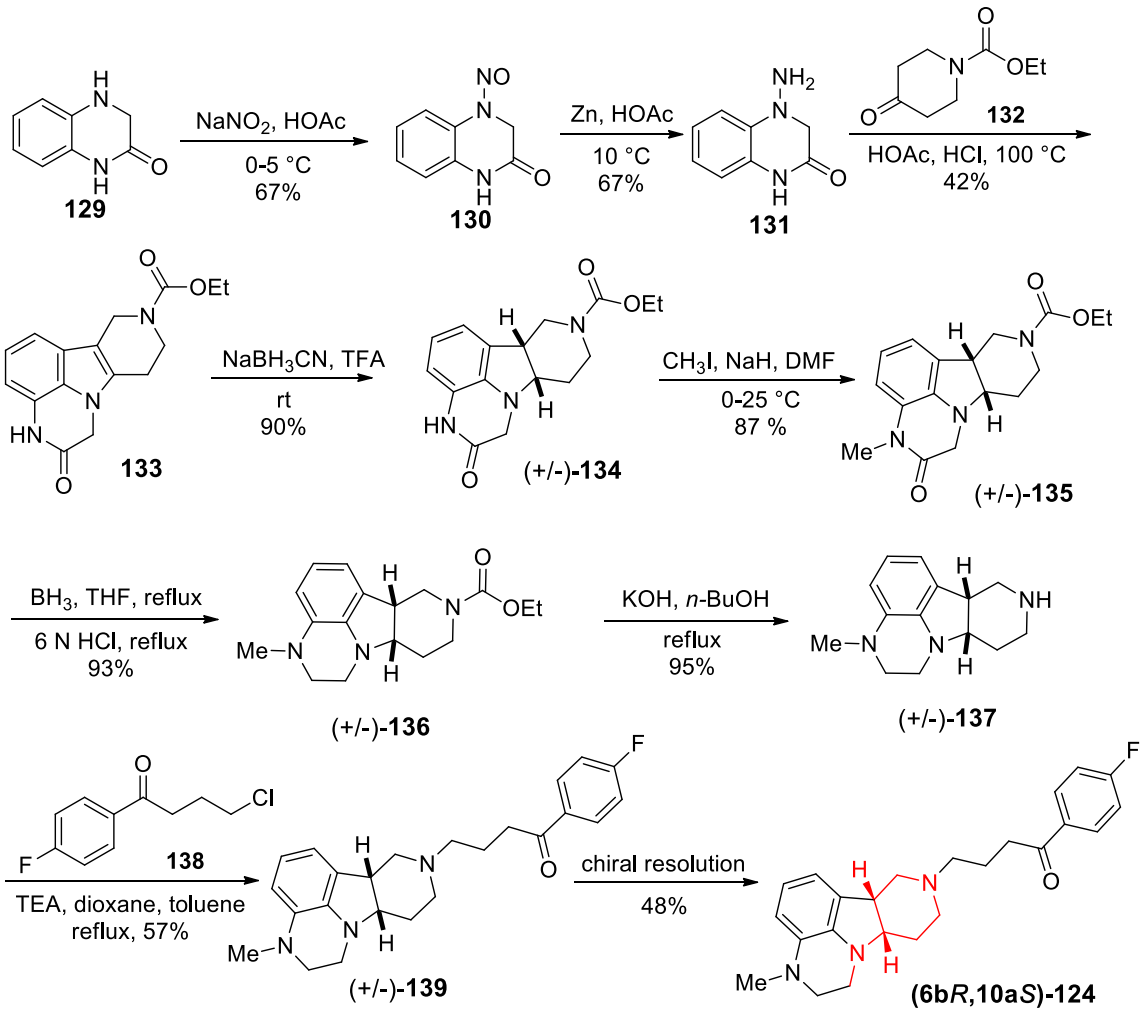
Shown in Scheme 16 is the second route for the synthesis of lumateperone (**124**) at a large scale (Li et al. 2014). Bromophenylhydrazine **140** was treated with **141** for the Fisher-indole cyclization to afford tricyclic indole **142**, which was reduced by triethylsilane in TFA to give racemic and indoline (*cis*)-**143**. The reaction of **143** with ethyl chloroformate afforded **144** which was then coupled with benzophenone imine **145** to afford **146**. *N*-akylation of **146** with ethyl bromoacetate followed by acidic hydrolysis of the diphenylketimine moiety and ring closure to give **134**. *N*-methylation with methyl iodide and reduction with borane afforded **136**. The conversion of **136** to product **124** was accomplished through the same procedures as that in the first route shown in Scheme 16.

Pitolisant (Wakix™)

Pitolisant (Wakix™) (**148**) is a histamine H_3 receptor competitive antagonist and inverse agonist developed by Bioproject Pharma (Fig. 20). It is for the treatment of excessive daytime sleepiness (EDS) in patients with narcolepsy, Parkinson's disease, or obstructive sleep apnoea (OSA) (Schwartz 2011). It can activate histamine release in the brain and enhances wakefulness. Pitolisant binds to H_3 receptors with a high affinity ($K_i = 1$ nM), and has no appreciable binding to other histamine receptors (H_1, H_2, or H_4 receptors; $K_i > 10$ μM) (Li and Yang 2020). Patients taking pitolisant exhibited significantly reduced EDS compared with placebo, but was not non-inferior to treatment with modafinil (Dauvilliers et al. 2013).

Pitolisant was approved as an oral drug in the European Union (EU) for the treatment of narcolepsy with or without cataplexy in adults (Syed 2016). In 2019, pitolisant was approved by the US FDA for treatment of EDS in adult patients with narcolepsy (Thorpy 2020).

Pitolisant (**148**), also named as FUB 649, contains a 3-(piperidin-1-yl)propanoic acid (**147**) derived amino ether moiety (Fig. 20). Extensive structure–activity relationship (SAR) studies have shown that *N*-piperidyl derivative



Scheme 15 First route for the synthesis of lumateperone (**124**)

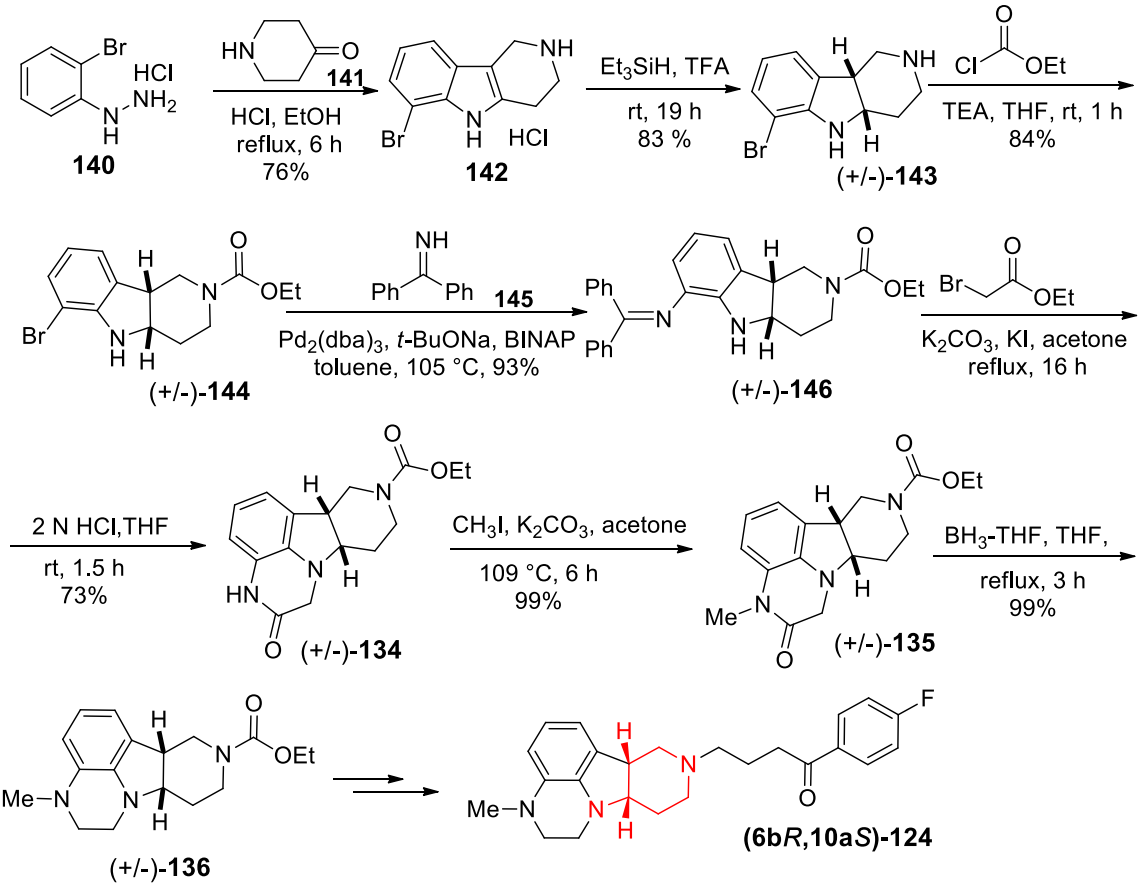
pitolisant gave the best result (Schwartz et al. 2000). For example, variation of piperidyl group to azepanyl group (**149**) or pyrrolidinyl group (**150**) led to increased K_i values (9 nM and 20 nM, respectively) (Fig. 21).

The synthetic method developed by Bioprojet Pharma is shown in Scheme 17. Starting material 3-(piperidin-1-yl) propan-1-ol (**152**) was treated with NaH to give sodium salt **153** which was then reacted with 3-(4-chlorophenyl) propyl methanesulfonate (**154**) under 15-crown-5 ether as a PTC for *O*-alkylation to give **148** (Schwartz et al. 2000). Compound **148** was salted with oxalic acid in a mixed solvent of ether and methanol to give pitolisant oxalate of **148**. This route used 15-crown-5 ether which posed problems such as high cost, high toxicity, and difficult post-processing. The purification of compound **148** requires column chromatography which was not suitable for industrial production. In addition, the mesylate **154** may have potential genotoxicity (Paim et al. 2013).

In 2014, an improved synthetic method for the preparation of pitolisant (**148**) was developed to avoid the using of mesylate (Scheme 18) (Hu et al. 2014). In this process, key intermediate 1-(3-bromopropyl)piperidine (**155**), prepared by *N*-alkylation of piperidine with 1,3-dibromopropane, was reacted with 3-(4-chlorophenyl)propan-1-ol (**156**) in the presence of NaH to give pitolisant (**148**) which was further converted to a salt by reacting with HCl gas. Recrystallization from EtOAc provided pitolisant hydrochloride.

Siponimod (Mayzent™)

Siponimod (Mayzent™), also known as BAF312, is a structural analog of sphingosine, which is an endogenous sphingolipid involved in the regulation of a variety of biological functions, including lymphocyte trafficking, cardiomyocyte function, vascular development, and cell survival (Fig. 22)



Scheme 16 Second route for the synthesis of lumateperone (**124**)

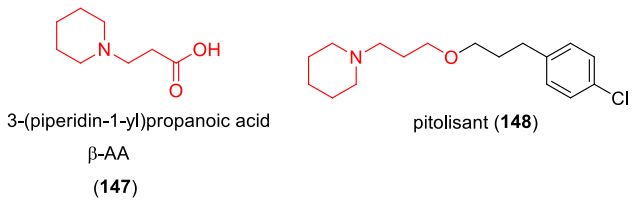


Fig. 20 Chemical structure of pitolisant (**148**)

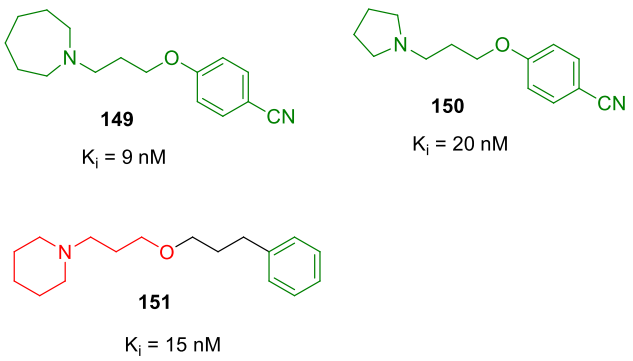
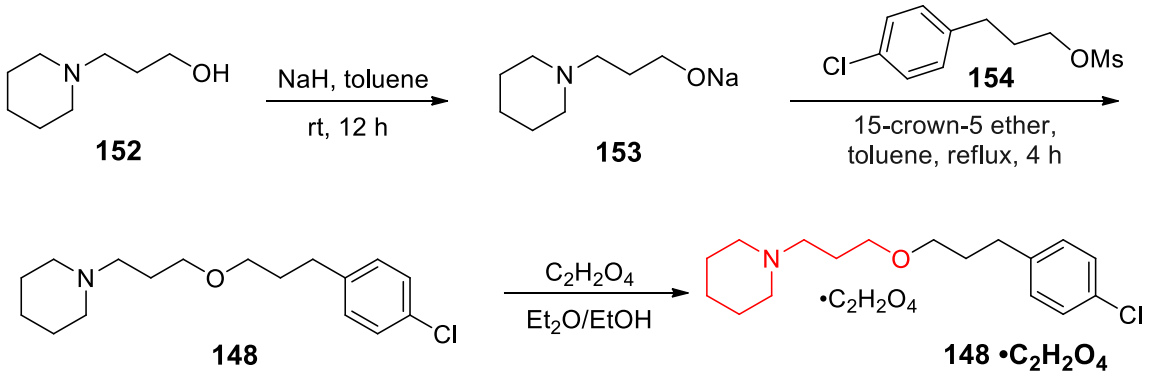


Fig. 21 SAR studies with variations of tetracyclic key unit

(Gajofatto 2017). Siponimod (**158**) is an oral selective sphingosine 1-phosphate receptor subtypes 1 and 5 ($S1PR_{1,5}$) modulator being developed by Novartis for the treatment of multiple sclerosis (MS) and intracerebral hemorrhage (Chaudhry et al. 2017). Siponimod binds with high affinity to subreceptors 1 and 5 ($S1PR_{1,5}$, EC_{50} values of 0.39 and 0.98 nM) and spares subreceptors 2, 3, and 4 ($S1PR_{2,34}$, $EC_{50} > 10{,}000, > 1000$, and 750 nM, respectively). Siponimod induces lymphopenia by preventing lymphocyte egress from lymph nodes. In healthy individuals, siponimod reduces circulating T and B cells within 4–6 h. Siponimod has a relatively short half-life and lymphocyte counts recover to baseline levels within a week after stopping treatment, but would allow once-daily oral dosing (Gergely et al. 2012).

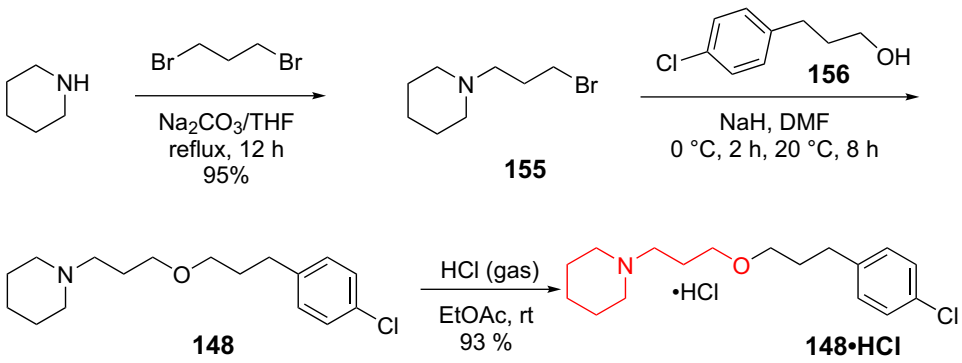
In March 2019, siponimod received its first global approval in USA for the treatment of adults with relapsing forms of MS, including clinically isolated syndrome, relapsing–remitting disease, and active secondary progressive disease. Siponimod is under-regulatory review in the EU and Japan for secondary progressive MS (Al-Salama 2019b).

Siponimod (**158**) was identified by de novo design, which contains an azetidine-3-carboxylic acid (**157**)



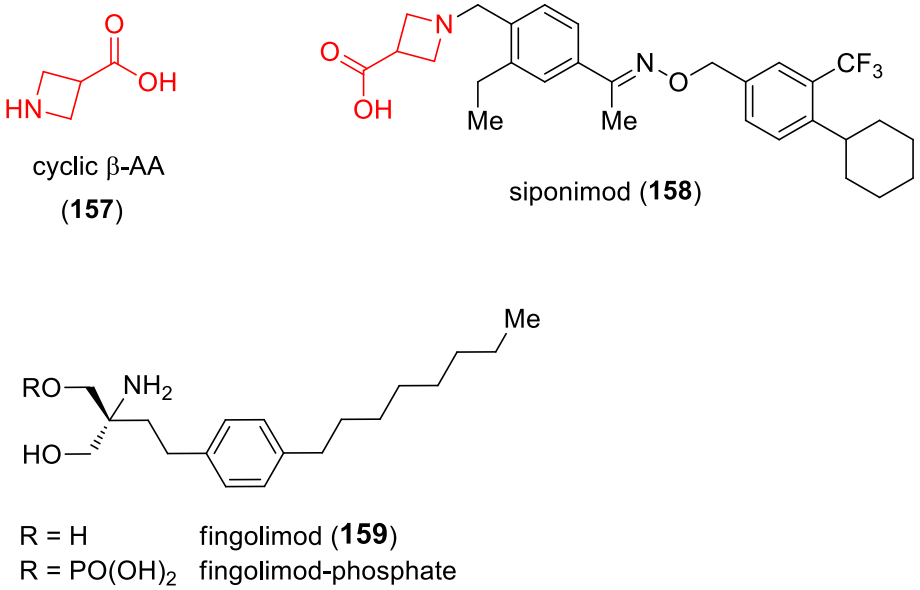
Scheme 17 Synthesis of pitolisant (**148**) and its salt

Scheme 18 Synthesis of pitolisant (**148**) and its salt



derived amino acid moiety (Fig. 22). Siponimod (**158**) used fingolimod (**159**) (FTY720) as the chemical starting point. Fingolimod has nonspecific-binding selectivity, and the volume of distribution was large and long elimination half-life. Through the structure–activity relationships (SAR) date, analogs containing substituted benzyloxy oximes that replace the *n*-octyl moiety were equally efficacious as fingolimod in inducing lymphocyte redistribution.

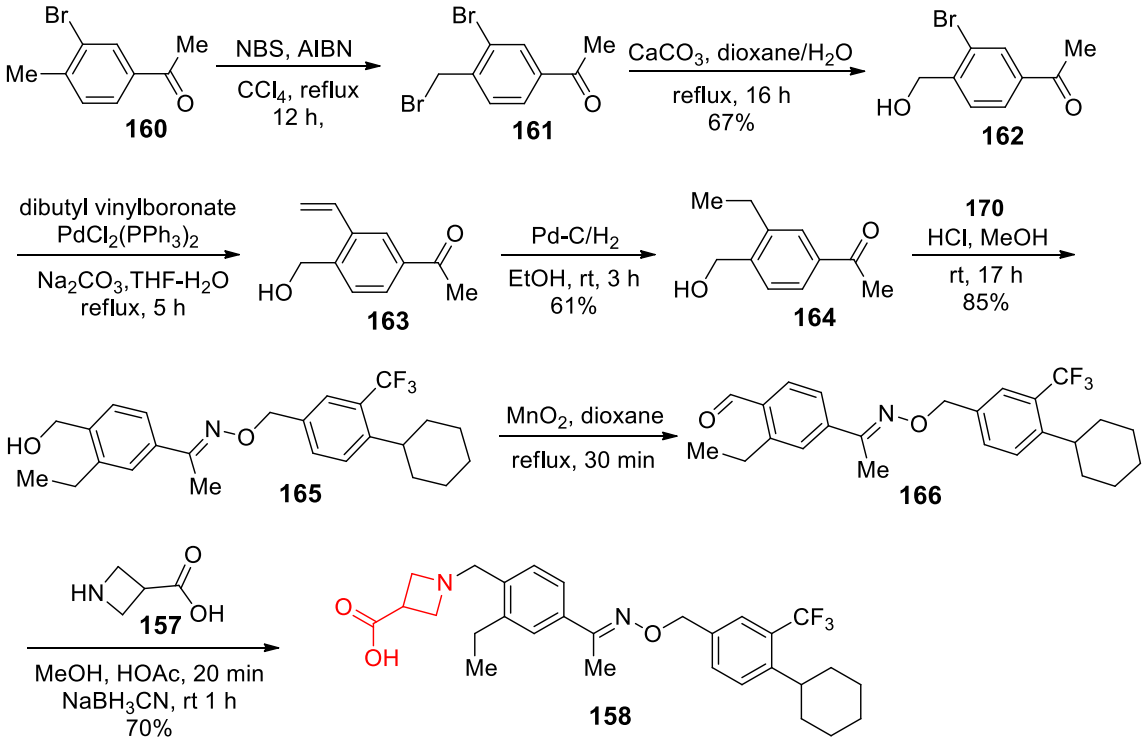
Fig. 22 Structures of siponimod (**158**) and fingolimod (**159**)



Siponimod was finally discovered by replacing the phosphate moiety with a carboxylic acid (Gergely et al. 2012; Briard et al. 2015).

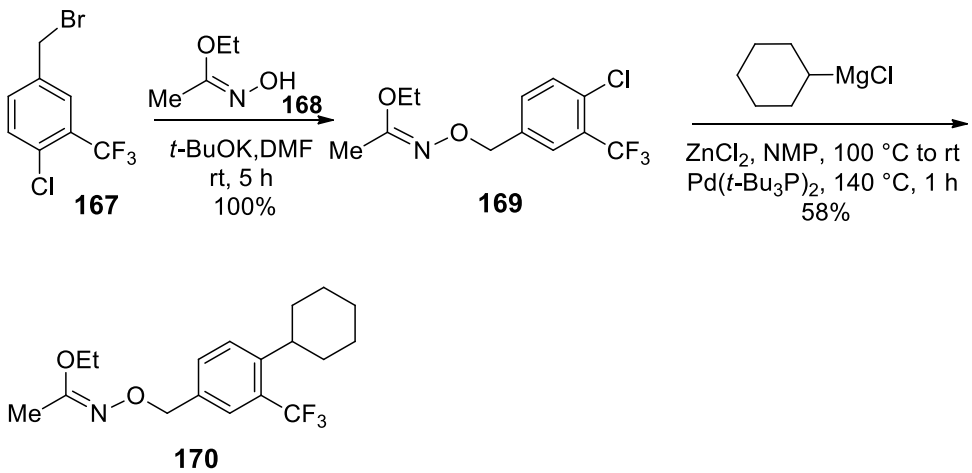
A synthetic route for siponimod was reported by Novartis in 2013 (Scheme 19) (Pan et al. 2013). Ketone **160** was converted to alcohol **162** by benzylic bromination with NBS in the presence of AIBN and then hydrolyzed under basic conditions. The Suzuki coupling reaction of **162** and dibutyl vinylboronate gave intermediate **163** which was hydrogenated to **164** by Pd–C/H_2. Condensation of **164** with oxyacetamidate intermediate **170** under an acidic condition yielded **165** which was treated with MnO_2 to provide aldehyde **166**. Reductive amination of **166** with azetidine-3-carboxylic acid **157** gave product **158**.

The synthesis of oxyacetamidate intermediate **170** is shown in Scheme 20. *O*-alkylation of **168** with **167** using *t*-BuOK as a base gave **169** which was then treated with cyclohexyl magnesium chloride in the presence of Pd catalyst to give oxyacetamidate **170**.



Scheme 19 Synthesis of siponimod (**158**)

Scheme 20 Synthesis of intermediate **170**



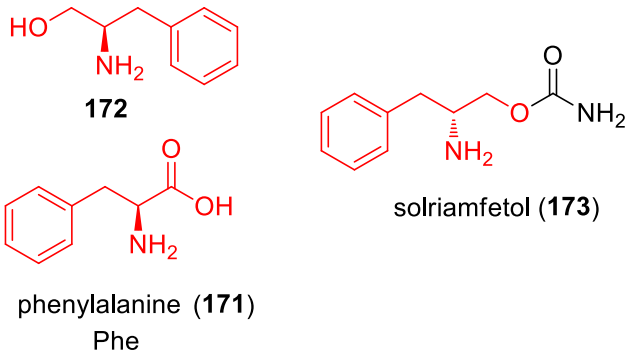


Fig. 23 Chemical structure of solriamfetol (**173**)

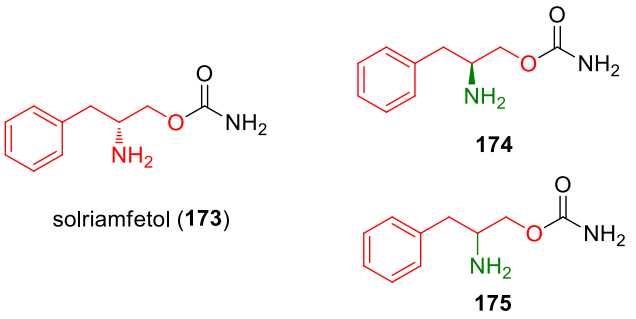


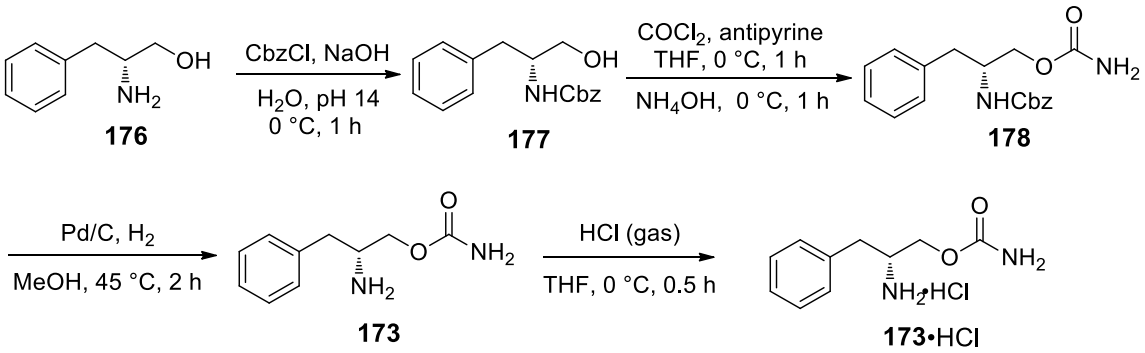
Fig. 24 Chemical structures of solriamfetol (**173**) and related dopamine and norepinephrine reuptake inhibitors

Solriamfetol (Sunosi™)

Solriamfetol (Sunosi™) (**173**), formerly known as JZP-110, is a selective dopamine and norepinephrine reuptake inhibitor (DNRI) (Fig. 23). It was discovered by SK Biopharmaceuticals and developed by Jazz Pharmaceuticals (Markham 2019c). The affinity of solriamfetol for these monoamine transporters dopamine transporter (DAT, $K_i = 14.2$ μM), norepinephrine transporter (NET, Ki = 3.7 μM), and serotonin transporter (SERT, $K_i = 81.5$ μM) was lower than that of cocaine in transfected cells and inhibits dopamine and norepinephrine reuptake with low potency ($IC_{50} = 2.9$ and 4.4 μM, respectively) (Baladi et al. 2018). In 2019, US FDA approved solriamfetol for using as an oral drug to improve wakefulness in adult patients with excessive daytime sleepiness associated with narcolepsy or obstructive sleep apnoea (OSA). It was granted as an orphan drug (Schweitzer et al. 2019).

The systematic name of solriamfetol is (*R*)-2-amino-3-phenylpropylcarbamate hydrochloride, which contains a phenylalanine (**171**)-derived (*R*)-2-amino-3-phenylpropan-1-ol (**172**) moiety (Fig. 23). Some alkyl carbamates have been introduced for controlling various central nervous system (CNS) disorders. Phenylethylamine derivatives are one of the important class of therapeutical medicines, useful for managing CNS diseases. After an intensive research, these two skeletons were combined to produce solriamfetol (**173**) as a drug for the treatment of CNS disorder, especially for depression. The compound **174** with a (*S*) carbon center showed almost no activity at all, which the racemic compound **175** displayed a half potency of the activity (Fig. 24) (Yang and Gao 2019; Choi and Byun 1996).

Solriamfetol (**173**) was discovered and patented by SK Biopharmaceuticals in 1996 (Choi and Byun 1996). The synthesis of solriamfetol using (D)-phenylalaninol (**176**) as a starting material is highlighted in Scheme 21. (D)-Phenylalaninol (**176**) was first converted to Cbz-protected D-phenylalaninol **177** by reacting with benzyl chloroformate. Carbamoylation of **177** with phosgene followed by ammonolysis with excess of concentrated ammonium hydroxide aqueous solation afforded (D)-*O*-carbamoyl-*N*-benzyloxycarbonylphenylalaninol **178**. Hydrogenolysis removal of the Cbz protection group gave solriamfetol **173** which was treated

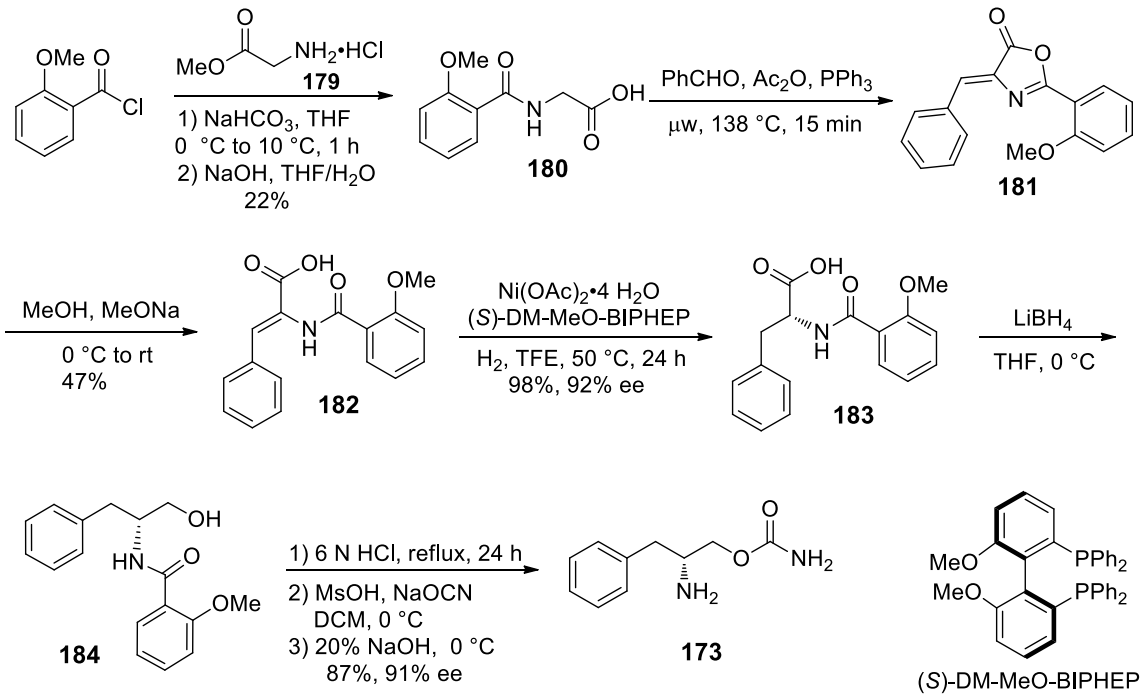


Scheme 21 Synthesis of solriamfetol (**173**)

with HCl (gas) to provide (D)-*O*-carbamoylphenylalaninol hydrochloride salt.

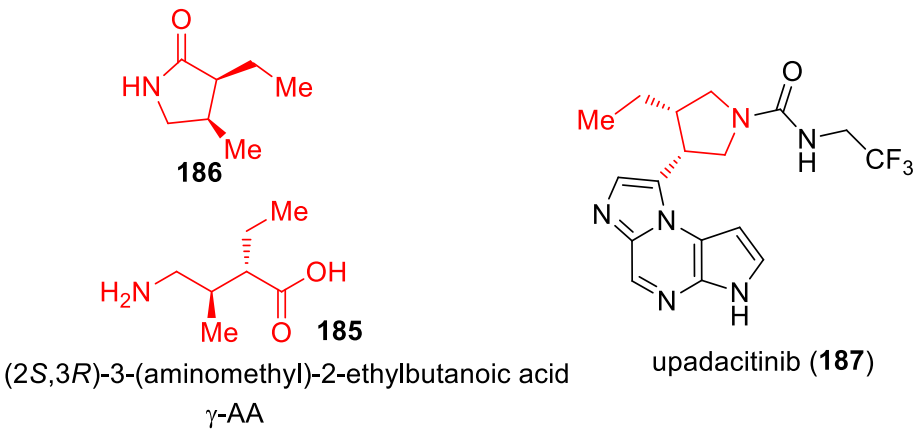
In 2020, the Zhang lab reported a method of Ni-catalyzehd asymmetric hydrogenation of 2-amidoacrylates for making solriamfetol (**173**) (Hu et al. 2020). In this method, *o*-methoxybenzoyl chloride reacted with glycine methyl ester hydrochloride **179** under a base condition and then hydrolysised in the presence of NaOH to afford desired *o*-methoxyhippuric acid **180**. The one-step construction of oxazolone **181** was accomplished by cyclization and condensation of **180** with benzaldehyde in acetic anhydride and PPh_3. Oxazolone **181** was then treated with MeOH and NaOMe to afford 2-amidoacrylate **182**. Hydrogenation of **182** using Ni salt and ligand (*S*)-DM-MeO-BIPHEP gave product **183** in 92% ee. The reduction of **183** with $LiBH_4$ followed by hydrolysised in the presence of NaOH provided intermediate (D)-phenylalaninol **184**. Then, (D)-phenylalaninol **184** was reacted with NaOCN yielded solriamfetol (**173**) in 91% ee (Scheme 22).

As a general comment related to this and other chiral compounds discussed here, we would like to emphasize the growing awareness about the Self-Disproportionation of Enantiomers (SDE) phenomenon and the problems related to accurate determination of the stereochemical outcome of enantioselective catalytic reactions (Han et al. 2018, 2019b, 2011a; Soloshonok et al. 2017; Sorochinsky et al. 2013c,



Scheme 22 An alternative route for solriamfetol (**173**)

Fig. 25 Chemical structure of upadacitinib (**187**)

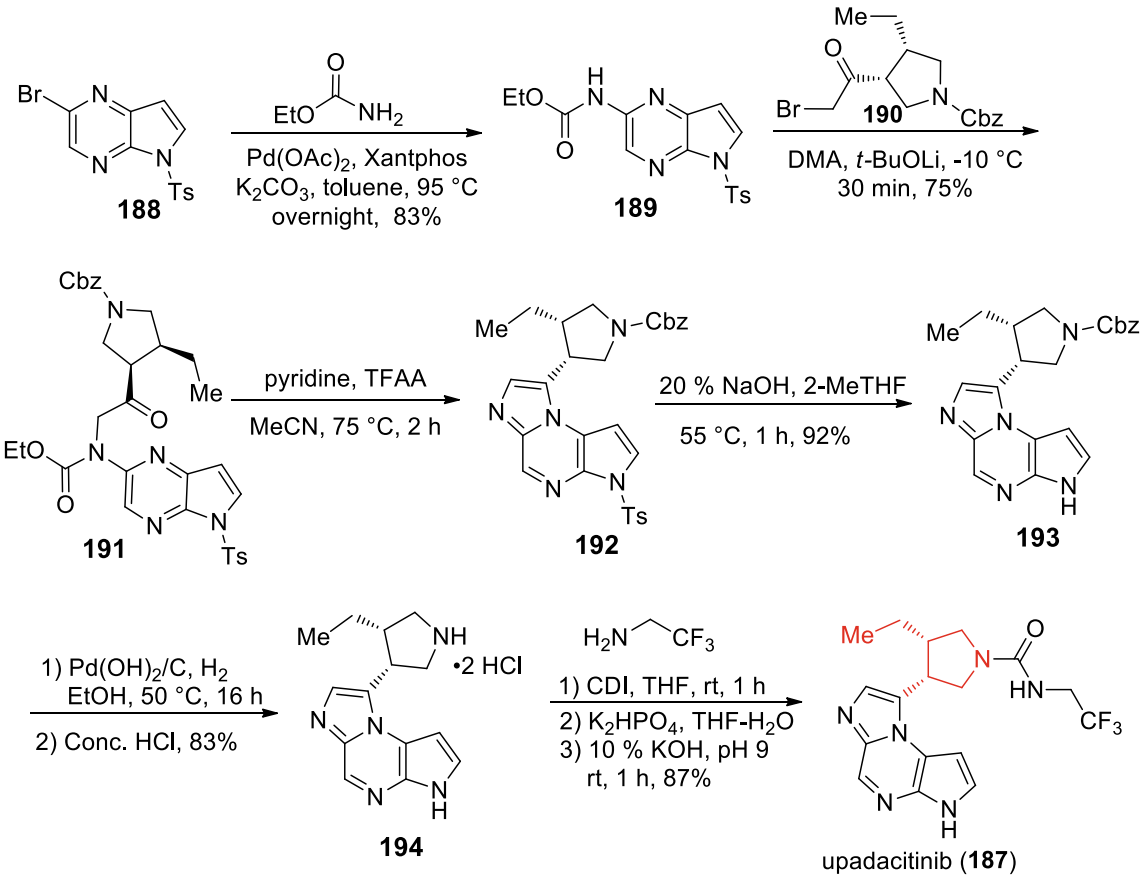


2013d). It was demonstrated that the SDE phenomenon is ubiquitous, being manifested virtually by all types of chiral compounds subjected to physicochemical phase transfer under totally achiral conditions (Han et al. 2019b; Soro-chinsky et al. 2013c, d). One of the most frequent cases is a separation of more and less enantiomerically enriched fractions as compared with the original enantiomeric purity of a chiral compound. Consequently, to ensure the accuracy in the %ee determination, it was suggested to perform SDE tests, in particular, under the conditions of achiral column chromatography (Soroshinsky et al. 2013c) and sublimation (Han et al. 2011a).

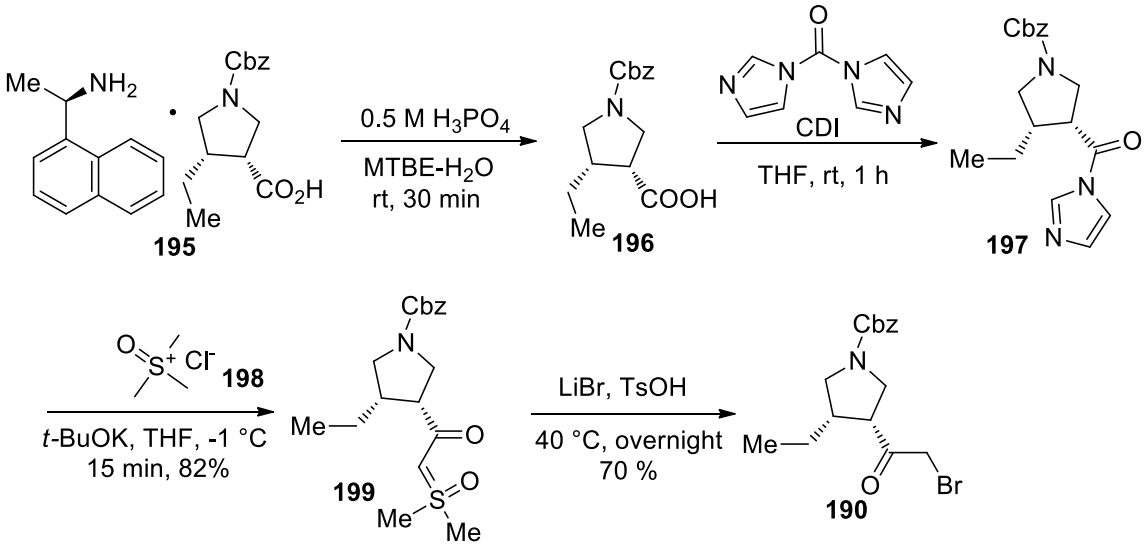
Upadacitinib (Rinvoq™)

Upadacitinib (Rinvoq™) (**187**), also known as ABT-494, contains a tricyclic core and an amino acid **185**-derived pyrrolidine moiety (Fig. 25). It is an orally administered Janus kinase 1 (JAK-1) inhibitor developed by the biotech company AbbVie for the treatment of rheumatoid arthritis and other immune-mediated inflammatory diseases. The first generation of non-selective JAKs inhibitors has been proven safe, efficacious, and has a broad inhibiting spectrum for cytokines inevitably leads to side effects by inhibiting many factors that can drive immunopathology (Shu et al. 2020). As a second-generation JAKs' inhibitor, upadacitinib is more selective, and it has IC_{50} of 14 nM in cellular assays, which was 42-fold selective for JAK1 over JAK-2 (IC_{50} = 593 nM), 133-fold selective over JAK-3 (IC_{50} = 1860 nM), and 194-fold selective over TYK-2 (IC_{50} = 2715 nM) (Parmentier et al. 2018).

On the basis of positive results from multinational clinical trials on patients with rheumatoid arthritis (O'Shea and Gadina 2019), upadacitinib was first approved by US FDA in August 2019 for the treatment of moderately-to-severely active rheumatoid arthritis (RA) and an inadequate response or intolerance to methotrexate. In December 2019, it was additionally approved by the European Commission for the same indication in patients with inadequate response or intolerance to one or more DMARDs and can be used as monotherapy or in combination with methotrexate. Clinical development of upadacitinib for the treatment of atopic dermatitis, Crohn's disease, psoriatic arthritis, ulcerative colitis, ankylosing spondylitis, and giant cell arteritis is currently underway (Duggan and Keam 2019).



Scheme 23 Synthesis of upadacitinib (**187**)



Scheme 24 Synthesis of bromomethyl ketone intermediate **190**

A synthetic route for upadacitinib (**187**) was reported by AbbVie in 2019 (Scheme 23) (Pangan et al. 2020). The Pd-catalyzed coupling reaction between 2-bromo-5-tosyl-5H-pyrrolo[2,3-*b*]pyrazine (**188**) and ethyl carbamate gave carbamate intermediate **189**. It was surprisingly discovered that when ethyl carbamate was used, compound **191** and subsequent compounds could be isolated as crystalline solids, which eased the purification of these intermediates. In contrast, a previously reported processes of using *t*-butyl carbamate gave compound **191** which was isolated as amorphous solids. The deprotonation of **189** by *t*-BuOLi in DMA, followed by a substitution reaction with pre-synthesized **190,** afforded intermediate **191**. Cyclization of **191** in the presence of trifluoroacetic anhydride (TFAA) and pyridine produced **192** which was then hydrolyzed with 20% of NaOH at 55 °C to give **193**. Hydrogenative Cbz deprotection with $Pd(OH)_2/C$ followed by the treated with HCl gave salt **194**. At the final step, salt **194** was neutralized with 10% KOH solution and then reacted with 2,2,2-trifluoroethylamine and CDI to get upadacitinib (**187**).

The synthesis of bromomethyl ketone intermediate **190** is shown in Scheme 24 (Pangan et al. 2020). Amino acid salt **195** was first treated with H_3PO_4 to give free acid **196** which was used for the reaction with CDI to form intermediate **197**. Sulfur ylide **199** was prepared by the treatment of **197** with trimethylsulphoxonium chloride **198** under a strong basic condition. Then, **199** reacted with LiBr and TsOH to give bromomethyl ketone **190**. In a previous patent filed by AbbVie, hazardous reagent trimethylsilyldiazomethane was used for the preparation of bromomethyl ketone **190** (Wishart et al. 2013).

Conclusions

This review article was written to emphasize the importance of tailor-made AAs in the modern drug design. It is estimated that about 30% of current pharmaceuticals are derived from AAs, including the fragments of closely related di-amines and amino-alcohols. We hope that the examples discussed in this article convincingly highlighted the structural and functional diversity provided by tailor-made AAs. The truly unique position of AAs as building blocks is that they are found in all three general classes of modern pharmaceuticals, which include, small molecules, peptides, and proteins. Consequently, regardless of the future trends, tailor-made AAs will remain in demand as key structural/functional components in drug design.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing financial interests.

Ethical approval All the study procedures were in accordance with the ethical standards.

Informed consent Written informed consents were obtained from all participants.

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