Indian Journal of Advances in Chemical Science

Article

New Drugs Approved by Food and Drug Administration in 2019 and Their Synthetic Approaches

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ABSTRACT

Every year several drugs were introduced into the market having particular biological applications. These new drugs will provide understanding of molecular recognition which will lead to new drugs synthesis. This review describes the synthetic approaches of 21 new chemical entities that were approved in 2019.

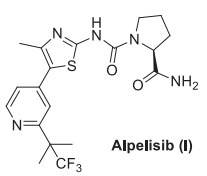
Key words: Food and drug administration approved drugs, Synthesis, 2019, New drugs

1. INTRODUCTION

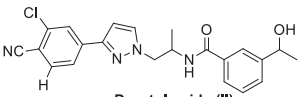
"*The most fruitful basis for the discovery of new a drug is to start from an old drug.*" – Sir James Whyte Black, winner of the 1988 Nobel Prize in medicine [1].

Inaugurated 16 years ago [2], this annual review presents synthetic methods for molecular entities that were approved for the first time by the governing bodies within various countries in the year 2019. Because drugs can have structural homology across similar biological targets, it is widely believed that the knowledge of new chemical entities (NCEs) and approaches to their construction will enhance the ability to discover new drugs more efficiently. A total of 48 new products, including NCEs, biological drugs, and diagnostic agents reached the market this year [3]. This review describes the most likely process-scale synthetic approaches to 28 small-molecule NCEs that were approved for the first time by the food and drug administration (FDA). This review attempts to present the most scalable routes for synthesis based on published or patent literature and is arranged in alphabetical order by the drug's generic name. The year 2019 has been a significant breakthrough within the field of cancer as well as in the field of CNS related diseases. A total of 11 new drugs are introduced for the treatment of various types of cancer. Besides this, ten new molecules are introduced for the treatment of various neurological disorders. New indications for previously launched medications, new combinations or formulations of existing drugs, and drugs synthesized purely through bioprocesses or peptide synthesizers have been excluded from this review. The synthetic schemes described in this review have all been previously published in the public domain.

Anti-cancer Drugs



Alpelisib (I)



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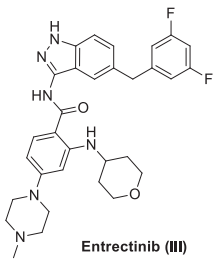

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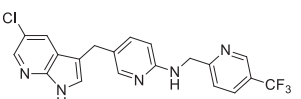

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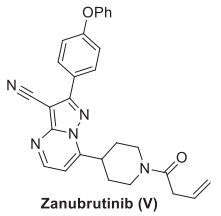
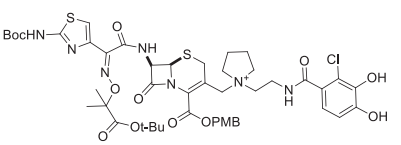
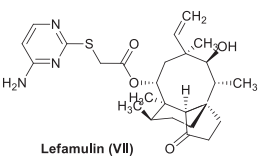


Zanubrutinib (V)

Anti-infective Drugs



Cefiderocol (VI)



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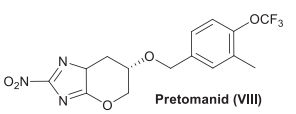
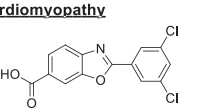


Pretomanid (VIII)

Cardiomyopathy



Tafamidis (XII)

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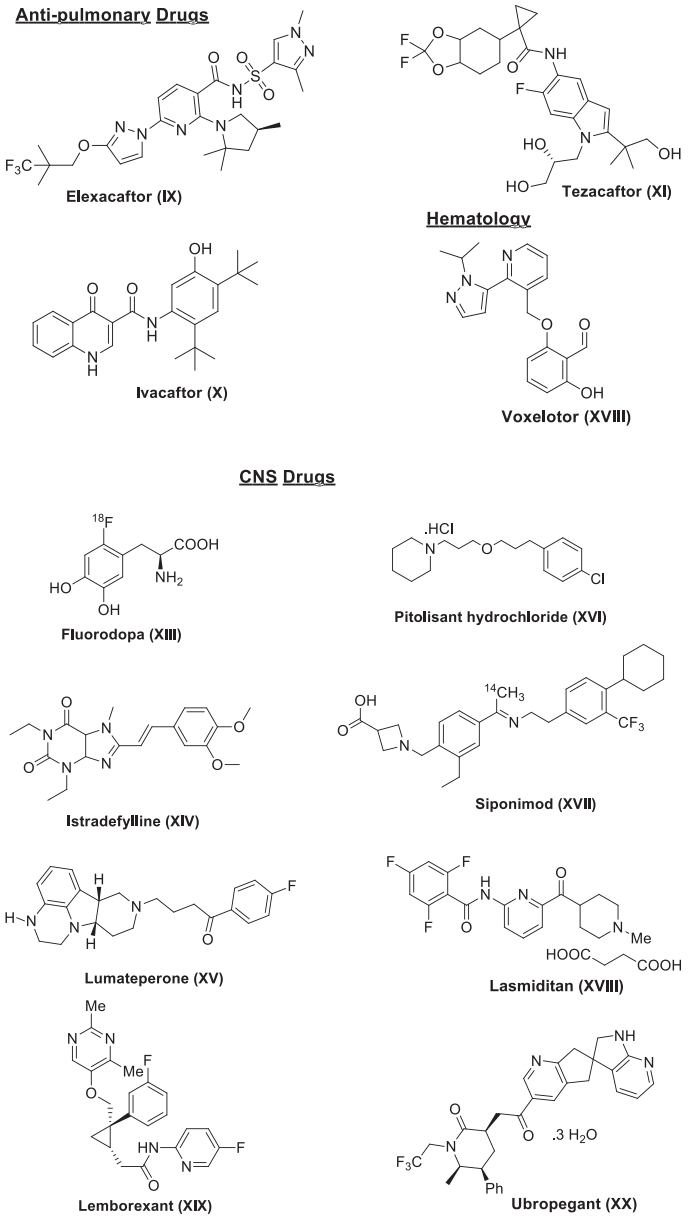
ISSN NO: 2320-0898 (p); 2320-0928 (e)
DOI: 10.22607/IJACS.2020.803005

Received: 21st June 2020;
Revised: 5th August 2020;
Accepted: 10th August 2020



2. ANTI-CANCER DRUGS

2.1. Alpelisib

Originally developed by Novartis Oncology which is a phosphatidylinositol 3-kinase (PI3K) inhibitor with specific activity against PI3K-alpha (PI3K-α) for the treatment of breast cancer. It is approved by US FDA in May 2019 to treat postmenopausal women in combination with fulvestrant. Mutation of PIK3CA gene encodes the catalytic (p110α) subunit of PI3K is observed in solid tumors including 40% of breast cancers [4,5]. The recommended dose of alpelisib is 300 mg once daily, in the event of adverse reactions the dose of alpelisib should be reduced to 250 mg once daily [6].

Several synthetic routes for alpelisib have been reported [7] the majority of these routes, including the route reported by Novartis, was described herein.

4,4,4-Trifluoro-3,3-dimethylbutanoic acid **1** was converted into corresponding acid chloride **2** using oxalyl chloride which on further reaction with enolized (E)-4-methoxy-3-buten-2-one afforded 2-(1,1,1-trifluoro-2-methylpropan-2-yl)-4H-pyran-4-one **3** in 55% yield. Compound **4** was prepared by heating compound **3** with aqueous ammonia in 65% yield. Compound **4** on bromination with $POBr_3$ yields compound **5** which is on direct arylation reaction with 4-methyl-2-acetamidothiazole using palladium acetate afforded compound **6**. Compound **6** on deprotection under acidic conditions gives compound **7** which was then converted to alpelisib by the introduction of the prolineamide urea function through the imidazolide (Scheme 1).

2.2. Darolutamide

Darolutamide is an androgen receptor inhibitor, developed by Orion Corporation and Bayer HealthCare to treat adult patients with non-metastatic castration-resistant prostate cancer. The title compound received its first approval on July 30, 2019, by the US FDA [8,9]. Androgen receptor is a potent target for CRPC therapy [10]. It competitively inhibits androgen binding, androgen receptor nuclear translocation, and androgen receptor-mediated transcription [11]. The recommended daily dosage of darolutamide is 1200 mg, i.e., two 300 mg of film-coated tablets to be taken orally twice a day. This is equivalent to 600 mg per dose of the drug. In case of an adverse reaction, the dosage is either withheld or reduced to 300 mg twice daily until symptoms improve [12].

Several methods for the synthesis of darolutamide are reported including the one described herein [13].

Bromination of 3-chloro-5- fluoroaniline **9** using N-bromosuccinimide gives compound **10**, which on reaction with copper (I) cyanide afforded nitrile **11**. Compound **12** formed by diazotizing compound **11**, couples with **13** through Suzuki coupling to afford compound **14**. Compound **14** was refluxed overnight under suitable conditions to yield **15**, which was then coupled with **16** through Suzuki coupling to yield compound **17**. Compound **17** forms an amide bond with **18** to yield compound **19**, which finally produced darolutamide after reduction with sodium borohydride (Scheme 2).

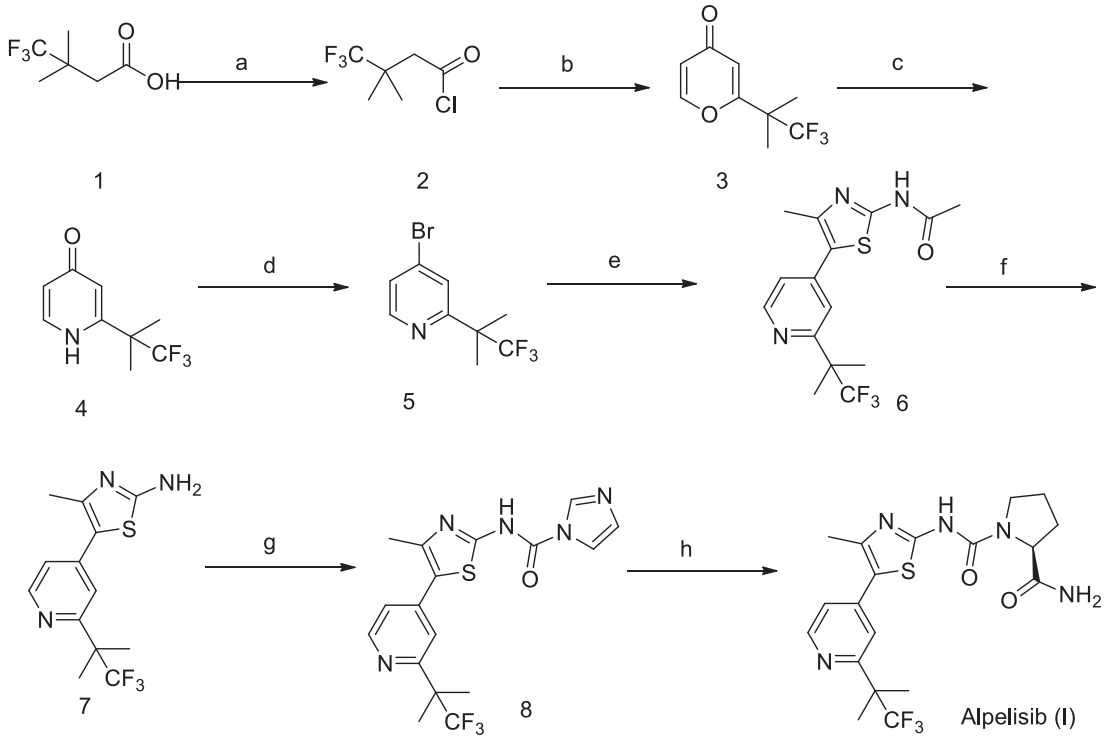
2.3. Entrectinib

Originally developed by Roche, entrectinib received its first approval on June 18, 2019, in Japan to treat adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are ROS1-positive. It also received approval to treat adult and pediatric patients 12 years of age and older with solid tumors [14,15]. Overexpression of the tyrosine kinases in cancer cells contributes to increased cell proliferation. Gene rearrangements in these target kinases can activate and dysregulate gene expression and signaling [16,17]. Entrectinib is a potent inhibitor of the tyrosine kinases TrkA/B/C (encoded by the gene *NTRK1/2/3*), and ROS1. The recommended dosage for NSCLC with positive *ROS1* is 600 mg orally once daily, and for *NTRK* gene fusion-positive solid tumors the recommended dosage for adults is 600 mg orally once daily. For pediatric patients age 12 and older, the recommended dosage is based on body surface area [18].

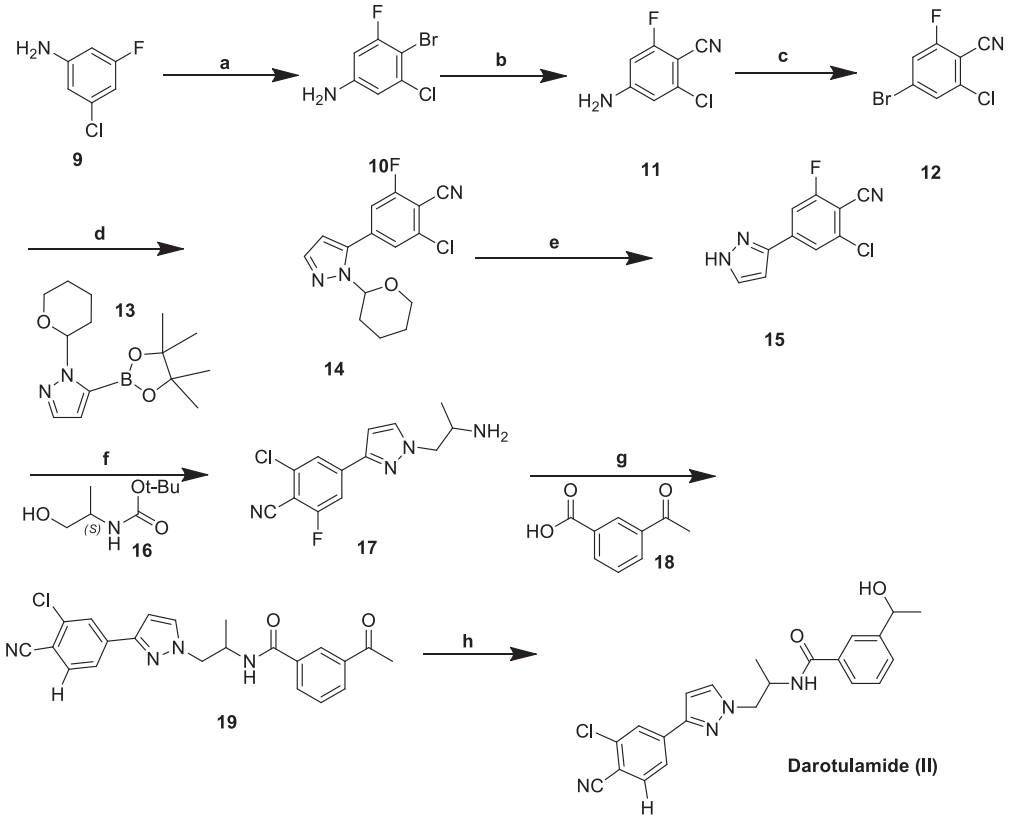
Various schemes have been reported for the synthesis of entrectinib. The one explained in this review is using readily available starting materials [19]. Entrectinib was synthesized through an amide bond formation between the properly protected acid **25** and compound **23**, which was again synthesized from easily available starting material **20**. Commercially available 3-cyano-4-fluorophenylboronic acid **20** undergoes Suzuki-Miyaura cross-coupling with benzyl bromide **21** to produce compound **22**, which further undergoes reduction at the cyanide center to form amine **23**. Compound **25** was prepared by protecting the acid group of the commercially available compound **24** (Scheme 3).

2.4. Pexidartinib

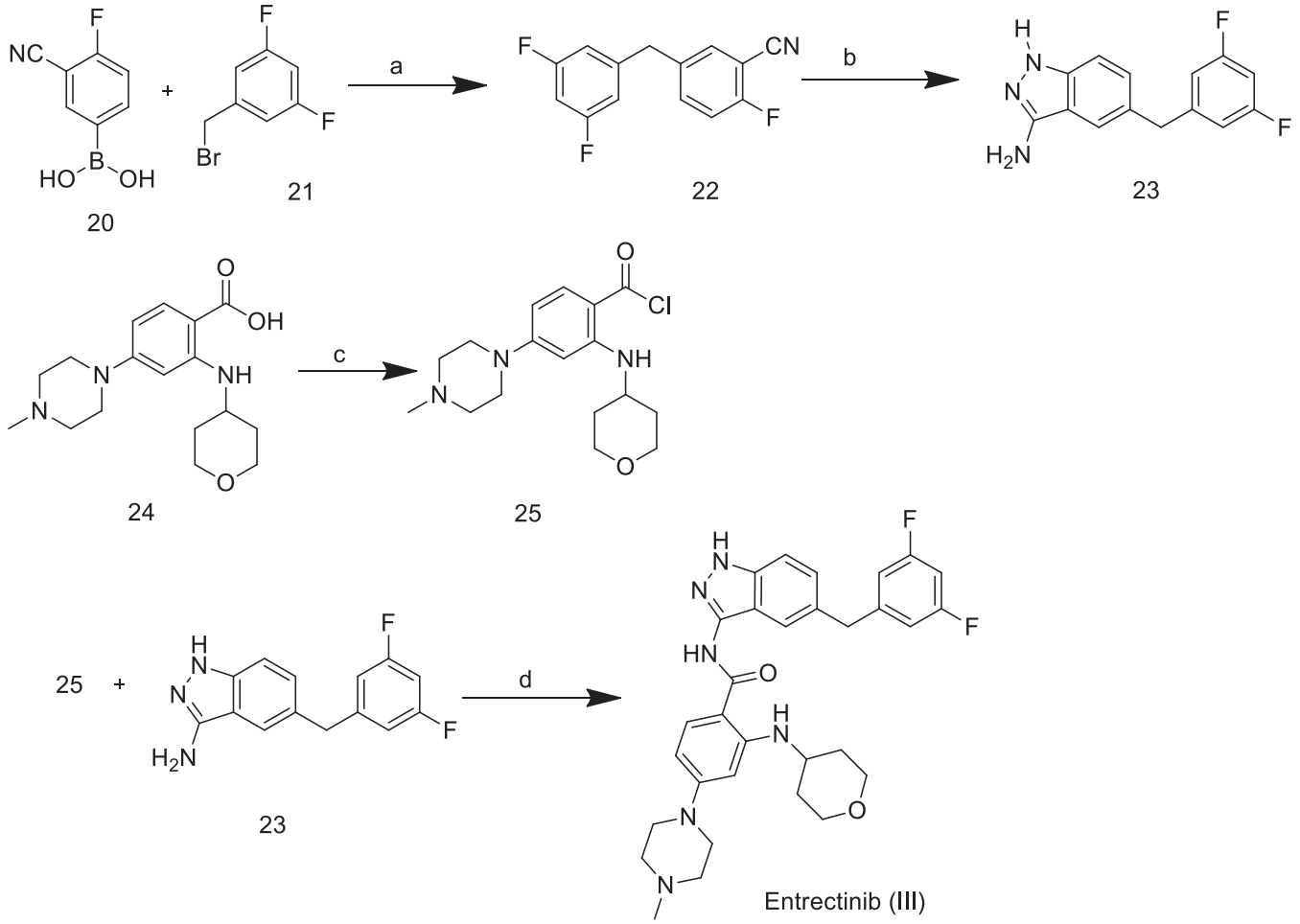
Pexidartinib is the first systemic treatment to be approved by the FDA for the treatment of adult patients with symptomatic tenosynovial giant



Scheme 1: Reagents and conditions: (a) Oxalyl chloride, chloroform, reflux, 4 h, quant; (b) (i) (E)-4-methoxy-3-buten-2-one and LiHMDS, THF, 78°C, 1 h, then solution of the acid chloride in THF was added at 78°C then in 2.5 h to rt, (ii) TFA, toluene, 10°C to rt, 55%; (c) aqueous ammonia, 65°C, 1 h, 65%. (d) $POBr_3$, 1,2-DCE, 85°C, 1 h, 51%; (e) 4-methyl-2-acetamidothiazole, $Pd(OAc)_2$/t Bu_3PHBF_4, Cs_2CO_3, DMF, 120°C, 2 h, 88%; (f) 6 N HCl, EtOH, 85°C, 1 h, 95%; (g) CDI, DCM, reflux, 15 h, 83%; (h) L-prolineamide, Et_3N, DMF, rt, 15 h, 87%.



Scheme 2: Reagents and conditions: (a) NBS, CH_3CN, <10°C, 4 h; (b) CuCN, NMP, 160°C, 6 h; (c) H_2SO_4, $NaNO_2$, KI, <10°C, overnight; (d) Suzuki coupling, boronic ester, Na_2CO_3, $PdCl_2(PPh_3)_2$, THF, 40°C, overnight; (e) HCl, EtOH, reflux, overnight; NaOH, H_2O, rt; (f) PPh_3, THF, DIAD, 0°C-rt; HCl, H_2O, rt, overnight; (g) EDCI, HOBt, DIPEA, DMF, rt, overnight; (h) $NaBH_4$, MeOH-THF, rt, 2 h.



Scheme 3: Conditions and reagents: (a) $Pd(PPh3)_4$, K_3PO_4, toluene, 100°C; (b) $NH_2NH_2.H_2O$, n-BuOH, 120°C; (c) $(COCl)_2$, DCM, DMF; (d) (i) DIPEA, THF, −20°C, (ii) MeOH, TEA.

cell tumor associated with severe morbidity or functional limitations and not amenable to improvement with surgery. It was developed by Daiichi Sankyo and received its first approval in August 2019 in the US [20,21]. Pexidartinib, like entrectinib, is a small molecule tyrosine kinase inhibitor. It has selective activity against the colony-stimulating factor 1 receptor which is expressed in high levels in several types of solid tumors [22,23]. The recommended dosage for pexidartinib is 400 mg orally twice daily empty stomach, at least 1 h before or 2 h after a meal or snack [24]. Several synthetic schemes are reported for the synthesis of the drug [25].

The commercially available starting material **26** reacts with isopropyl Grignard's reagent to produce compound **27** in 89% yield, which then reacts with **28** via Tsuji–Trost reaction and undergoes Heck coupling to yield compound **29** in 69% yield. The tosyl protection in **29** was removed by treatment with KOH/MeOH at 70°C for 4 h. This was followed by the removal of PMB and Boc using hydrochloric acid at the same temperature for 8 h after distillation of methanol, to obtain a 91% yield of compound **30**. The title compound was formed by the reduction of the oxime that was again formed by the reaction of aldehyde **31** with the amine group in **30** [25] (Scheme 4).

2.5. Zanubrutinib

Zanubrutinib is a highly potent and selective Bruton tyrosine kinase (BTK) inhibitor developed by BeiGene for the treatment of B-cell malignancies [26]. It received its first approval by US FDA in November 2019 for the treatment of patients with mantle cell lymphoma, who have received at least one prior therapy [27,28]. BTK has been an important target due to its proximal location in the B-cell antigen receptor and FcR signaling pathways. The title drug forms a covalent bond with BTK active site, therefore, inhibiting its activity [29,30]. The recommended dosage for zanubrutinib is 160 mg orally twice daily or 320 mg orally once daily until there is any disease progression or unacceptable toxicity. The drug can be administered with or without food [31].

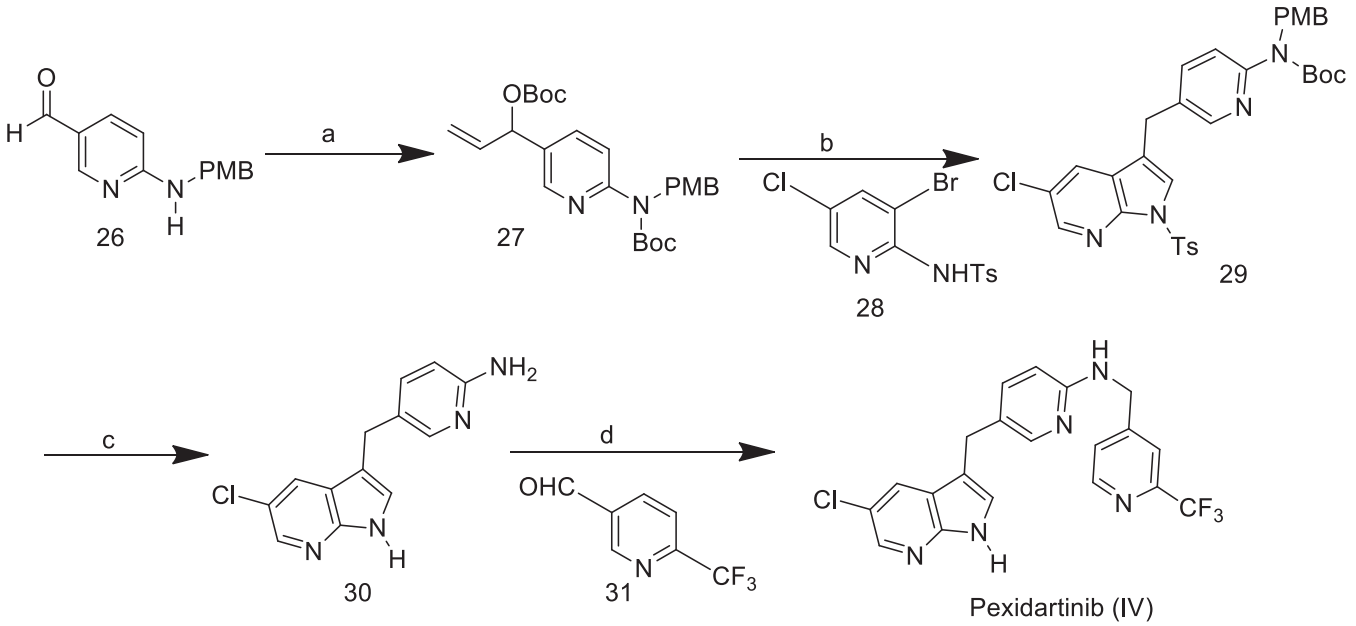
A synthetic scheme for the synthesis of the drug has been reported [32]. However, the starting material is commercially unavailable; the synthesis is cited herein.

The key intermediate **33**, formed from the starting material **32** [33], was reduced over three steps to give the amine compound **34**, which further reacted with acryloyl chloride in DCM and pyridine/Et_3N at room temperature to produce a mixture of enantiomers **35**. Zanubrutinib was obtained after chiral separation (Scheme 5).

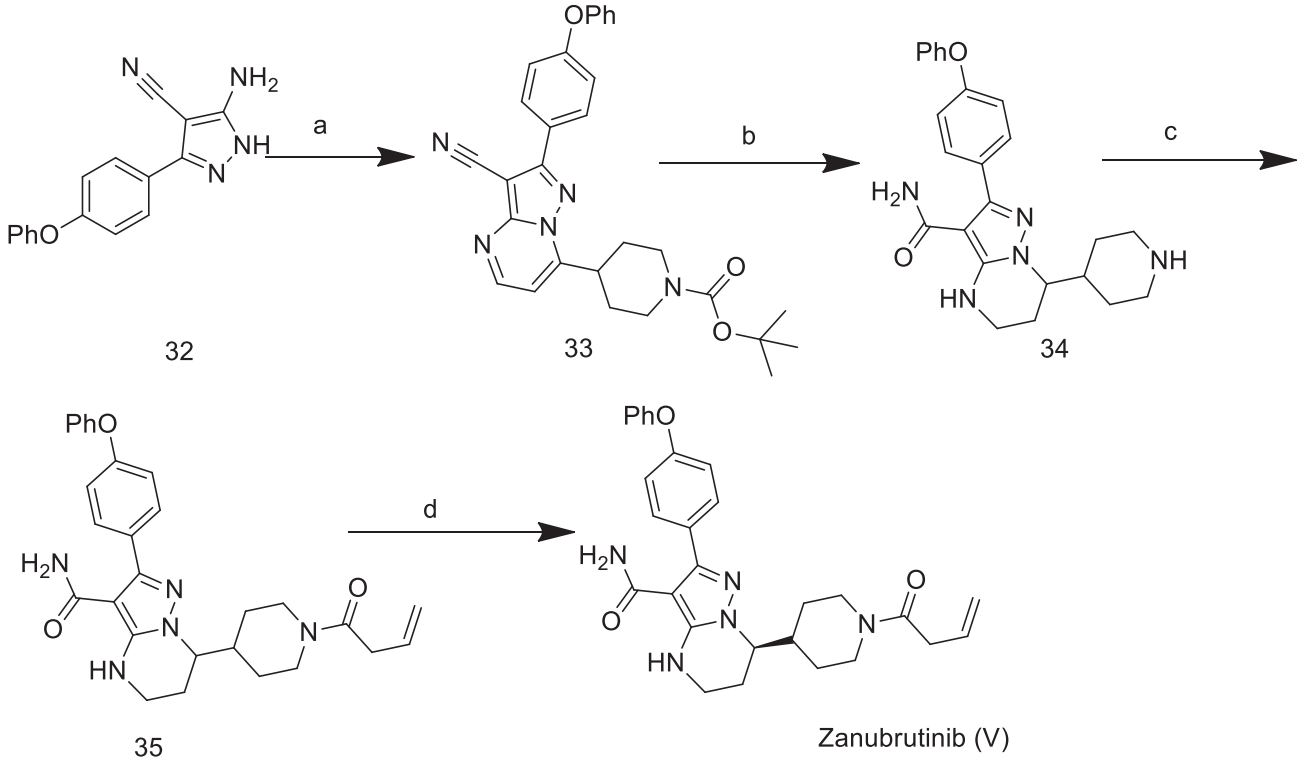
3. ANTI-INFECTIVE DRUGS

3.1. Cefiderocol

Cefiderocol is a first in its class antibacterial drug for the treatment of patients 18 years of age or older with complicated urinary tract infections (cUTI). It was approved for the first time by the US FDA in November 2019 [34]. It is a cephalosporin antibacterial drug that has a mechanism of action similar to other β-lactam antibiotics. However, unlike others, cefiderocol can undergo active transport into the bacterial cell through ion channels because of its chlorocatechol C-3 side chain [35,36]. The recommended dosage is 2 g to be injected



Scheme 4: Reagents and conditions: (a) (i) *i*-PrMgCl (2 equivalent), THF, 150°C to rt, 0.5 h, then Boc_2O (2.1 equiv), 0°C, 1 h, 89%; (b) (i) **23** (0.83 equiv), $Pd(OAc)_2$ (0.05 equiv), $P(o\text{-tol})_3$ (0.1 equiv), (ii) Ag_2CO_3 (0.8–1.0 equiv), DIPEA (2.0 equiv), DMSO, 70–100°C, 24 h, 69%; (c) KOH/MeOH, 70°C, 4 h, then HCl (con.), 70°C, 8 h, 91%; (d) **26** (1.8 equiv), Et_3SiH (6.0 equiv), CF_3CO_2H (6.0 equiv), CH_3CN, 65°C, 36 h, 88%.



Scheme 5: Reagents and conditions: (a) 3-dimethylamino-1-(piperidine)-2-propen-1-one, acetic acid, reflux; (b) (i) EtOH or MeOH, HCl (conc), 75 or 60°C, or hydrazine hydrate, MeOH/dioxane, 60°C, or Pd/C (10%), MeOH/DCM, rt, H_2, (ii) EtOH, $NaBH_4$, 60°C, (iii) DMSO/EtOH, (v:v = 1:1), 5 N NaOH, H_2O_2 (30%), 60°C; (c) DCM, pyridine or Et_3N, acryloyl chloride, rt; (d) chiral separation.

every 8 h by intravenous (IV) infusion over 3 h in patients with creatinine clearance 60–119 mL/min [37]. Several synthetic schemes for the synthesis of cefiderocol have been reported [38,39].

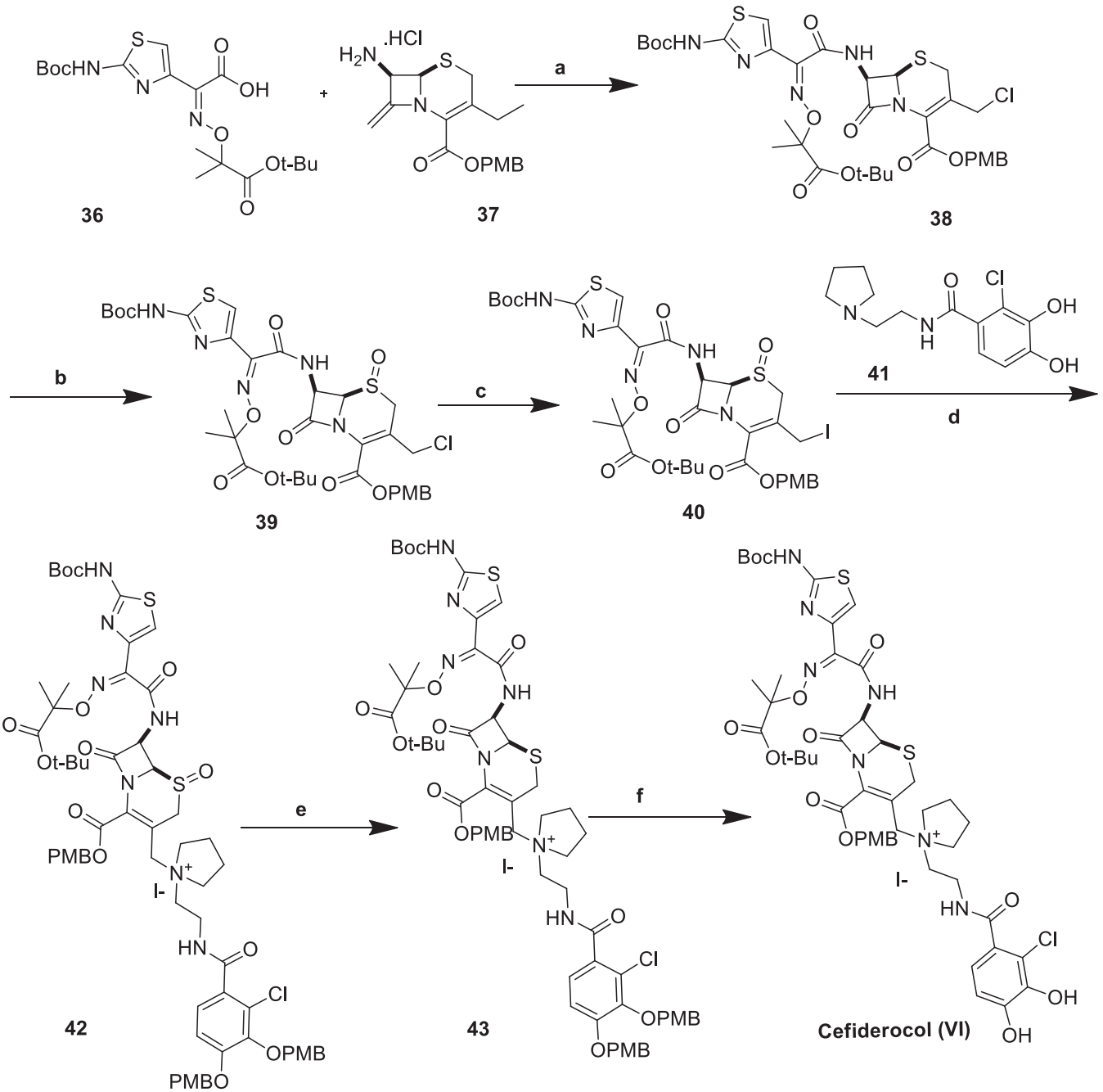
The reaction starts with the formation of an amide bond between the two commercially available starting materials, i.e., acid **36** and amine **37**. The reaction was mediated with the help of PhO–$POCl_2$ and 4-methylmorpholine 4-oxide in the presence of DCM at a low temperature of −40°C for 4 h to get compound **38** in 86% yield. Compound **38** was treated with m-CPBA in presence of DCM for an hour at 40°C to obtain thio-ketone **39**, which was again reacted with 3.0 equivalent of NaI for half an hour at room temperature to replace the chloride into iodide and obtain compound **40** in 95% yield. A tertiary ammonium salt **42** was formed by the reaction of compound **41** and **40**

in DMF at room temperature for three and a half hours. Cefiderocol was formed after the removal of the keto-group by treatment with potassium iodide in compound **43**, followed by the deprotection of two hydroxyl groups in compound **44** mediated by AlCl3 and anisole in the presence of $MeNO_2$-CH_2Cl_2 at 0°C for 80 min (Scheme 6).

3.2. Lefamulin

Lefamulin is the first among the pleuromutilin antibiotics to be used for systemic treatment of bacterial infections in humans. It was developed by Nabriva Therapeutics and received its first approval for medical use in the United States in 2019 for treating adults with community-acquired bacterial pneumonia [40,41]. Earlier, the title drug was also investigated for the treatment of acute bacterial skin structure infections [42]. XENLETA is a systemic, empiric pleuromutilin antibiotic with activity against specific Gram-positive, Gram-negative, and other respiratory bacteria. It inhibits bacterial protein synthesis through various chemical interactions with the A- and P-sites in the PTC of the 23s rRNA of the 50S subunit [43,44]. The recommended dosage for lefamulin is 150 mg every 12 h by IV infusion over 60 min for 5–7 days, or orally 600 mg orally every 12 h for 5 days [45]. Several synthetic routes for the synthesis of lefamulin have been reported [46-48].

The total synthesis of this drug is a lengthy one. The starting material **44,** prepared from (+)-trans-dihydrocarvone [49], was subjected to conjugate addition of the cuprate derived from **45**, followed by Pd-catalyzed desaturation to furnish **46** in 91% yield over two steps. A second conjugate addition was done to obtain a quaternary center in the ketal compound, which was then treated with trichloroisocyanuric acid



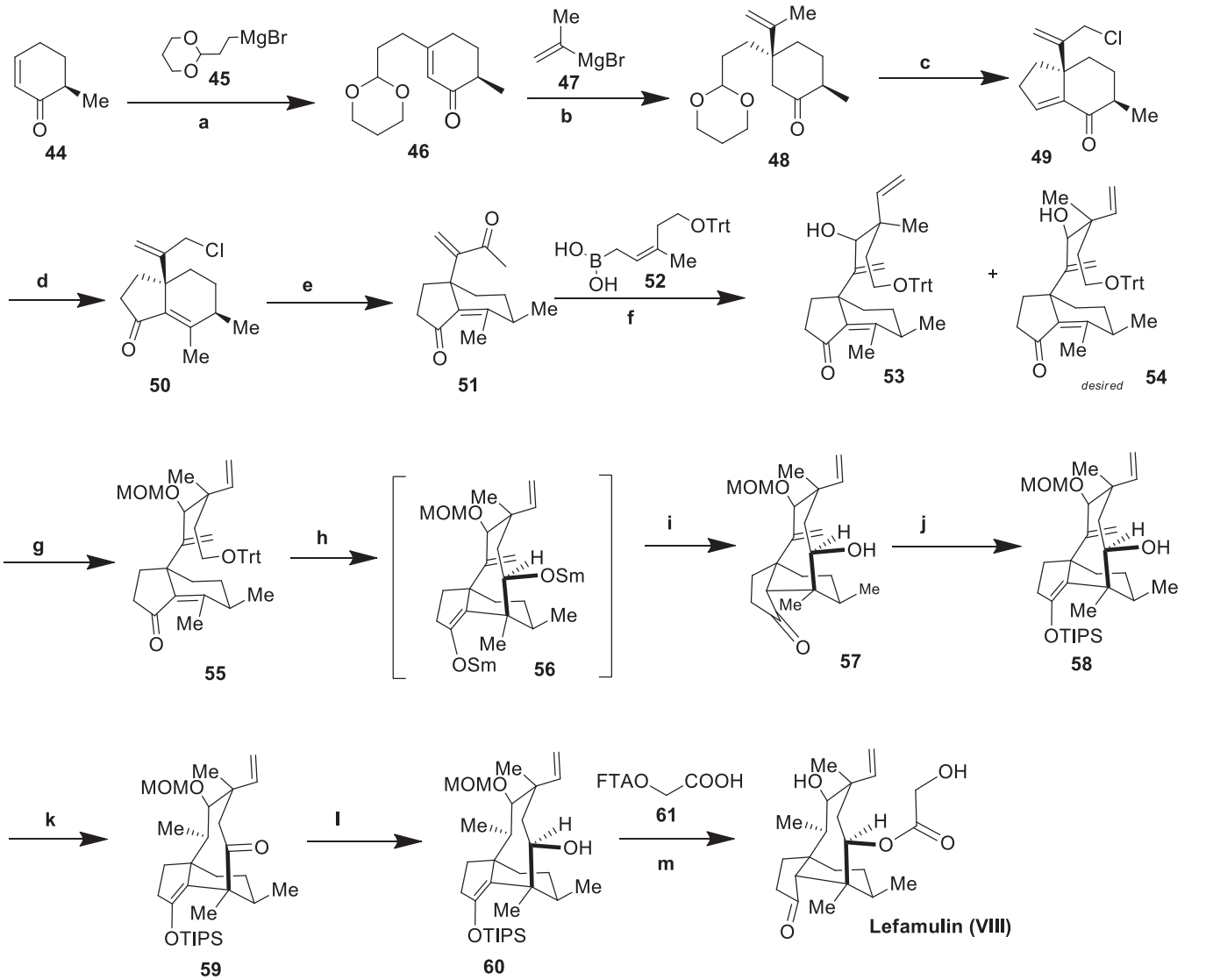
Scheme 6: Conditions and reagents: (a) PhO–$POCl_2$ (1.5 equiv), NMM (4.5 equiv), CH_2Cl_2, –40°C, 4 h; (b) m-CPBA (0.9 equiv), CH_2Cl_2, 40°C, 1 h; (c) NaI (3.0 equiv), THF, r.t., 0.5 h, 95% (25 mmol scale); (d) 35 (1.0 equiv), DMF, r.t., 3.5 h, 8.51 mmol scale; (d) KI (7.0 equiv), AcCl (4.0 equiv), 0°C, 1 h; (e) AlCl3 (10 equiv), anisole (10 equiv), $MeNO_2$-CH_2Cl_2, 0°C, 80 min.

followed by hydrochloric acid to obtain enone **48** as a 4.4:1 mixture of diastereomers at C6; the major diastereomer was isolated in 52% yield. An oxidative transposition in **48** was mediated by the addition of methyl magnesium chloride in the presence of $CeCl_3$•2LiCl followed by the submission of diastereomeric mixture to PCC. Kornblum oxidation of **50** helped in the formation of the key compound **51**.

The enal **51** was treated with boronic acid **52** to produce a mixture of diastereomers **53** and **54** in a 1.2:1 ratio. These were subjected to the protection of alcohol and ketone groups using methoxymethyl ether and trityl ether, respectively, over two steps to produce the aldehyde compound **55** in 92% yield. Ring cyclization of **55** was done by its treatment with freshly prepared SmI_2 in THF at 0°C for rigorous deoxygenation in the absence of water to yield an eight-membered ring compound **57** formed in 93% yield. The ketone in **57** was converted to a triisopropyl silyl enol ether **58**, which was then subjected to radical reduction to obtain **54**. Pleuromutilin was synthesized after a reduction of **59** using excess lithium in ammonia, which furnished alcohol **60**. Subsequently, one-pot acylation with 2-(2,2,2-trifluoroacetoxy)acetic acid, followed by methanolysis, which was again followed by acidic hydrolysis for a global deprotection (Scheme 7).

3.3. Pretomanid

Pretomanid is a bacterial agent developed by TB Alliance under license from Novartis for the treatment of drug-resistant forms of tuberculosis [50]. The drug got its first approval in August 2019 under the Limited Population Pathway for Antibacterial and Antifungal Drugs (LPAD pathway) as part of the BPaL (bedaquiline, pretomanid, and linezolid) regimen. It is not only the second drug to be approved in the USA under the LPAD pathway but has also received the US FDA Qualified Infectious Disease Product (QIDP) designation [51-53].



Scheme 7: Conditions and reagents: (a) (i) **40**, CuCN•2LiCl, TMSCl, THF, –45°C, then **39**; (ii) **42**, $Pd(OAc)_2$ (10 mol %), DMSO, O_2, rt, 91% yield, 2 steps; (b) CuI, THF, –78°C to –50°C, 4.8:1 dr, 71% yield; (c) (i) TCCA, EtOAc, 0°C, 77% yield, (ii) HCl (*aq*), THF, 70°C, 4.4:1 dr, 52% yield; (d) (i) $CeCl_3$•2LiCl, MeMgCl, 0°C, (ii) PCC, CH_2Cl_2, 78% yield, 2 steps; (e) KH_2PO_4, NaI, DMSO, 95°C, 69% yield; (f) **47**, (*R*)-3,3'-Br_2-BINOL, (20 mol %) *t*BuOH, 3 Å MS, PhMe, 0°C, 80% yield, 99% brsm, 1.2:1 (**48**:**49**); (g) (i) MOMCl, *i*Pr_2Net, (ii) HCO_2H, Et_2O, 70% yield, 2 steps, (iii) $[Cu(MeCN)_4]OTf$, 4-OMebpy, ABNO, NMI, MeCN; (h) SmI_2, THF, 0°C; (i) SmI_2 (3 equiv), H_2O (6 equiv), THF, 0°C, 5 min, then TMSCl (5 equiv), 93% yield, 23:1 dr; (j) LiHMDS, TIPSOTf, THF, –78 to 0°C, 76% yield; k) $Mn(dpm)_3$, (13 mol %), $PhSiH_3$, TBHP, iPrOH, rt, 55% yield, Single diastereomer; (l) Li/NH_3, EtOH, Et_2O, –78°C, 61% yield, 14:1 dr; (m) **56**, EDCI, DMAP, CH_2Cl_2, rt, 1 h, then MeOH, Et_3N, then HCl/THF, 50°C, 80% yield.

Pretomanid kills the replicating bacteria by inhibiting mycolic acid biosynthesis, thereby blocking cell wall production. For non-replicating bacteria, it acts as a respiratory poison following nitric oxide release [54]. The recommended dosage of pretomanid is 200 mg orally daily for 26 weeks to be administered only as part of a regimen in combination with bedaquiline and linezolid [55]. Several synthetic routes are reported for the synthesis of the drug [56-58].

The synthesis of pretomanid was rather simple as it included two consecutive coupling reactions followed by the formation of an oxazine ring. 1-bromo-4-(trifluoromethoxy)benzene on coupling with oxiran-2-ylmethanol **62** afforded **63** in 62% yield, which was again coupled with **64** to produce compound **65** in 61% yield. Compound **65** underwent cyclization by losing one molecule of HBr in the last step to form the desired compound in 87% yield (Scheme 8).

4. ANTI-PULMONARY DRUGS

4.1. Trikafta

Trikafta is a triple combination regimen (using elexacaftor, ivacaftor, and tezacaftor) developed for the treatment of patients 12 years of age and older with who have at least one copy of the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. It is an orally administered drug developed by Vertex Pharmaceuticals that received its very first approval in August 2019 [59,60]. The combination helps in increasing the amount of CFTR protein delivered to the cell surface, while ivacaftor aids in the gating of the CFTR protein at the cell surface. The combined effect of the three drugs boosts the amount and function of F508del-CFTR at the cell surface [61,62]. The drug needs to be administered twice daily in a gap of at least 12 h. The morning dose includes two elexacaftor 100 mg, tezacaftor 50 mg, and ivacaftor 75 mg tablets, and the evening includes only one ivacaftor 150 mg tablet [63].

Many synthetic approaches for the components of the title compound have been reported earlier [64]. The most approachable schemes for the individual components in trikafta are hereby described.

4.1.1. Elexacaftor

The scheme described here is the first-generation scheme as provided by Vertex [64]. Pyrazolone derivative **68** formed from the cyclization of (E)-methyl 3-methoxyacrylate **66** through a two-step process, undergoes Mitsunobu reaction with compound 3,3,3-trifluoro-2,2-dimethylpropanol **69**, which is again formed by the reduction of carboxylic group in 3,3,3-trifluoro-2,2-dimethylpropanoic acid **67**, to form compound **70** in 57% yield. Compound **70** was deprotected to form **73**, which when coupled with acid-protected 2,4-dichlorobenzoic acid **72** produced compound **74** in 99% yield. Compound **74** was deprotected to form **75** and coupled with **76** to produce **77** in 93% yield. Finally, elexacaftor was formed by the coupling of **78** with compound **79** in 90% yield (Scheme 9).

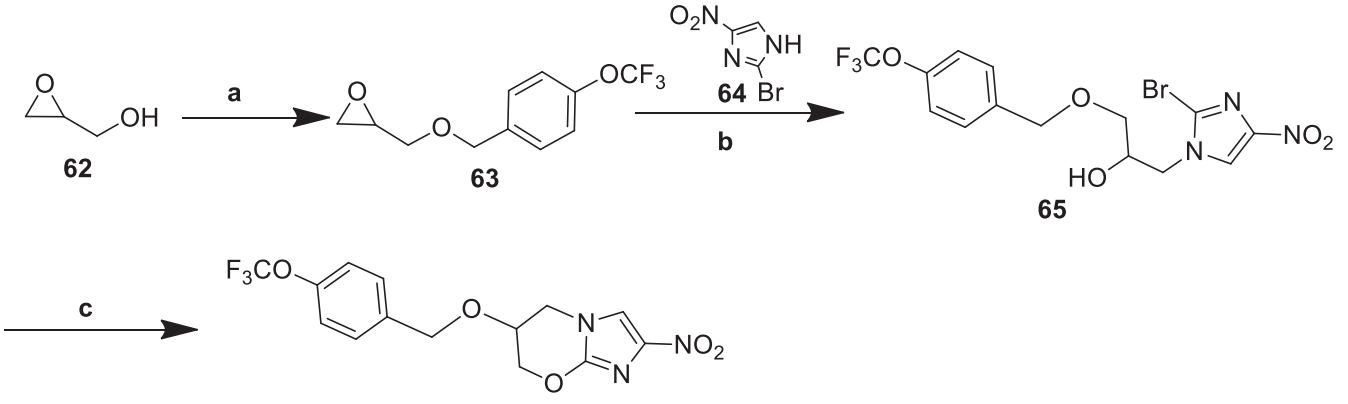
4.1.2. Ivacaftor

Several approaches have been proposed for the synthesis of ivacaftor [64]. The one described here was patented by Laurus Laboratories and it involves the formation of the quinoline ring through a nucleophilic aromatic substitution reaction. The starting material 2-fluorobenzoic acid **83** undergoes 3-carbon homologation after reaction of ethyl 3-dimethylaminoacrylate mediated by trimethylamine to afford **84** in 87% yield, followed by amine exchange with benzylamine to produce compound **55** in 82% yield. Cyclization of **85** through nucleophilic aromatic substitution gave compound **86**, which was then hydrolyzed and coupled with compound **82** through an amide bond formation to produce **88**. Compound **82** was synthesized from 3-aminophenol **89** which was amine protected to give **80** in 92% yield, which was again followed by electrophilic alkylation with t-BuOH in presence of sulfuric acid in dichloromethane to afford **81** in 74% yield. Deprotection of **81** with HCl in EtOH/water produced compound **82**. Finally, deprotection of benzyl ivacaftor **88** through transfer hydrogenation with ammonium formate produced ivacaftor in 79% yield (Scheme 10).

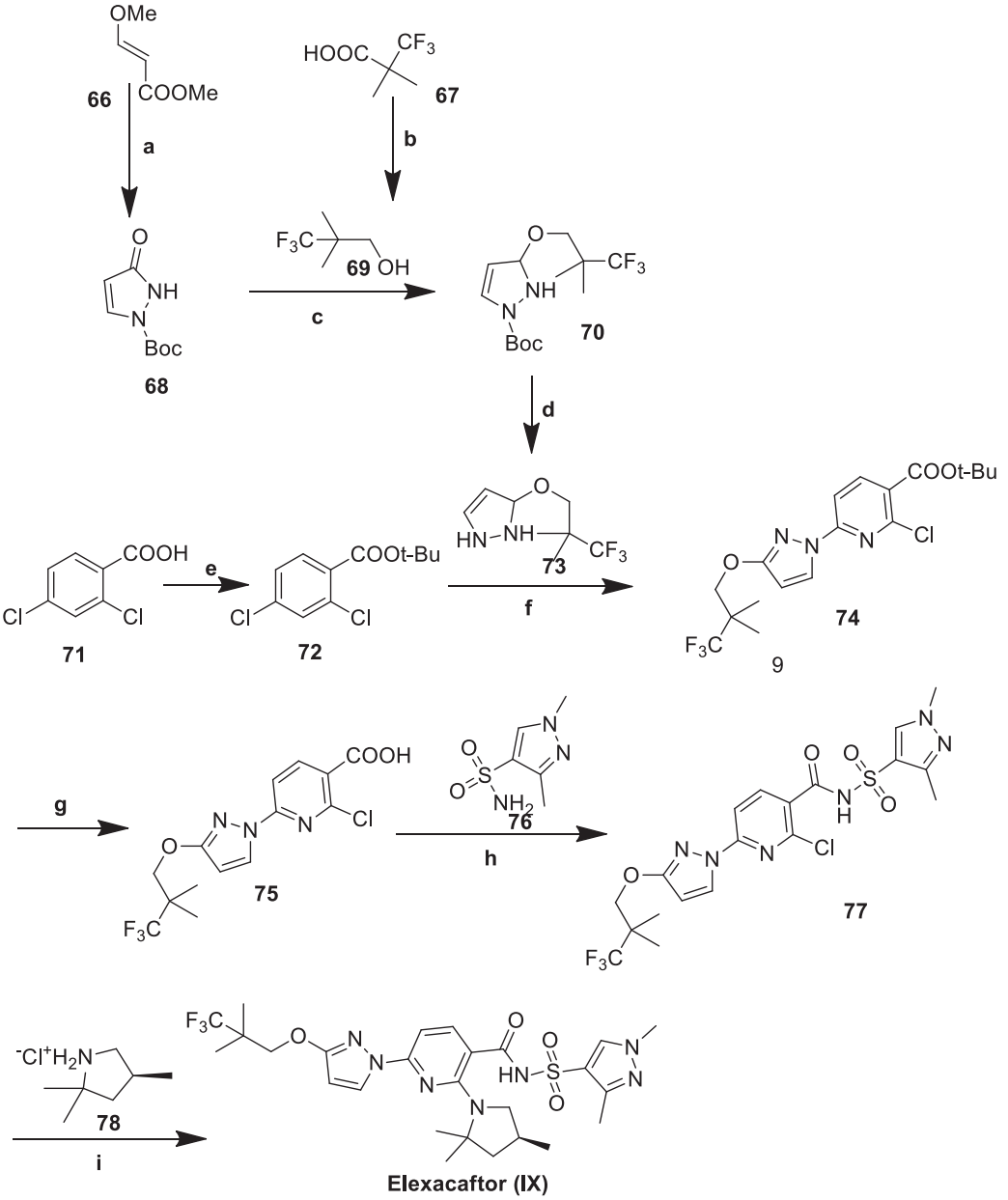
4.1.3. Tezacaftor

The scheme described here is the first-generation route that employs Sonogashira coupling; it was provided by Vertex [64]. The synthesis of tezacaftor can be achieved by the reaction of acyl chloride fragment 102 and alkyne compound 94. The required alkyne fragment was synthesized by double methylation of methyl 3-oxobutanoate **89** with MeI in THF to produce **90** in 53% yield, which was then chlorinated with PCl5 in dichloromethane using catalytic DMF to produce **91** in 82% yield, followed by hydrolysis of ester to afford **92** in 44% yield. Alkyne **93** was formed in 94% yield using sodium amide in DMSO, and this was followed by the formation of benzyl ester **94** mediated by DCC in dichloromethane (Scheme 11).

For the synthesis of aryl chloride fragment, compound **95** was carbonylated using Pd(0) in MeOH to provide ester **96**, followed by a reduction of **96** with LiAlH4 in THF to afford **97** in 76% yield over the two steps. This alcohol was then converted to chloride which was then displaced with nitrile **98** using NaCN in DMSO. Compound **100** was formed by the introduction of a cyclopropane group in the nitrile **98** after its reaction with 1,2-bromochloroethane **99** using a phase transfer catalyst in NaOH, which was then hydrolyzed in NaOH to afford **101**



Scheme 8: Reagents and conditions: (a) 4-OCF_3BnBr, NaH, DMF, 0−20°C, 7−21 h; (b) DIPEA, 105−108°C, 6.5−15 h; (c) NaH, DMF, 0°C for 0.7−1.4 h or 0−20°C for 2−3 h.



Scheme 9: Reagents and conditions: (a) (i) $NH_2NH_2.H_2O$, 40°C; (ii) $(Boc)_2O$, Et_3N, rt, 71%; (b) $LiAlH_4$, THF, 79%; (c) 4, DIAD, PPh_3, toluene, 110°C, 57%; (d) HCl, dioxane, 96%; (e) $(Boc)_2$, DMAP, THF, 96%; (f) 8, K_2CO_3, DABCO, DMF, rt, 99%; (g) HCl, 2-PrOH, reflux, 91%; (h) **76,** CDI, DBU, THF, 93%; (i) **78,** K_2CO_3, DMSO.

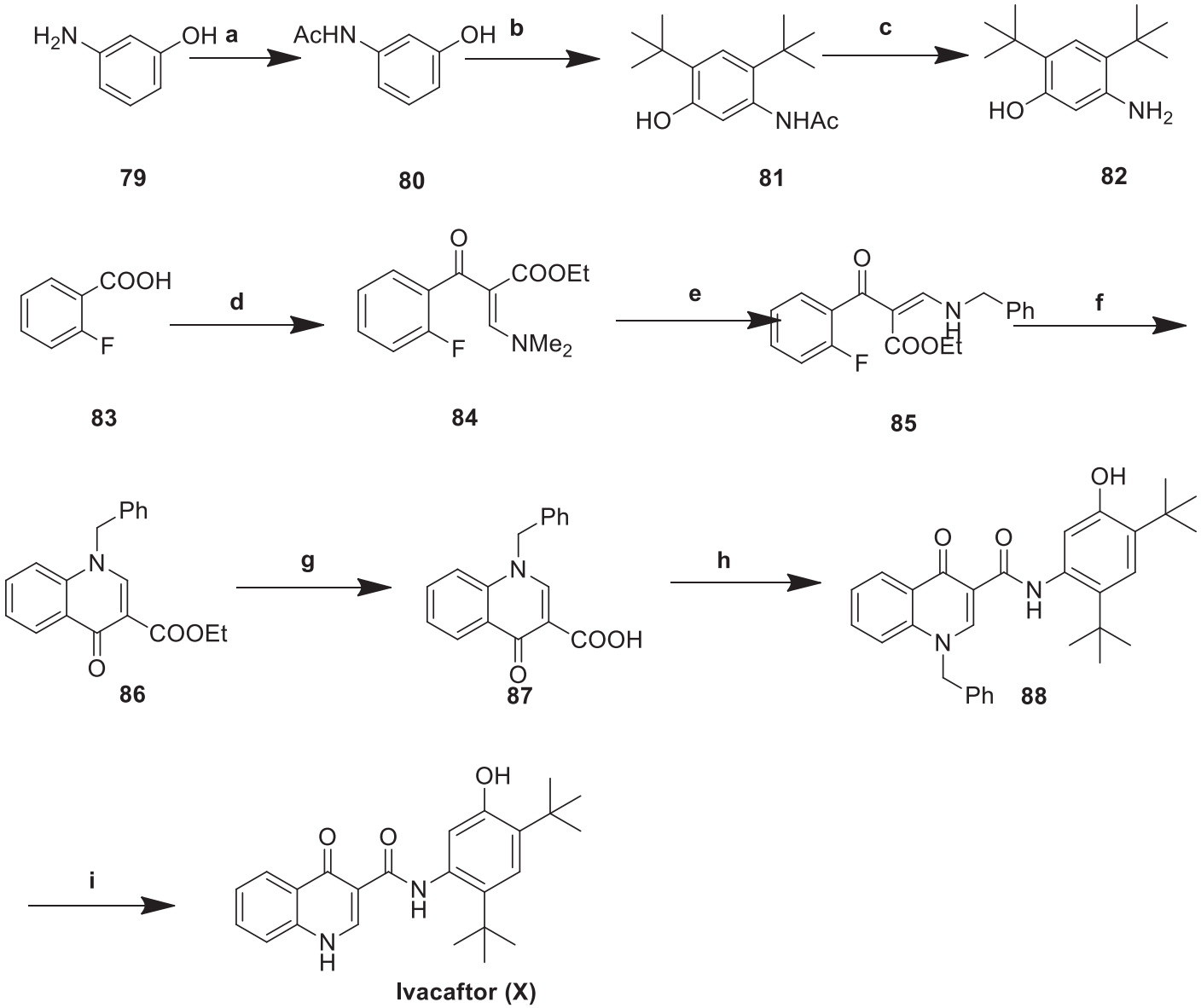
in 1.6% yield over four steps. It was then chlorinated with SOCl2 in DMF to get the required acyl chloride fragment **102** (Scheme 12)

The synthesis of tezacaftor is outlined in Scheme 3. It starts with the coupling of aryl bromide **103** with compound **94** through Sonogashira coupling to afford **104** in 56% yield. This was followed by cyclization in **104** with PdCl2 in acetonitrile at 80°C to form an indole **75** in 90% yield. The nitrogen in indole **105** was tosylated using **106** with cesium carbonate in DMF at 80°C to afford a mixture of **107** and transesterified product **108**, which was then reduced with lithium aluminum hydride in THF to produce compound **109** in 87% yield over the two steps. Aniline **110** was formed in 79% yield from the hydrogenation of the nitro group in **109**, which was followed by coupling with acid chloride **111** in dichloromethane to produce amide **112** in 100% yield. Deprotection of **112** using p-TsOH-H2O in MeOH at 80°C furnished tezacaftor in 47% yield.

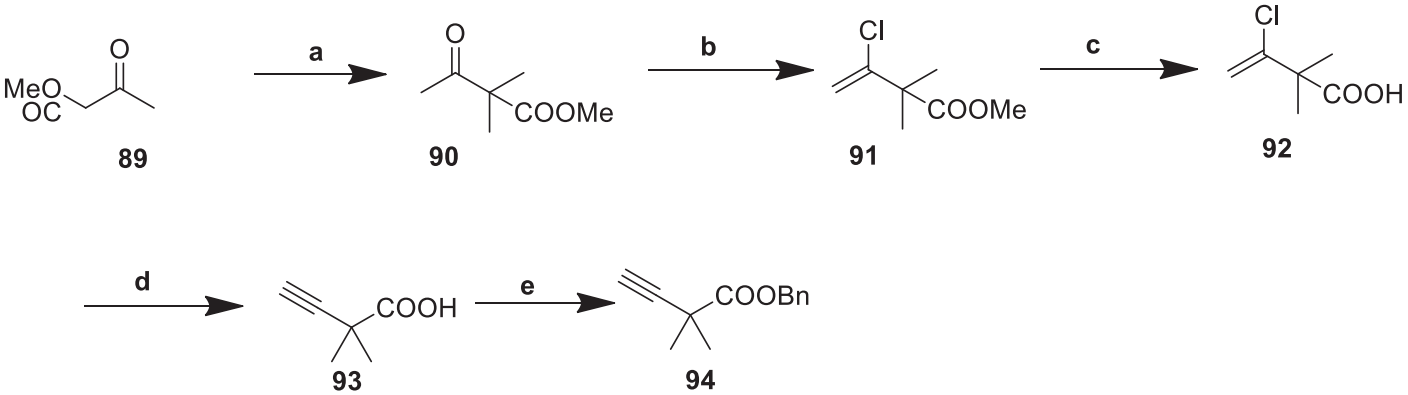
5. CARDIOMYOPATHY

5.1. Tafamidis Meglumine

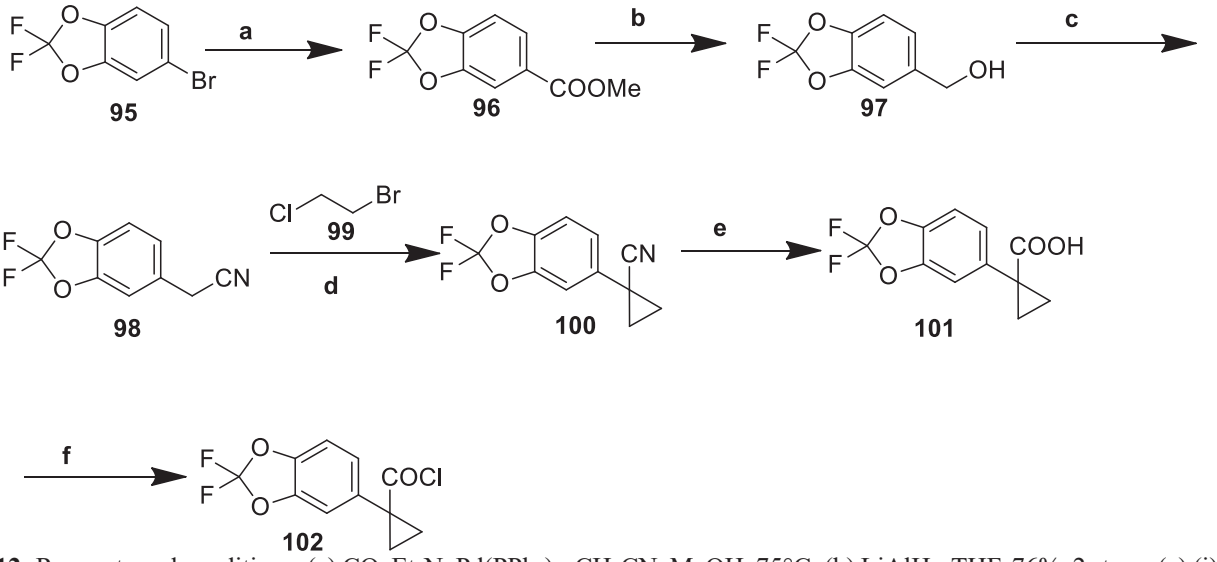
Tafamidis meglumine (vyndaqel) is a transthyretin stabilizer indicated for the treatment of heart disease caused by transthyretin mediated amyloidosis (ATTR-CM) in adults. Tafamidis and tafamidis meglumine are the first and only medicines approved for patients with either wild-type or hereditary transthyretin amyloid cardiomyopathy [65]. Tafamidis selectively binds to transthyretin, stabilizing the tetramer of the transthyretin transport protein and slowing the formation of amyloid that causes ATTR-CM [66]. Tafamidis meglumine received its first approval on November 16, 2011, in the European Union for the treatment of ATTR-PN in adult patients with Stage 1 symptomatic polyneuropathy to delay peripheral neurologic impairment. It has since been approved for the treatment of ATTR-PN in 41 countries [67]. It got its approval by the US FDA in May 2019 [65,68]. The recommended dosage for vyndaqel is 80 mg/day, to be taken twice as 40 mg of capsule [69].



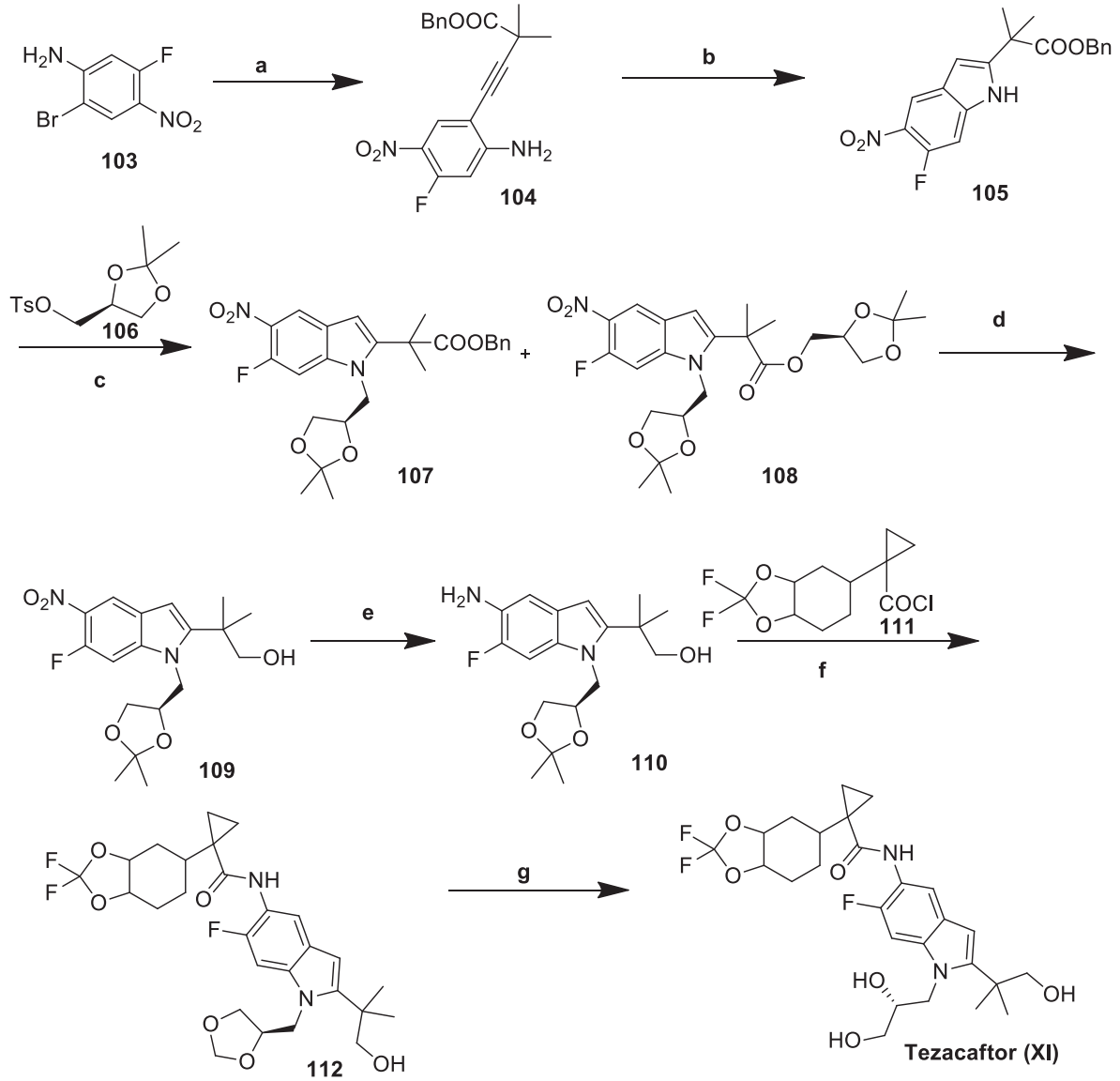
Scheme 10: Reagents and conditions: (a) Ac_2O, HOAc, 50°C, 92%; (b) H_2SO_4, CH_2Cl_2, t-BuOH, rt, 74%; (c) HCl, EtOH, H_2O, 89% (d) (i) $SOCl_2$, toluene, (ii) (Z)-ethyl 3-(dimethylamino)acrylate, Et_3N, toluene, 50–55°C, 87% (e) $PhCH_2NH_2$, toluene, 25–35°C; (f) K_2CO_3, DMF, 85–90°C, 83%; (g) Aq. NaOH, 93%; (h) HATU, i-Pr_2NEt, DMF, 91%; (i) $Pd(OH)_2$, $HCOONH_4$, DMF, 70–80°C, 79%.



Scheme 11: Reagents and conditions: (a) NaH, MeI, THF, 53%; (b) PCl_5, DMF (cat.), CH_2Cl_2, reflux, 82%; (c) aq. NaOH, reflux, 44%; (d) $NaNH_2$, DMSO, 94%; (e) BnOH, DCC, CH_2Cl_2, 59%.



Scheme 12: Reagents and conditions: (a) CO, Et_3N, $Pd(PPh_3)_4$, CH_3CN, MeOH, 75°C; (b) $LiAlH_4$, THF, 76%, 2 steps; (c) (i) $SOCl_2$, CH_2Cl_2, (ii) NaCN, DMSO; (d) $BnNEt_3Cl$, NaOH, 70°C; (e) 10% aqueous NaOH, reflux, 1.6% (4 steps); (f) $SOCl_2$, DMF.



Scheme 13: Reagents and conditions: (a) **94,** $Pd(PPh_3)_2Cl_2$, Et_3N, CuI, 80°C, 56%; (b) $PdCl_2$, CH_3CN, 80°C, 90%; (c) Cs_2CO_3, DMF, 80°C; (d) $LiAlH_4$, THF, 87%, (2 steps); (e) H_2, Pd/C, EtOH, 79%; (f) Et_3N, CH_2Cl_2, 100%; (g) p-TsOH-H_2O, MeOH, H_2O, 80°C, 47%.

The coupling of commercially available starting materials **113** and **114** was done at 100°C using 1% loading catalyst giving the key intermediate **115**, which was then cyclized in presence of p-TsOH in refluxing xylene, followed by methylation with Me_3SiCHN_2 in benzene/MeOH affords the benzoxazole methyl ester **116**. Finally, hydroxylation of compound **116** affords the desired drug (Scheme 14).

6. CNS DRUGS

6.1. Fluorodopa

6-[18F] Fluoro-L-DOPA is a diagnostic radiopharmaceutical for positron emission tomography (PET) imaging [70]. First reported in 1983, fluorodopa or [18F] FDOPA PET imaging has been used to image Parkinson's disease and brain tumor. It was able to make its way to the multi-discipline review by FDA in 2010 but was able to get its approval only in 2019 [71]. Fluorodopa F 18 Injection is a radioactive diagnostic agent indicated for use in PET to visualize dopaminergic nerve terminals in the striatum for the evaluation of adult patients with suspected parkinsonian syndromes [72]. The advised dosing regimen is 5 mCi IV infusion over 1 min and for single administration only [71,72].

Several synthetic schemes have been proposed for the synthesis of fluorodopa [73]. However, the one described herein is a one-pot synthesis scheme describing a fully automated method involving Cu-mediated radiofluorination of a pinacol boronate ester precursor **117** [74] (Scheme 15).

6.2. Istradefylline

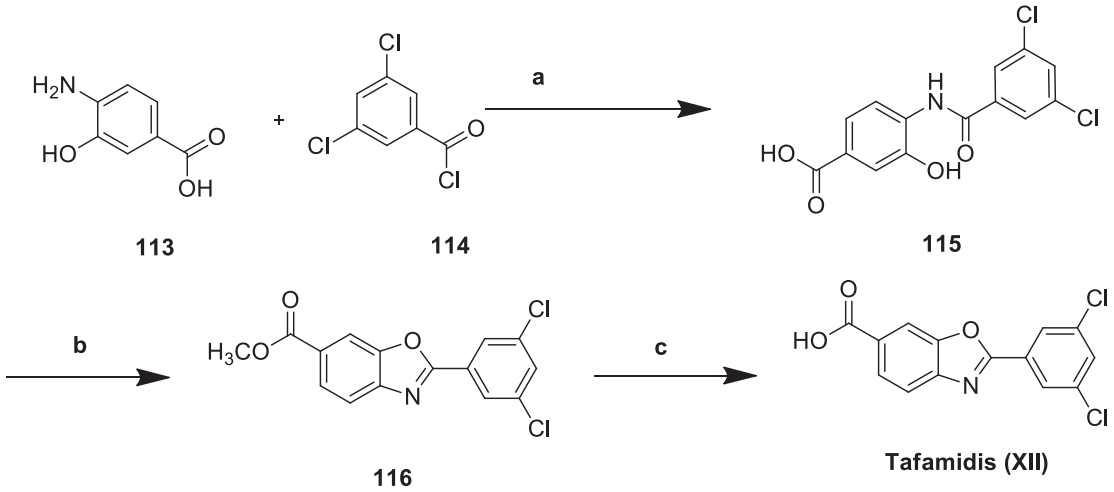
Istradefylline is a selective adenosine A2A receptor antagonist developed by Kyowa Hakko Kirinfor the oral treatment of Parkinson's disease [75]. It was first approved in March 2013 in Japan for use as an adjunctive treatment and is indicated for the improvement of wearing-off phenomena in patients with Parkinson's disease on concomitant treatment with levodopa containing medications. An application was filed in the USA in February 2008, but the FDA issued a non-approvable letter for the title drug [76,77]. However, its approval in August 2019 istradefylline became the first non-dopaminergic drug to be approved by the FDA for PD in the past two decades [78]. The maximum recommended dosage with moderate hepatic impairment is 20 mg once daily, and for patients who smoke 20 or more cigarettes per day (or equivalent of any other tobacco product), the recommended dosage is 40 mg once daily [79].

Methods for the synthesis of istradefylline have been reported [80].

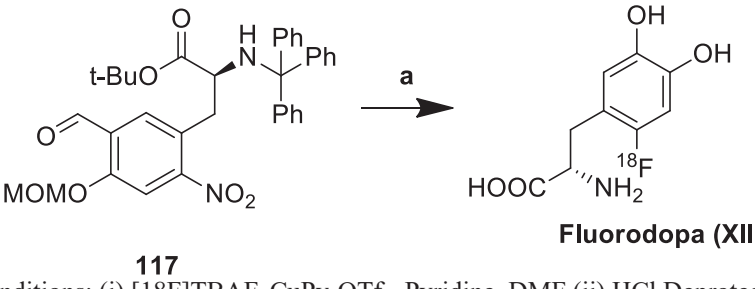
The synthesis requires the formation of diaminouracil **122** and an acid chloride **124**, which further undergo a convergent pathway to form istradefylline. (E)-3-(3,4-dimethoxyphenyl)acrylic acid **123** was treated with thionyl chloride in toluene at 75°C for 32 h to afford compound **124** in 97% yield. The cyclic compound **120** was formed by the direct reaction of the dialkyl urea **119** with cyanoacetic acid **118** in 83% yield [81]. This was followed by the introduction of nitroso group in the so-formed compound to produce **121** in 86% yield, after which it was reduced using sodium dithionite in ammonium hydroxide to afford **122** in 98% yield [82] (Scheme 16).

6.3. Lumateperone

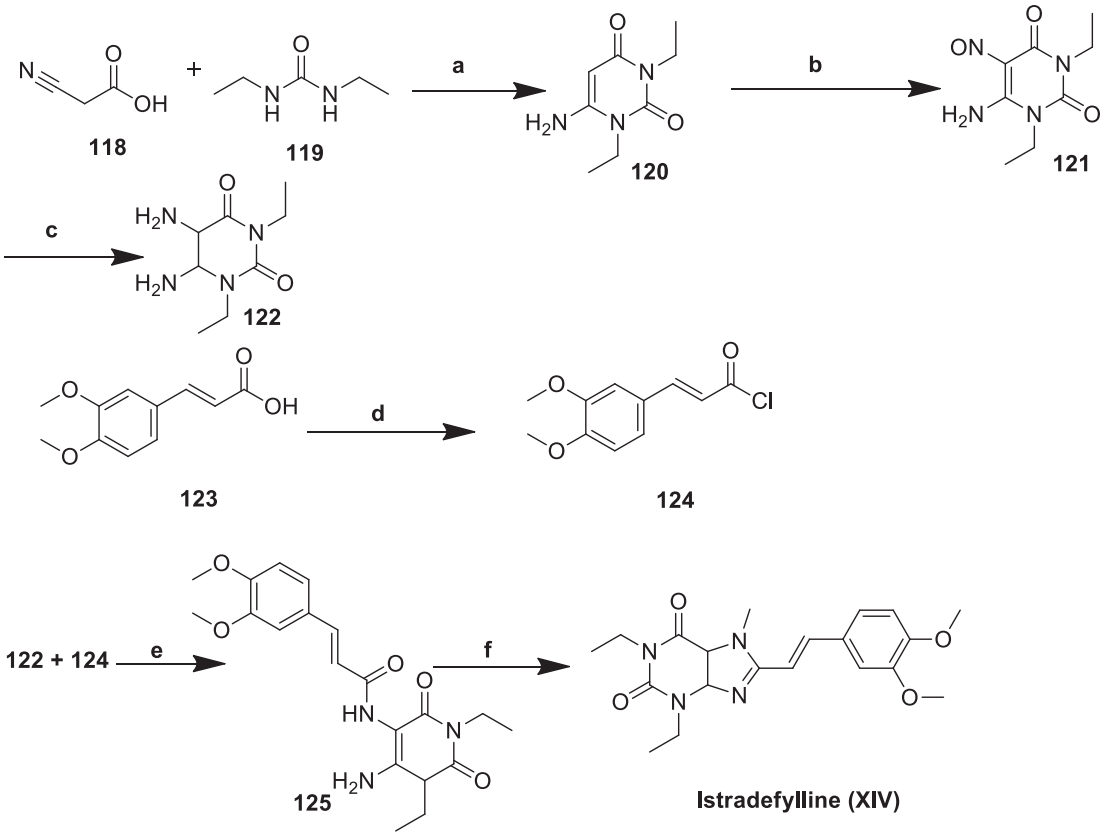
Lumateperone is a novel antipsychotic drug developed by Intra-Cellular Therapies for the treatment of schizophrenia, bipolar depression, behavioral disorders, sleep maintenance insomnia, and major depressive disorders [83]. Lumateperone is a selective and simultaneous modulator of serotonin, dopamine, and glutamate, which is the three key neurotransmitters involved in neuropsychiatric disorders. It has potent antagonistic activity at serotonin 5-HT2A receptors and



Scheme 14: Reagents and conditions: (a) Pyridine, reflux; (b) (i) p-TsOH, xylene, reflux, (ii) $TMSCHN_2$, benzene, MeOH; (c) LiOH, H_2O/THF/MeOH.



Scheme 15: Reagents and conditions: (i) [18F]TBAF, $CuPy_4OTf_2$, Pyridine, DMF (ii) HCl Deprotection.



Scheme 16: Reagents and conditions: (a) Acetic anhydride, 80°C, 2 h, 83%; (b) sodium nitrite, 50% acetic acid, 60°C, 15 min, 86%; (c) sodium dithionite, NH_4OH solution (12.5%(w/v)), 60°C, 30 min, 98%; (d) $SOCl_2$, toluene, 75°C, 2 h, 97%; (e) pyridine, DCM, rt, 16 h, 66%; (f) HMDS, cat. $(NH_4)_2SO_4$, CH_3CN, 160°C, microwave, 5 h, 100% followed by (g) MeI, K_2CO_3, DMF, rt, 2 h, 75%.

is a serotonin transport inhibitor acts as a presynaptic partial agonist and a post-synaptic antagonist at dopamine D2 receptors [84,85]. The drug received its first global approval on December 20, 2019, in the USA [86]. The recommended daily dosage for lumateperone is 42 mg/day to be administered orally [87]. A synthetic scheme for lumateperone has been reported [88].

The reaction started with the introduction of a nitro-group in 3,4-dihydroquinoxalin-2(1H)-one **126** in the presence of sodium nitrite and acetic acid to produce compound **127** in 60–80% yield, which was reduced with zinc in acetic acid followed by a Fisher-indole cyclization using ethyl 4-oxopiperidine-1-carboxylate to produce compound **128**. The indole derivative **129** was afforded in 85–95% yield when the bridging double bond was reduced by treatment of compound **128** with sodium cyanoborohydride in trifluoroacetic acid. Further reduction of **129** with borane in THF helped in removing the carbonyl group to produce **130**. This was followed by deprotection using potassium hydroxide in n-butanol to afford compound **131** in 90–99% yield. Butyrophenone side chain was introduced through alkylation of **131** under basic conditions to furnish the racemic mixture **132**, which was finally separated through chiral separation and lumateperone was isolated in 30–45% yield (Scheme 17).

6.4. Pitolisant

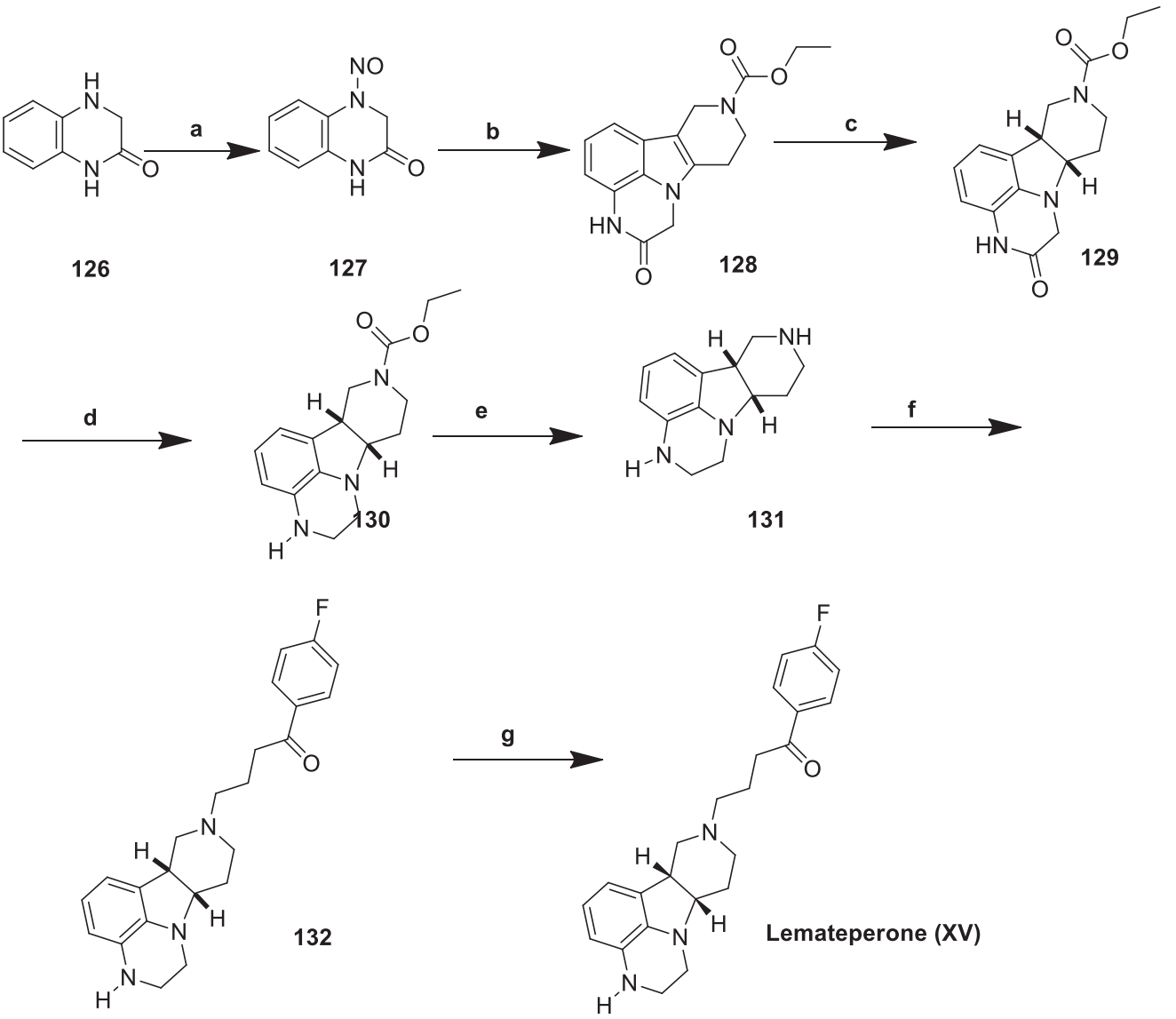
Pitolisant is the first H_3 receptor inverse agonist to be tested in humans or introduced for clinical use [89]. It received its approval by the US FDA for the treatment of excessive daytime sleepiness (EDS) associated with narcolepsy in July 2019 [90]. Designed and developed by Bioprojet, pitolisant received its very first approval by the European Medicines Agency in 2016 in Europe for the treatment of EDS in adults with narcolepsy with or without cataplexy [91,92]. Pitolisant was also granted orphan drug designation by the European Medicines Agency in 2007 [93] and by the US FDA in 2010 [94] for use in narcolepsy. Histaminergic neurons are known to improve a person's wakefulness. Pitolisant enhances the activity of these neurons in the brain and decreases the number of cataplexy attacks in people who suffer from narcolepsy [95,96]. The recommended daily dosage for pitolisant 17.8 mg or 35.6 mg once daily [97].

The synthetic scheme for pitolisant has been previously explained as a first-in-class inverse agonist of the histamine H_3 receptor [98]. The first two steps of the synthesis involve proton abstraction followed by coupling of the commercially available **133** with compound **134** to afford the required pitolisant hydrochloride (Scheme 18).

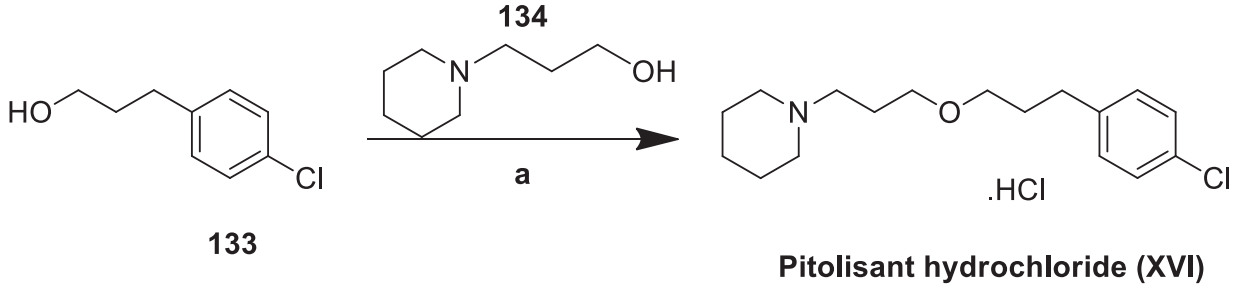
6.5. Siponimod

Siponimod is an sphingosine 1-phosphate (S1PR) modulator that was originally developed by Novartis for the treatment of adults with relapsing forms of multiple sclerosis, including clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease. It received its first global approval in the USA, in March 2019 [99,100]. Siponimod has a preferential selectivity for S1PR which has an established key role in the immune, cardiovascular, and central nervous systems through its interaction with five G protein-coupled receptors S1PR [101]. The recommended maintenance dosage is 2 mg [102]. Synthetic schemes for the drug have been reported [103].

The starting material is commercially available aniline **135**, which was converted into a diazonium salt and then into the corresponding aldoxime, and subsequently was hydrolyzed to give aldehyde **136** in 26% yield. Reduction of this aldehyde using sodium borohydride afforded benzyl alcohol **137** in 70% yield, which was then protected with tert-butyldimethylsilyl chloride to obtain **138** in 87% yield. The

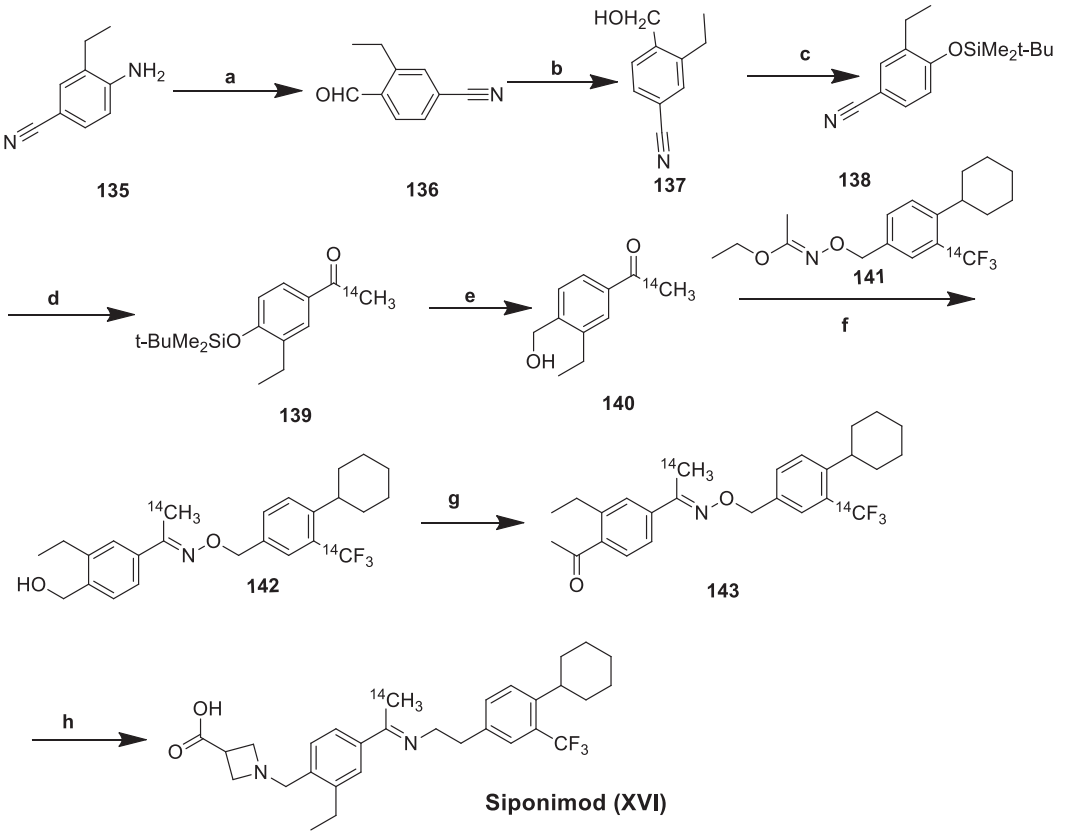


Scheme 17: Reagents and conditions: (a) $NaNO_2$, HOAc, 0−5°C, 60−80%; (b) (i) Zn, HOAc, 10°C; (ii) ethyl 4-oxopiperidine-1-carboxylate, HOAc, HCl, 100°C, 40–60% (two steps); (c) $NaBH_3CN$, TFA, rt, 85−95%; (d) borane, THF, reflux, then 6N HCl, reflux, 85−95%; (e) KOH, nBuOH, reflux, 90−99%; (f) 4-chloro-1-(4-fluorophenyl)butan-1 one, NEt_3, dioxane, toluene, reflux, 50−70%; (g) chiral HPLC separation, 30−45%.

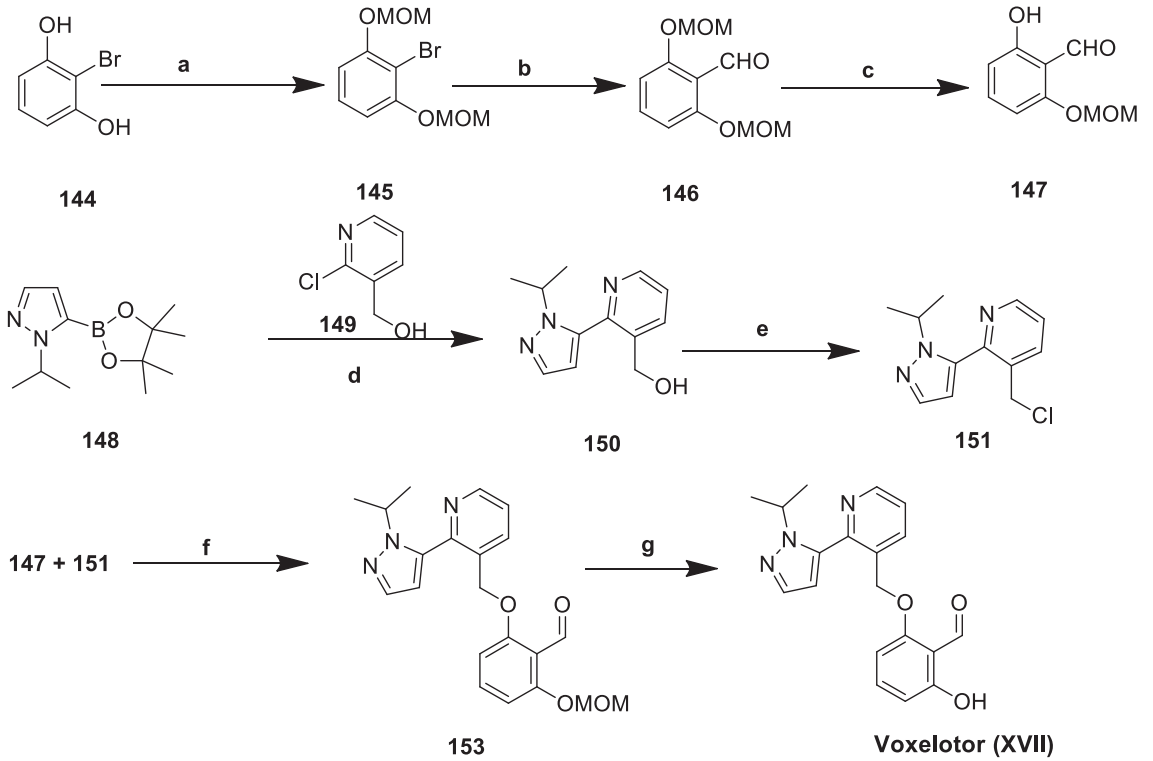


Scheme 18: Reagents and conditions: (a) (i) MsCl, Et_3N, DCM, 0°C to rt; (ii) **94**, NaH, DMA, 50°C, then mesylate, 22°C; (iii) HCl (g), EtOAc, 20–25°C; (iv) EtOAc, IPA, 55–60°C, 78% for 4 steps.

radioactive label was introduced using [^{14}C] methyl lithium in the presence of cuprous bromide to yield ketone **139**, which was again deprotected using 1M n-Bu_4NF in THF over two steps to afford **140** in 49% yield. Coupling of the latter with compound **141** [104] provided the oxime derivative **142**, which was then oxidized using manganese dioxide to form the aldehyde **143**. Reductive amination of **143** with 3-azetidinecarboxylic acid followed by reduction with $NaBH(OAc)_3$ in methanol gave siponimod (Scheme 19).



Scheme 19: Reagents and conditions: (a) (i) $NaNO_2$, conc. HCl, 0°C, 30 min, (ii) H_2C=NOH, $CuSO_4$, Na_2SO_3, NaOAc, 0°C, 1.5 h, (iii) conc. HCl(aq), reflux, overnight, 26%; (b) $NaBH_4$, EtOH, 0°C, 30 min, 70%; (c) $tBuMe_2SiCl$, Et_3N, DMAP, THF, rt, overnight, 87%; (d) $^{14}CH_3I$, nBuLi, CuBr, THF, 1 h; (e) 1M n-Bu_4NF in THF, 30 min, 49% (two steps); (f) **101**, conc. HCl(aq), CH_3OH, Et_3N, pH 4–6, RT, 5.5 h, [14C]11: 77%, [14C]26: 97%; (g) MnO_2, dioxane, 50°C, 2 h; (h) 1. 3-azetidine carboxylic acid, CH_3OH, Et_3N, 55°C, 30 min, 2. $NaBH(OAc)_3$, CH_3OH, RT, 1 h, 64%.



Scheme 20: Reagents and conditions: (a) MOMCl, DIEPA, DCM, 0°C to rt 2 h, 90%; (b) n-BuLi, DMF, THF, −78 to 0°C, 94%; (c) 12 N HCl, THF, rt, 1.5 h, 81%; (d) Pd(dppf)Cl_2, $NaHCO_3$, H_2O/dioxane, 100°C, 12 h, 40%; (e) $SOCl_2$, DCM, rt, 100%; (f) Na_2CO_3, DMF, 65°C, 1.5 h, 81%; (g) 12 N HCl, THF, rt, 3 h, 96%.

7. HEMATOLOGIC DRUGS

7.1. Voxelotor

Voxelotor is a new class of therapy for sickle cell anemia. It is the first medicine that specifically targets the root cause of sickle cell disease [105]. It was originally developed by Global Blood Therapeutics, this hemoglobin S polymerization inhibitor received its first global approval in November 2019, in the USA, for the treatment of sickle cell disease in adults and pediatric patients aged ≥12 years [106]. The novel mechanism of action of the drug increases oxygen affinity for hemoglobin and thus exhibits dose-dependent HbS polymerization inhibition [107]. The recommended general dosage for voxelotor is 1500 mg orally once daily with or without food, and 1000 mg orally once daily in patients with severe hepatic impairment [108]. The synthetic schemes for voxelotor have been reported [109].

Voxelotor is synthesized by simple coupling of two key molecules **147** and **151**, followed by deprotection. The syntheses of those key components have been explained.

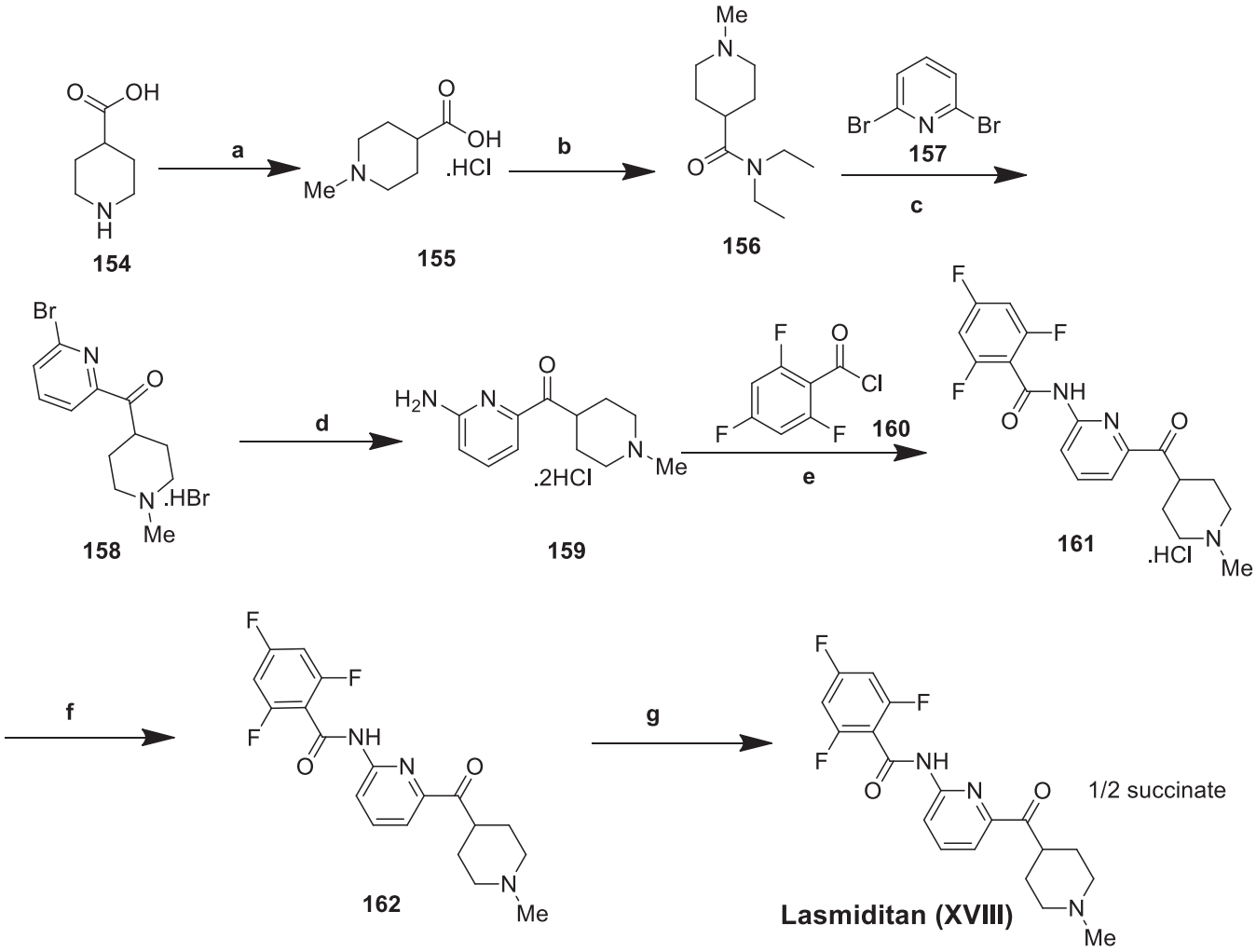
2-bromoresorcinol **144** was first MOM-protected, treated with butyl lithium, and quenched with DMF and HCl to afford compound **146** in 94% yield. It was then deprotected partially to afford the key molecule **147** in 84% yield. Compound **151**, on the other hand, was formed through Suzuki coupling of the pyrazole boronate ester **148** with chloropyridine **149**. This was followed by the chlorination of the coupled product **150** to produce compound **151** in 100% yield (Scheme 20).

7.2. Lasmiditan

Lasmiditan is an orally available serotonin receptor agonist developed by Eli Lilly and Company. It received its first approval in October 2019 and became the first and the only FDA approved medicine in a new class of acute treatment for migraine [110,111]. Lasmiditan penetrates the blood–brain barrier and could, therefore, block c-Fos (a 380 amino acid protein) expression by activating centrally located 5-HT1F receptors on trigeminal neurons [112]. The recommended dose is 50 mg, 100 mg, or 200 mg taken orally, as needed, with not more than one dose to be taken in 24 h [113].

Synthesis route for lasmiditan has been reported [114].

The commercially available starting material piperidine-4-carboxylic acid **154** was methylated using transfer hydrogenation conditions to form l-methylpiperidine-4-carboxylic acid **155**, followed by treatment with thionyl chloride and diethyl amine to afford **156** in 75–95% yield. Compound **158** was formed in 50–80% yield after the reaction of the carboxime **156** with a solution of 2,6-dibromopyridine **157** and Grignard's reagent, followed by hydrobromic acid. An amine group



Scheme 21: Conditions and reagents: (a) CH_2O, HCOOH, Pd/C, water, ambient pressure, (80–90%); (b) (i) $SOCl_2$, THF, (ii) Et_2NH/THF/Et_3N, (75–95%); (c) (i) **115**, i-PrMgCl/LiCl, THF, 25°C, (ii) HBr/HOAc (50–80%); (d) Ethylene glycol, ammonia, Cu_2O, 70°C, 4 barG, (50–75%); e) **118**, Chlorobenzene, 100°C, (75–95%); (f) $NaHCO_3$, Ethanol, (80–100%); g) Succinic acid, Ethanol, (70–95%).

was introduced in compound **158** using copper oxide in ethylene glycol and ammonia to produce **159**. This was followed by reaction with 2,4,6-trifluorobenzoylchloride **160** in the presence of chlorobenzene to afford the hydrochloride salt **161** in 75–95% yield. Treatment of the hydrochloride salt **161** with sodium bicarbonate in ethanol gave the intermediate **162** which was then converted to lasmiditan in 70–95% yield using succinic acid in the presence of ethanol (Scheme 21).

7.3. Lemborexant

Lemborexant is an orally administered, dual orexin receptor (OXR) antagonist that exhibits reversible competitive antagonism at OXR1 and OXR2 [115,116]. Discovered and developed by Eisai Inc., lemborexant received its first approval in December 2019 for the treatment of adult patients with insomnia, characterized by difficulties with sleep onset and/or sleep maintenance [117]. The mechanism of action of lemborexant is presumed to be through its dual OXR antagonism [118]. The recommended dose is 5 mg taken no more than once per night, immediately before going to bed, with at least 7 h remaining before the planned time of awakening. However, dosage may be increased to 10 mg based on clinical response and tolerability [119].

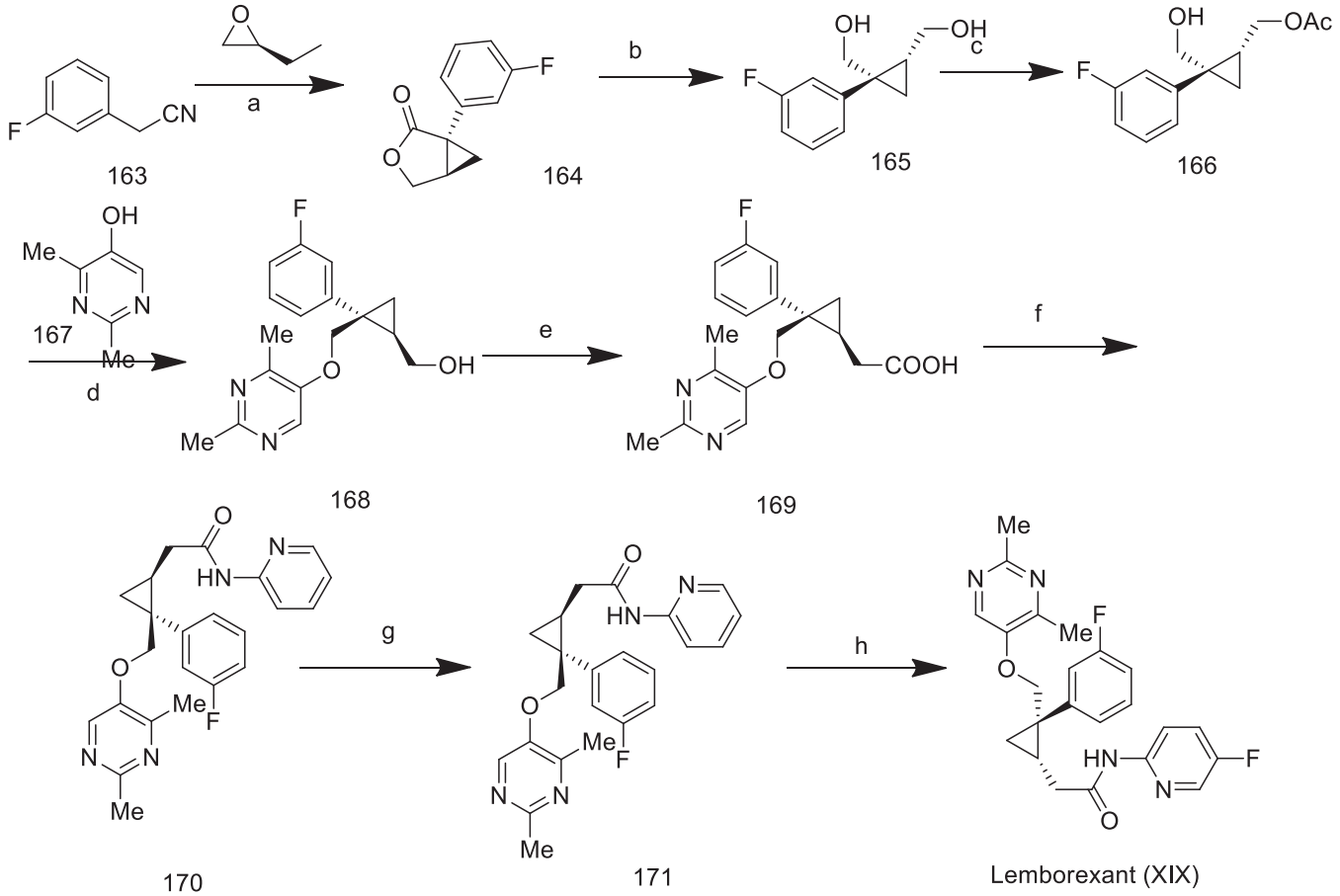
Synthesis scheme for the title compound has been reported [120].

A cyclopropane ring is introduced in the commercially available acetonitrile **163** to convert it into lactone **164**. It was then easily hydrolyzed using sodium borohydride to produce diol **165**. Regioselective acetylation was done at the 2-methanol position using Novozyme (lipase acrylic resin from Candida antarctica), to give a monoacetylated compound **166**, which further reacted with hydroxyl pyrimidine **167** through Mitsunobu reaction to produce compound **168**. Oxidation of compound **168** using suitable oxidizing agents yielded the required key compound **169**. Finally, amidation of **169** with aminopyridine gave compound **170**, which was followed by its condensation with 2-chloro-5-fluoropyridine to give the title compound (Scheme 22).

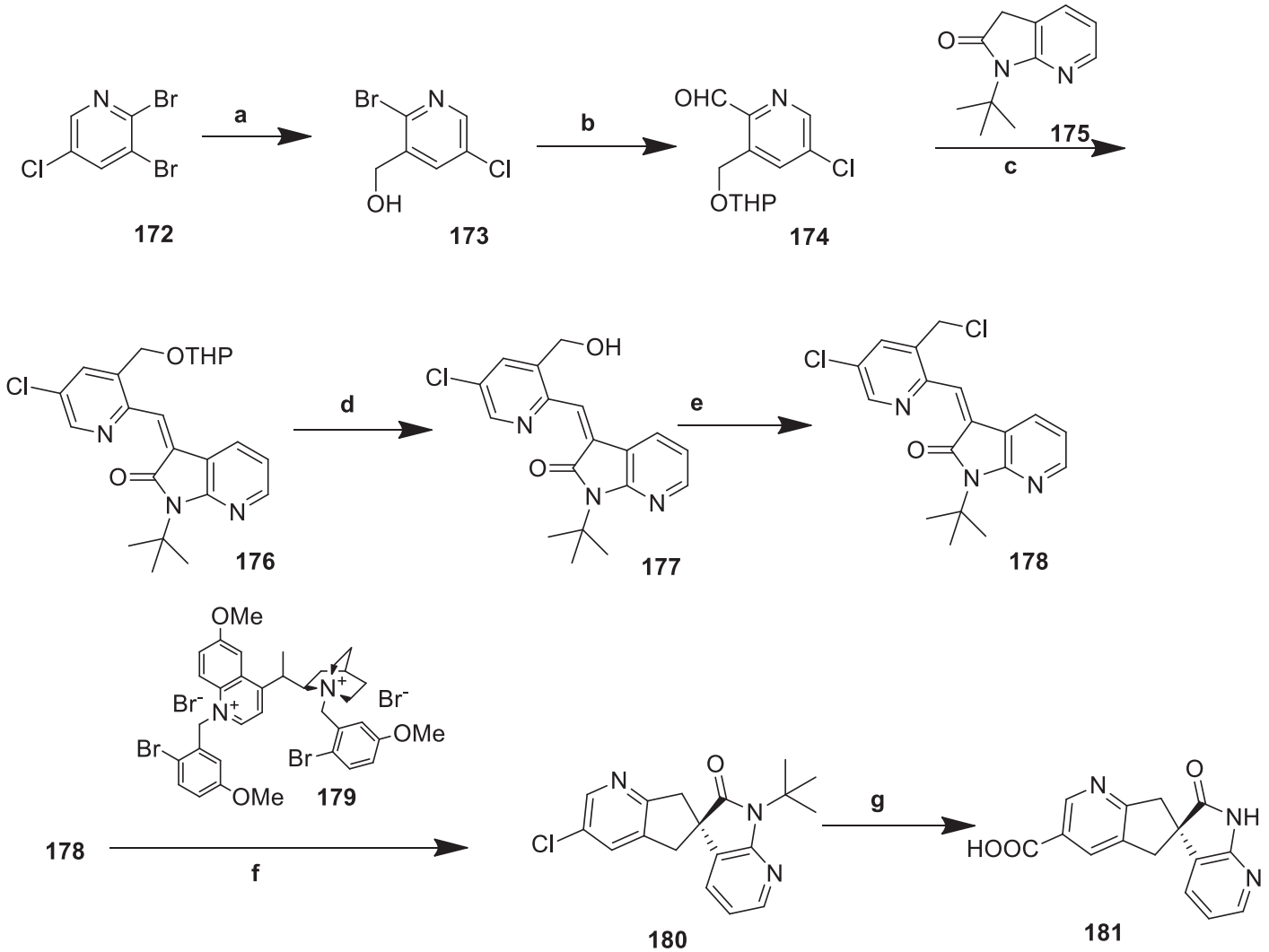
7.4. Ubrogepant

Ubrogepant is first in class of orally administered calcitonin gene-related peptide (CGRP) antagonist which was developed by Allergan under license to Merck & Co. as an acute treatment for migraine [121]. CGRP is a vasodilatory neuropeptide involved in nociceptive transmission and modulation, and its receptors are widely expressed in central and peripheral regions of the nervous system [122-124]. Ubrogepant is a highly selective CGRP antagonist that received its global approval in December 2019 [125]. The recommended daily dosage for ubrogepant is 50 mg or 100 mg; however, if required a second dose may be taken only after 2 h of initial administration. The maximum dose for a day is 200 mg [126].

The spiro-acid 181 plays a key role in the synthesis of the title compound and is subsequently used in the final step of the synthesis. The synthesis of this key ingredient is described herein.



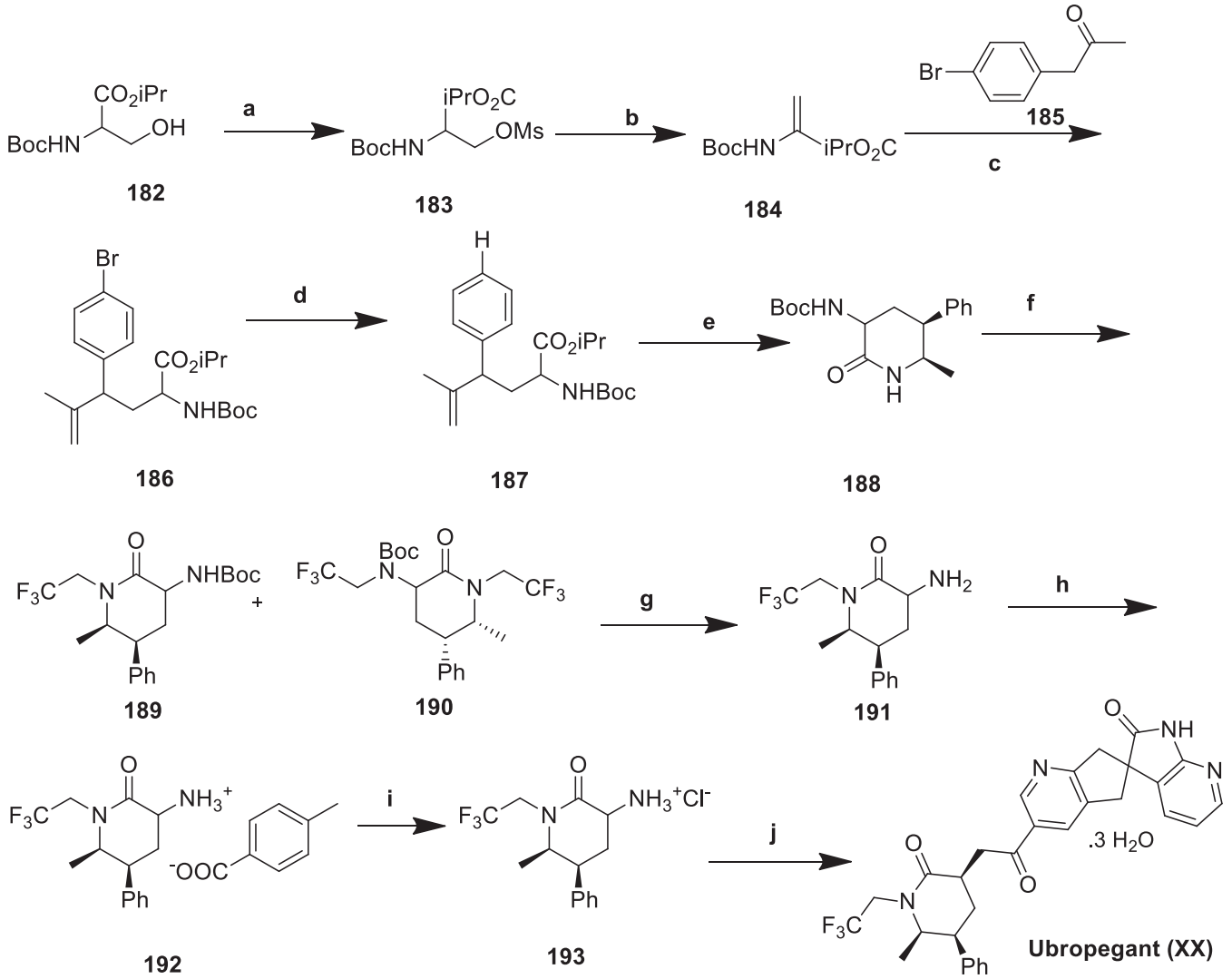
Scheme 22: Reagents and conditions: (a) NaHMDS, THF, 0°C, 3 h, then KOH, EtOH, reflux, 8 h, then HCl, 0°C-rt, 3 h; (b) $NaBH_4$, MeOH-THF, 0°C-rt, 1 h; (c) Novozym 435, vinyl acetate, rt, 17 h; (d) DIAD, PPh_3, 0°C-rt, 15 h, then NaOH, EtOH-H_2O, rt, 1 h; (e) $(COCl)_2$, DMSO, TEA, DCM, °60°C-rt, 1 h, then 2-methyl-2-butene, $NaClO_2$, NaH_2PO_4, acetone-H_2O, rt, 14 h; (f) WSC, HOBt, NH_4Cl, DIPEA, DMF, rt, 7 days; (g) 2-chloro-5-fluoropyridine, K_3PO_4, Xant phos, $Pd_2(dba)_3$, dioxane, 80°C, 1 day.



Scheme 23: Reagents and conditions: (a) (i) i-PrMgCl LiCl, THF, −40°C, 30 min, then DMF; (ii) $NaBH_4$, MeOH, rt, 30 min, 93%; (b) (i) DHP, conc. H_2SO_4, 2-MeTHF, rt, 10 min; (ii) iPrMgCl, toluene−THF, 0°C, 2 h, then DMF, 0°C, 1 h, 97%; (c) **4** (1.1 equiv), DBU (5 mol %), iPA, −2°C 2 h then rt 3 h, 87%; (d) (i) NaBH4, EtOH, rt, 1 h; (ii) HCl, iPA, 40°C, 3 h, 86%; (e) $SOCl_2$, CH_2Cl_2, 5°C, 30 min, 93%; (f) **8** (0.3 mol %), 0.3 N NaOH (1.1 equiv), toluene, −1°C, 3 h, 83%; (g) (i) $Pd(OAc)_2$ (1 mol %), DCPP (2 mol %), K_2CO_3, NMP, CO (30 psi), 120°C, 24 h, 95%; (ii) conc. HCl, 94°C, 48 h, 94%.

A regioselective transmetallation of 2,3-dibromo-5-chloropyridine **172**, after quenching with DMSO, gave an aldehyde which was readily reduced to provide alcohol **173**. The alcohol was protected and a second selective transmetallation was done in presence of i-PrMgCl in toluene to produce an anion that was converted to compound **174** in 97% yield by addition of DMF. The highly crystalline alkene as its Z-isomer **176** was produced after the condensation of aldehyde **174** with N-tert butyl azaindole **175**. It was reduced with sodium borohydride followed by a THP deprotection to produce compound **177**. Chlorination of **177** with $SOCl_2$ in the presence of DMF provided **178**. The spirocyclization of **178** was done in the presence of the novel N,N-doubly quaternized PTC **179** [127] to give the desired spiro compound **180**. The tert-butyl protecting group was removed under acidic conditions (HCl or H_2SO_4) and the desired spiro-compound **181** was finally obtained in 94% yield (Scheme 23).

Mesylation of N-Boc serine isopropyl ester **182** gave **183**, which was alkylated to form alkene **184** in 93% yield. Compound **186** was formed with 85% yield from the conjugate addition of the enolate anion of **185** to the activated alkene **184**, when enolized with 0.5 equivalent of Cs_2CO_3 in DMSO. Finally, transfer hydrogenation mediated by Pd/C of bromide **184** provided the key substrate **187** in 71% yield. Trans-amination of **187** using ATA-426 as the lead enzyme produced the desired compound **188**. A mixture of compounds was formed, following alkylation of **188** with an excess of LiOtBu and triflate in THF at sub-ambient temperature in 87% yield. The undesired compound **190** was separated after Boc deprotection, and the desired product **191** was recovered in 96% yield as a 4:1 diastereomeric mixture in favor of the β-isomer at the C-3 position, and then treated with p-toluic acid in the presence of 3,5-dichlorosalicylaldehyde at 50°C. Crystals of compound **192** were precipitated as the pure β-isomer of the p-toluic acid salt in 86% yield. After removing the salt 192 converts into 193 which upon coupling with the spiro acid 181in the presence of EDC (1.2 equivalent) and a catalytic amount of HOPO yields the desired compound in good yields (Scheme 24) [127,128].



Scheme 24: Reagents and conditions: (a) MsCl (1.1 equiv), TEA (1.1 equiv), DCM, rt, 1 h, 92%; (b) MsCl (1.3 equiv), TEA (2.5 equiv), DMF, 0°C then rt, overnight, 93%; (c) Cs_2CO_3 (0.5 equiv), DMSO, rt, 79%; (d) 10% Pd/C, HCO_2K, K_2CO_3, iPA, 60°C, 2 h, 71%; (e) i-$PrNH_2$, ATA-426 (15%), PLP (2%), pH 10.5, DMSO: H_2O (1:1), 0.2 M borate buffer, 55°C, 92% assay yield; (f) CF_3CH_2OTf (1.3 equiv), LiOtBu (1.2 equiv), THF, 16−22°C, 18 h, 87%; (g) (i) 3 N HCl, TBABr (3.8 mol %), toluene, 35°C, 3 h; (ii) 4.5 N HCl, MTBE/MeOH, 50°C, 5 h, 96%; (h) p-toluic acid (1.0 equiv), 3,5-dichlorosalicylaldehyde (1 mol %), 50°C, 3-5 h, 86%; (i) 22 (0.3 mol %), 0.3 N NaOH (1.1 equiv), toluene, −1°C, 3 h, 83%; (j) (i) **10**, $Pd(OAc)_2$ (1 mol %), DCPP (2 mol %), K_2CO_3, NMP, CO (30 psi), 120°C, 24 h, 95%; ii) conc. HCl, 94°C, 48 h, 94%.

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****Bibliographical Sketch***

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