Synthetic Approaches toward the Synthesis of Brivaracetam: An Antiepileptic Drug

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ABSTRACT: Epilepsy is a chronic neurological disorder in the brain, affecting individuals of all age groups. Nearly 1% of the world population is affected by seizure disorder, of which about 80% of the patients are observed in underdeveloped and developing countries. The predominant treatment option for epilepsy includes an antiepileptic drug named brivaracetam. This drug emerged as an unusual success of rational drug discovery in clinical development by exhibiting magnificient affinity toward synaptic vesicle glycoprotein as compared to conventional drug levetiracetam and piracetam. Given its efficiency in limiting the progression of epilepsy, this drug has drawn considerable attention of researchers to devise novel routes of its synthesis. The present review encapsulates the reported literature on synthetic strategies for brivaracetam, which will assist medicinal chemists in the further progress of its synthesis.

1. INTRODUCTION

“Epilepsy” is the condition of repeated, unjustifiable seizures, or a group of neurological disorders, affecting the nervous system of individuals of all age groups. Nearly 1% of the world population (~50 million) is affected by seizure disorder, of which about 80% of the patients are from underdeveloped and developing countries, such as focal seizures, generalized seizures, and a combination of generalized and focal seizures. In India alone, ~10 million people suffer from these disorders. According to World Health Organization (WHO), in poor and developing countries, epileptic seizures occur most commonly in juvenile and young adults, while in developed countries, the trend is observed in toddlers and elders. A recent study has shown that the occurrence of epilepsy is slightly higher in elderly men as compared to that in women, which is reflected by higher possibilities of strong stroke, neurodegenerative diseases, and tumors in this age group. In poor countries, owing to the lack of proper treatment, the number of deaths due to epilepsy seizures has exponentially increased, whereas insufficient knowledge and myths among people in developing countries make the treatment of epilepsy complicated. However, timely treatment by an anticonvulsant drug can treat epilepsy efficiently.

Among the different forms of epilepsy, focal-onset seizures with or without secondary generalization are commonly seen in patients aged 16 years onward. Unfortunately, most of the initially approved antiepileptic drugs (AEDs) were only effective over 50% of the patients. Then, in 2000, the first effective drug, levetiracetam, was approved for the treatment of adults. An overview analysis revealed that in the last 3 decades, >30% of patients failed to achieve freedom from prolonged seizures following treatment with ~14 conventional drugs AEDs. In 2004, brivaracetam was introduced as an AED, which proved to be an unusual success of rational drug discovery in clinical development by exhibiting 13-fold more affinity toward synaptic vesicle glycoprotein (SV2A) than levetiracetam and 400-fold more affinity than piracetam. Piracetam is a nootropic drug used in the treatment of central nervous system disorders. Brivaracetam is an n-propyl analogue of levetiracetam developed by the Belgian company Union Chimique Belge (UCB Pharma). In 2016, brivaracetam was approved in the United States and Europe, and it is manufactured under the brand name Briviact to treat focal-onset seizures and generalized seizures. AEDs are majorly differentiated according to their mode of action such as calcium current inhibitors, sodium channel blockers, glutamate blockers, carbonic anhydrase inhibitors, and γ-aminobutyric acid (GABA) enhancers. Brivaracetam shows a higher affinity toward SV2A in the brain, which is believed to contribute to the anti-seizure effect. The main function of SV2A is in epileptogenesis through the modulation of synaptic GABA release and inhibiting Na+ channels, thereby leading to its anti-epileptogenic action. The precise

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mode of action of brivaracetam is still unknown, but it plays an important role in regulating neurotransmitter release.22 However, its metabolism proceeds through hydrolysis of the acetamide group into the carboxylic acid metabolite.23 The potential of brivaracetam caught the attention of researchers around the world to synthesize in several ways such as through exercising enzymatic resolution, chiral pool synthesis, and asymmetric synthesis. Brivaracetam is the first AED that was discovered through optimization of pharmacodynamic activity of the molecular target.24

2. BRIVARACETAM MECHANISM OF ACTION

SV2A is a prototype protein that specifically recognizes the synaptic vesicles of endocrine granules and neurons.25,26 Brivaracetam is an analogue of levetiracetam; both bind to the human SV2A protein at nearly the same site. However, they interact with different conformational states of proteins.25 Various animal model studies state that the affinity of SV2A increased due to brivaracetam than levetiracetam in drug-resistant, focal, and generalized seizures.27 Unlike levetiracetam, brivaracetam does not inhibit high-voltage-gated-calcium current channels and is not believed to contribute to anticonvulsant properties.28 The proposed mechanism of action is illustrated in Figure 1.29

In order to synthesize brivaracetam, numerous different synthetic routes have been explored, and subsequently, a considerable number of literature studies have been published. The common approaches for the synthesis of brivaracetum are shown in Figure 2. The aim of the present review is to encourage medicinal chemists to develop new synthetic approaches for synthesizing brivaracetam. In the present review, we underline the merits and limitations of approaches employed for the synthesis of brivaracetam. Realizing the presence of impurities is important for studying the efficacy and safety of the drug. A literature review reveals that the synthetic routes of brivaracetam have nine impurities, illustrated in Figure 3 which is disclosed by Liao et al.30 Apart from that, we include four different categorization of synthetic approaches through which chirality can be introduced in the brivaracetam molecule. The categories are as follows:

(i) Separation by chiral high-performance liquid chromatography (HPLC),
(ii) Chiral pool/enantiomeric scaffold method,
(iii) Asymmetric method, and
(iv) Resolution methods.

2.1. Separation by Chiral HPLC. In this section, we illustrate the synthesis and purification of brivaracetam (1) by using separation through chiral HPLC reported in the literature.

2.1.1. Synthesis of Brivaracetam (1) by Morpholine-Catalyzed Condensation. In 2003, an initial strategy for the synthesis of brivaracetam was described in the US patent US2003120080A1.31 At the beginning, morpholine-catalyzed condensation32 of valeraldehyde (2) and glyoxylic acid (3) was carried out to form a hydroxy furanone (4) (Scheme 1). Intermediate 4 was subjected to reductive amination to obtain intermediate 6 as a crude orange oil, followed by reduction of the double bond to form a diastereomeric mixture of crude pyrrolidone as a white solid. Two diastereomers are separated by preparative HPLC on the chiral phase with EtOH/heptane (1:1) to afford brivaracetam (1) with a moderate yield. Brivaracetam (1) has been observed in two solid states, which is characterized by diffraction peaks. A further improved route to brivaracetam (1) is disclosed in the US patent US7629474-B2,33 in which synthesis of brivaracetam (1) was published by minimizing one step and improving the yield using two different methods for reductive amination, followed by hydrogenation in one pot. Later, in 2017, UCB Biopharma Sprl reported a continuous flow process for the synthesis of brivaracetam (1) disclosed in the publication WO2017076737A1.34 The diastereomers are separated by a multi-column continuous (MCC) technique in an n-heptane/ethanol (45:55%) mixture, followed by crystallization from 2-PrOAc. In the modern era of drug discovery, flow chemistry is playing a crucial role in API process development and bulk
manufacture in the pharmaceutical plants and chemical industries.\textsuperscript{35} In different aspects of the slight modification in the scheme, some other groups also filed a batch process patent.\textsuperscript{36} The drawback accompanying these schemes is separation of diastereomers by using chiral HPLC which is not industrially viable for large-scale synthesis of brivaracetam.

2.1.2. Synthesis of Brivaracetam (1) by Using Two Different Synthetic Strategies. In 2004, a new synthetic route was published by Kenda et al.\textsuperscript{15} (Scheme 2). Route-I starts with 1,4-Grignard addition on furan-2(5$H$)-one (7) in the presence of CuI in diethyl ether to afford 4-propylidihydrofuran-2(3$H$)-one (8). The ring-opening was done by trimethylsilyl iodide to obtain intermediate (9). Further acyl chloride 3-(iodomethyl)-hexanoyl chloride (10) was obtained from acid intermediate 9 using thionyl. Finally, cyclization reaction takes place with S-2-aminobutyramide (5) in basic media, affording a racemic mixture of brivaracetam (11).

Brivaracetam (1) was recrystallized in di-isopropyl ether and separated by chiral HPLC.

Route-II starts with the synthesis of methyl-3-formylhexanoate (13) from the aldehyde (2) via alkylation of the enamine\textsuperscript{37,38} with methyl bromoacetate (12). Reductive amination of 12 with S-2-aminobutyramide was done to afford methyl-3-(((R)-1-amino-1-oxobutan-2-yl)amino)-methyl)-hexanoate (14). The yielded 14 undergoes acid amine coupling with HOBT and DCE to obtain a racemic mixture of brivaracetam (11). The pure brivaracetam (1) was obtained via recrystallization in di-isopropyl ether and separated by chiral HPLC. The present report could not explore the yield of 1. The major limitation of this method is separation of isomers by using chiral HPLC.

2.1.3. Synthesis of Brivaracetam (1) by Michael Conjugate Addition. In 2007, the published PCT WO2007031263A\textsuperscript{19} by UCB pharmaceutical limited reported the synthesis of brivaracetam (1) using (R)-4-propylpyrrolidin-
2-one (18) as the intermediate, which was granted in the Japanese Patent JP2009507870A1 (Scheme 3). Racemic γ-nitro ester (16) was synthesized by Michael conjugate addition of nitro-methane with (E)-ethyl-hex-2-enoate (15) in the presence of diazabicycloundecene. Further reduction of the nitro group provides the racemic 4-pyrrolidin-2-one (17). Separation of the racemic mixture of 17 was done by liquid chromatography to obtain pure (R)-4-propyl-pyrrolidin-2-one (18). The obtained intermediate 18 reacts with methyl 2-bromobutanoate in the presence of NaH to obtain racemic methyl 2-((R)-2-oxo-4-propylpyrrolidin-1-yl)butanoate (19).

Later, intermediate 19 was treated with aq. ammonia 50% (w/w) to obtain the racemic intermediate 11. The separation of a racemic mixture of brivaracetam (11) was done through a chiral column in EtOH/heptane (1:1). The separation affords (44%) brivaracetam (1). In a given synthetic strategy, inexpensive starting materials and reagents were used but chiral HPLC separation was performed twice, hence resulting in 2 times loss of undesired isomers.

2.1.4. UCB Pharmaceutical Alternative Route for the Synthesis of Brivaracetam (1) by Using (R)-Methyl-2-bromobutanoate. In 2008, an alternative route to the

Figure 3. Known impurities of Brivaracetam (1).

Scheme 1. Therapeutic Synthesis Route to Brivaracetam (1) Developed by UCB Limited
synthesis of brivaracetam (1) was reported by UCB pharmaceutical in the US patent US20080009638 (Scheme 4). The synthetic strategy begins with (R)-methyl-2-bromobutanoate (21) with HCl salt of methyl 3-(aminomethyl)hexanoate (20) in the presence of K$_2$CO$_3$ to obtain a crude yellow oil residue of methyl-3-(((1-methoxy-1-oxobutan-2-y1)amino)methyl)hexanoate (22), which was subjected to cyclization in the presence of hydroxypyridine to afford crude methyl (2S)-2-(2-oxo-4-propylpyrrolidin-1-y1)butanoate (23). Then, ester hydrolysis of 19 in 1 M NaOH solution was done to obtain (2S)-2-(2-oxo-4-propylpyrrolidin-1-y1)butanoic acid (24), which was treated with triethylamine in the presence of ethyl chloroformate and liq. ammonia to provide 32% yield of a mixture of (2S)-2-(2-oxo-4-propylpyrrolidin-1-y1)butanamide (11). Finally, separation through chiral HPLC obtained brivaracetam (1).
reported a new synthetic approach for the preparation of brivaracetam (1) disclosed in IN201711038420 (Scheme 5). The synthetic route starts from condensation of butyraldehyde (25) and 3-ethoxy-3-oxopropanoic acid (26) in the presence of DMAP to obtain an adduct intermediate, followed by Michael addition of nitro methane to form ethyl 3-(nitromethyl)hexanoate (27), which undergoes acid hydrolysis through the Nef reaction, formation of aldehyde, followed by protection to obtain ethyl-3-(dimethoxymethyl)hexanoate (28). Further ester hydrolysis under basic conditions was done to obtain an intermediate 29. Intermediate 29 undergoes acid amine coupling by using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride salt (EDC-HCl) and HOBt to afford N-((S)-1-amino-1-oxobutan-2-yl)-3-(dimethoxymethyl)-hexanamide (30). The obtained molecule 30 transforms into a diastereomeric mixture 11 via deprotection of aldehyde, followed by reductive amination. The diastereomeric mixture 11 introduced for column chromatography yielded 35% brivaracetam (1) with 99.7% purity. The major limitation of this reported synthetic route is poor yield.

2.1.6. Synthesis of Brivaracetam (1) by Using Palladium-Catalyzed Oxidative Cyclization and Grubbs’ II Gen. Catalyst. In route-I, in 2019, Chavan et al. reported the synthesis of brivaracetam, which is illustrated in Scheme 6. The synthesis begins with transformation of (E)-pent-2-en-1-ol (31)
to allylic bromide \((32)\) using PBr\(_3\). The crude bromide intermediate \(32\) was subjected to \(N\)-alkylation with \(5\) by using K\(_2\)CO\(_3\) to afford \((S,E)\)-2-(pent-2-en-1-ylamino)butanamide \((33)\). Further compound \(33\) undergoes reflux with dimethyl malonate \((34)\) to obtain a key intermediate \((35)\). Compound \(35\) is the key precursor that undergoes ring-closing metathesis reaction by using Grubbs’ II gen. catalyst to provide intermediate \(6\). Brivaracetam \((1)\) was obtained from compound \(6\) via hydrogenation, followed by chiral HPLC separation. The overall yield in the reported synthetic scheme is good; however, the undesired isomer of brivaracetam \((1)\) was also obtained, which limits the general utility of the scheme.

2.2. Chiral Pool/Enantiomeric Scaffold Method. Recently, several synthetic advancements have been introduced to the synthesis of brivaracetam using commercially available chiral starting materials to increase the chiral purity of brivaracetam.

2.2.1. Synthesis of Brivaracetam \((1)\) by Using \((R)\)-Epichlorohydrin. In 2018, Foshan Longxin Pharmaceutical Technology Co. Ltd. developed a novel process for the preparation of brivaracetam \((1)\) (Scheme 7).\(^{48}\) The synthesis begins with condensation of diphenyl malonate \((41)\) and the commercially available enantiomeric scaffold, \((R)\)-epichlorohydrin \((42)\), to obtain \((S,E)\)-2-oxo-3-oxabicyclo[3.1.0]hexane-1-carboxylate \((43)\). The obtained compound \(43\) was treated with ethyl magnesium bromide and cuprous iodide to afford the intermediate \((44)\). Later, \(44\) treated with lithium chloride yielded \((R)\)-4-propyldihydrofuran-2(3\(H\))-one \((45)\) via the well-known reaction Krapcho decarboxylation. Further ring-opening with trimethylsilane was performed to obtain methyl \((R)\)-3-(bromomethyl)hexanoate \((46)\). Finally, brivaracetam \((1)\) was obtained via cyclization of \(46\) with amine \(5\) in the presence of alkaline media. The present synthetic method merits on selective chiral transformation from the chiral pool with an overall good yield. Also, Wang and co-workers\(^{49}\) reported a similar synthetic method distinguished only via \(N\)-alkylation, followed by ester amine coupling to obtain pure brivaracetam \((1)\).

2.2.2. Synthesis of Brivaracetam \((1)\) by Using \((R)\)-(Methoxycarbonyl)hexanoic Acid. In 2017, Shanghai Bocimed Pharmaceutical Co. Ltd. was reported to improve the synthesis method of brivaracetam \((1)\) disclosed in Scheme 7. Foshan Longxin Pharmaceutical Technology Co. Ltd. Developed a Novel Process for the Preparation of Brivaracetam \((1)\) (Scheme 8). Shanghai Bocimed Pharmaceutical Co. Ltd. Reported Route toward the Synthesis of Brivaracetam \((1)\).
In the present advancement, the synthesis of brivaracetam (1) was performed by using (R)-3-(methoxycarbonyl)hexanoic acid (47) to minimize the extent of racemization and to also increase the chemical purity. Using 47 as a starting precursor, intermediate (45) was produced through reduction of ester, followed by cyclization. Compound 45 was employed for the nucleophilic substitution reaction by using trimethylsilyl iodide (TMSI) to afford (R)-3-(iodomethyl)hexanoic acid (48). Later, acyl chloride 46 was obtained from acid intermediate 48 by using thionyl chloride. Finally, N-alkylation of compound 46 using S-2-amino-butyramide (5) yielded pure brivaracetam (1). The analogous embodiments were used for the synthesis of intermediate 45 and brivaracetam (1). The utilized embodiments were made from different starting materials, which are enclosed in the given reported literature.

2.2.3. Synthesis of Brivaracetam (1) by Using Two Chiral Precursors. In 2017, Emeishan Hongsheng Pharmaceutical Co. Ltd. reported a new synthetic method for the preparation of brivaracetam (1). In the chiral pool method, naturally occurring, enantiomerically pure precursors are convenient to carry chirality; however, the synthetic/unnatural chiral pool precursors are expensive.

2.2.4. Synthesis of Butyrolactone (45) by Using (S)-2,3-Dihydroxypropanoic Acid (52). In 2018, Anhui Huasheng Pharmaceutical Technology Co. Ltd. reported a new synthetic route for the preparation of butyrolactone (45). In the present patent CN107698543, an inexpensive chiral precursor such as glyceric acid (52) was utilized; however, a number of steps are reported for intermediate 45 (Scheme 10). First, glyceric acid (52) converts into (S)-tert-butyl 2,3-dihydroxypropanoate (53) using di-tert-butyl dicarbonate (Boc) 2O. The crude residue of intermediate 53 undergoes protection of primary alcohol with benzyl chloride obtained (S)-tert-butyl-3-(benzyloxy)-2-hydroxypropanoate (54). Further protection of the secondary alcohol of 54 was done by using trifluoromethanesulfonic anhydride to produce (S)-tert-butyl-3-(benzyloxy)-2-(((triﬂuoromethyl)sulfonyl)oxy)propanoate (55). Later, compound (R)-tert-butyl-2-((benzylxoy)-methylpentanoate) (56) was obtained via alkylation of compound 55 using Grignard reagent by introducing n-propyl instead of the triﬂate group. Debenzylation of 56 in the presence of H2, Pd/C obtained (R)-tert-butyl-2-(hydroxymethyl)pentanoate (57). The yielded intermediate 57 was introduced with the carbon benzene sulfonylate (51). Finally, alkylation of compound 51 by using the Grignard reagent yielded brivaracetam (1).
elongation step by nitrile group insertion in the presence of methanesulfonyl chloride, non-nucleophilic base, phase-transfer catalyst, and potassium cyanide to obtain \((R)-\text{tert-butyl-2-(cyanomethyl)-pentanoate (58)}\). Ester hydrolysis of intermediate \((58)\) produced \((R)-2-(cyanomethyl)pentanoic acid (59)\), which was subjected to reduction by using the borane−tetrahydrofuran complex to afford \((R)-3-(\text{hydroxymethyl})\)hexanenitrile (60). Hydrolysis of nitrile functionality of 60 was performed by using sodium hydroxide to obtain \((R)-3-(\text{hydroxyethyl})\)hexanoic acid (61). Last, the cyclization of intermediate 61 yielded \((R)-4\text{-propyldihydrofuran-2(3H)-one (45)}\) with good yield.

2.3. Asymmetric Method. In this section, we demonstrate the synthesis of brivaracetam (1) by using various organochiral catalysts and chiral auxiliaries reported in the literature.

2.3.1. Using Catalyst. Generally, organocatalysis has a diverse range of activities, having cost-effective starting materials and good moisture and air stability along with recovery. It is proven to be more economical and fruitful in synthetic chemistry.

2.3.1.1. Stereoselective Synthesis of Brivaracetam (1) by Using AD Mix-β. In 2007, an unconventional synthetic route of brivaracetam (1) with high stereoselectivity was developed by UCB pharma disclosed in PCT WO2007065634. It is granted in US patent US8076493B2 (Scheme 12). The synthetic route begins with the asymmetric catalyst Sharpless asymmetric dihydroxylation, which makes high enantiomeric enrichment in the field of synthetic chemistry. Pent-1-ene (64) was used with the catalyst AD Mix-β to furnish the required enantiomerically pure \((R)-\text{pentane-1,2-diol (65)}\). Further, compound \((R)-4\text{-propyl-1,3,2-dioxathiolane-2,2-dioxide (66)}\) was added to obtain \((R)-3\text{-hexanenitrile (60)}\). The hydrolysis of nitrile functionality of 60 was performed by using sodium hydroxide to obtain \((R)-3\text{-hexanoic acid (61)}\). Last, the cyclization of intermediate 61 yielded \((R)-4\text{-propyldihydrofuran-2(3H)-one (45)}\) with good yield.
Scheme 13. Preparation of Brivaracetam (1) by Shanghai Xuantai and Shanghai Bopu Nuo Ltd.

Scheme 14. Process for Preparing Brivaracetam (1) by Jiangxi Qingfeng Pharmaceutical

was synthesized by the treatment of thionyl chloride with intermediate 65 in the presence of a catalytic amount of ruthenium(III) chloride. Compound (S)-dimethyl-2-propylcyclopropane-1,1-dicarboxylate (67) was synthesized from 66 and 34 in the presence of NaH base. Hydrolysis of intermediate 67 affords (S)-2-propylcyclopropane-1,1-dicarboxylic acid (68). Further protection of dioic acid was performed with acetone in the presence of acetic anhydride and sulfuric acid to afford (S)-6,6-dimethyl-1-propyl-5,7-dioxaspiro[2.5]octane-4,8-dione (69). Later, the next step involves the homoconjugate58 reaction for ring-opening of the spiro acylal 59 with amine 5, followed by intramolecular cyclization15 to afford the mixture of (4R)-1-((S)-1-amino-1-oxobutan-2-yl)-2-oxo-4-propyl pyrrolidine-3-carboxylic acid (70) and as an impurity 1-((S)-1-amino-1-oxobutan-2-yl)-2-oxo-5-propyl pyrrolidine-3-carboxylic acid (71).60 In the last step, decarboxylation of compound (70) in MIBK at 120 °C obtained brivaracetam (1). The use of the expensive asymmetric chiral catalyst AD Mix/β limits the general utility of the protocol.

2.3.1.2. Synthesis of Brivaracetam by Using the Q-BTBSA Catalyst. In 2020, Shanghai Xuantai Pharmaceutical Technology Co. Ltd. and Shanghai Bopu Nuo Technology Development Co. Ltd. reported a new process for the synthesis of brivaracetam (1). By using the chiral catalyst [(N-((S)-(6-methoxyquinolin-4-yl)-((1S,2S,4S,SR)-5-vinyl-quinuclidin-2-yl)methyl)-3,5-bis-(trifluoromethyl)-benzenesulfonamide)] (Q-BTBSA) (74) catalyst, the synthesis of brivaracetam (1) is disclosed in WO2020051796A1 (Scheme 13). In the beginning, dehydration of 3-propyl pentanedioic acid (72) by acetic anhydride obtained 4-propyl dihydro-2H-pyran-2,6(3H)-dione (73). Compound 73 undergoes stereoselective anhydride-opening with the Q-BTBSA catalyst 74 to afford (R)-3-(2-methoxy-2-oxoethyl)hexanoic acid (75) with a desired stereocenter, followed by aminolysis of intermediate 75 to afford (S)-3-(2-amino-2-oxoethyl)-hexanoic acid (76). Later, amide reduction of compound 76 to amine intermediate 77 was performed, followed by esterification to earn (R)-tert-butyl-3-(((1-cyanopropyl)-amino)methyl)hexanoate (80). The obtained intermediate 80 undergoes resolution of amine through di-benzoyl tartaric acid (D-(+)-DBTA) (81) in diisopropyl ether (cautions: diisopropyl ether can form explosive peroxides upon standing in air for long periods) to form a (R)-tert-butyl-3-(((S)-1-cyanopropyl)-amino)methyl)-
hexanoate (82). Last, brivaracetam (1) was synthesized in two steps: lactamization of compound 82, followed by reduction of the nitrile intermediate 83.

2.3.1.3. Organocatalyst-Mediated Asymmetric Synthesis of Brivaracetam (1). In 2019, Jiangxi Qingfeng Pharmaceutical Co. Ltd. reported a new synthetic approach for the preparation of brivaracetam (1) disclosed in the Chinese patent CN109574778A62 (Scheme 14). The synthetic route starts with the organocatalyst-mediated asymmetric reaction using (2R,5S)-2-(tert-butyl)-3,5-dimethyl-imidazolidin-4-one (85) (MacMillan imidazolidinone) as a catalyst. Valeraldehyde (2) and diethyl 2-bromomalonate (84) was treated in the presence of bismuth trioxide and 25w of compact fluorescent lamp (CFL) to obtain (R)-diethyl-2-(1-oxopentan-2-yl)malonate (86) with a desired stereocenter. Intermediate 86 was subjected to reductive amination by using (S)-2-amino-butaneamide (5) with sodium triacetoxy-borohydride (STAB) to obtain intermediate 87. Brivaracetam (1) was obtained by 87 undergoes Krapcho decarboxylation at higher temperature in MIBK. This synthetic route provides good yield in minimum synthetic steps.

2.3.2. Using Chiral Auxiliary. Stereoselective generation of chiral center was performed by using the temporarily incorporated chiral substrate (chiral auxiliary) with diastereofacial control in the reaction. Chiral auxiliaries can be recycled to minimize the cost of the chiral reagents used routinely. The major drawback is that one enantiomer is readily available but the other one is far more expensive; both the enantiomers of chiral auxiliaries are usually not available, and hence, chiral auxiliaries need to be synthesized.

2.3.2.1. Synthesis of the Key Intermediate (45) and Brivaracetam (1) Using Chiral Auxiliaries. In 2016, a new synthetic pathway for the preparation of substituted butyrolactone (45) developed by Chinese companies Shanghai Hua Moxi Pharmaceutical Technology Co. Ltd. and Jiangxi Qingfeng Pharmaceutical Co. Ltd. is reported in CN106008411A,64 which is useful in the preparation of brivaracetam (1) (Scheme 16). The synthetic scheme begins with the mixed anhydride method65 for the coupling of oxazolidinone (95), in which pivaloyl chloride (96) is used to activate valeric acid (94) to form a mixed anhydride, and (S)-
4-benzyloxazolidin-2-one (95) was added to a fordox (S)-4-benzyl-3-pentanoyl oxazolidin-2-one (97). Further, compound (R)-3-((S)-4-benzyl-2-oxazolidinone-3-carbonyl)-hexanoic acid tert-butyl ester (99) was prepared by alkylation of intermediate 97 with tert-butyl bromoacetate (98). Later, amide hydrolysis accomplished to remove the chiral auxiliary by using LiOH and peroxide to obtain (R)-2-(2-(tert-butoxy)-2-oxoethyl)-pentanoic acid (100) with a desired stereogenic center. Selective reduction of acid intermediate 100 by borane dimethyl sulfide (BMS) for lactonization afforded (R)-4-propyl dihydrofuran-2-(3H)-one (45). Jiangxi Qingfeng Pharmaceutical Co. Ltd. works on the structural chemistry for reducing the cost of production and strongly practicable on plant scale. This method is disclosed in CN109535107.6. Astatech (Chengdu) Pharma Co. Ltd. reported a new synthetic route for brivaracetam (1) by using chiral auxiliaries, in which they proposed the same chemistry until the synthesis of intermediate (45) CN107216276A. New steps were introduced with nucleophilic substitution ring-opening by the alkylation reagent TMSI to form (R)-3-(iodomethyl)hexanoic acid (48). The obtained intermediate 48 undergoes chlorination, followed by coupling with (S)-2-aminobutanamide (5) to provide brivaracetam (1). The analogous embodiments for the synthesis of intermediate (45) and brivaracetam (1) are reported in the patent literature. However, they used different substituents on auxiliary and different reagents for ring-opening to produce brivaracetam (1).

2.3.2.2. Synthesis of Brivaracetam (1) Using the Chiral Auxiliary (S)-4-Benzyl-3-Pentanoyl Oxazolidin-2-One (95). In 2018, Beijing Abeno Pharmaceutical Co. Ltd. reported a new synthetic approach for the preparation of brivaracetam (1) disclosed in the Chinese patent CN108689903B and PCT (Scheme 17). In the beginning, generation of a stereogenic center through alkylation of (S)-4-benzyl-3-pentanoyl oxazolidin-2-one (97) by using 2-bromoaceto-nitrile (101) in the presence of LiHMDS obtained alkylated intermediate 102. Compound 102 undergoes cleavage of the chiral auxiliary, followed by reduction of acid, by using sodium borohydride to afford (R)-
3-(hydroxymethyl)hexanenitrile (60). Protection of the hydroxyl group was carried out via benzyl bromide to form a protected intermediate (R)-3-((benzyloxy)-methyl)hexanenitrile (103). Reduction of nitrile was performed to afford an acid intermediate 104, followed by acid amine coupling with (S)-2-aminobutanamide (5) to obtain (R)-N-(((S)-1-amino-1-oxobutan-2-yl)-3-((benzyloxy)methyl)hexanamide (105). Intermediate 105 was subjected to deprotection of benzyl ether using H2, 10% Pd/C afford (R)-N-((S)-1-amino-1-oxobutan-2-yl)-3-(hydroxymethyl)hexanamide (106). A further halogenation reaction was carried out to afford an intermediate (R)-N-((S)-1-amino-1-oxobutan-2-yl)-3-(chloromethyl)hexanamide (107). Last, condensation reaction takes place in the presence of LiHMDS to obtain brivaracetam (1). Stereokem Private Ltd., India, reported analogous embodiments in patent IN201741028352, but they started their synthesis with the preparation of chiral auxiliaries.

2.4. Resolution Method. With the help of a single enantiomer of a chiral reagent conversion of a racemic mixture into a mixture of diastereomers, this can be easily separated by recrystallization or chromatographic technique. The limitation of the method is to lose another 50% undesired isomer; however, it can be recycled by racemization.

2.4.1. Chemical Resolution. 2.4.1.1. Synthesis of Brivaracetam (1) Using Stereochirnal Resolution with R-Phenethyl-amine. In 2017, Chengdu Meiyugao Pharmaceutical Co. Ltd. published a new synthetic process for the preparation of brivaracetam (1). Avoiding a chiral chromatographic column by using stereochirnal resolution in the presence of R-phenethylamine (110) is disclosed in CN106748950A. The synthetic route starts with the preparation of intermediate 4 from valeraldehyde (2) and glyoxylic acid (3) in the presence of morpholine. Compound 4 undergoes reductive amination with S-2-amino-butric acid methyl ester hydrochloride (108) to afford (2S)-methyl-2-(2-hydroxy-5-oxo-3-propyl-2,5-dihydro-1H-pyrrol-1-yl)butanolate (109). Further hydrogenolysis was carried out using ammonium formate, 10% Pd/C, to obtain (2S)-methyl 2-(2,oxo-4-propyl pyrrolinid-1-y1)butanolate (23). Later, ester hydrolysis was carried out in the presence of sodium hydroxide along with methanol, water, and THF at a ratio of 1:1:1 to afford an acid intermediate (24). Stereohemical resolution of intermediate 24 by using (R)-1-phenyl-ethanamine (110) obtained chiral acid amine salt 111. The yielded amine salt 111 dissolves in water and adjusts the pH to 10 by using the base to afford (S)-2-((R)-2-oxo-4-propyl pyrrolindin-1-yl)butanoic acid (112). In the last step, conversion of acid 112 by using DIPEA, ammonium chloride, and HATU obtained brivaracetam (1). The overall yield is good; however, the loss of half undesired isomer is observed. Later on, the synthesis of brivaracetam was also shown by many research groups using stereochirnal resolution of the racemic acid intermediate with (S)-1-phenyl-ethanamine (111).

2.4.1.2. Synthesis of Butyrolactone (45) by Using Stereochemical Resolution for Acid with (1R,2S)-2-Amino-1,2-diphenylethanol (115). In 2019, Chengdu Clermont Pharmaceutical Technology Co. Ltd. reported a synthetic route for the preparation of butyrolactone (45) by using stereoselective chiral resolution, which is disclosed in CN109942516A. The synthetic scheme begins with dehydrogenation of 5-hydroxy-4-propyl-furan-2(5H)-one (4) using sodium borohydride to afford 4-propyl furan-2(5H)-one (113). The obtained intermediate 113 undergoes
hydrogenolysis in the presence of 10% Pd/C with hydrogen to afford a racemic mixture of 4-propyl dihydrofuran-2(3H)-one (8). Further ring-opening of intermediate 8 by hydrolysis of lactone yielded intermediate (114). 3-(Hydroxymethyl)hexanoic acid (114) undergoes stereoselective separation by using (1R,2S)-2-amino-1,2-diphenylethanol (115) to afford salt 116. The obtained salt was neutralized by using concentrated HCl to afford the enantiopure (R)-3-((S)-1-phenylhexanamido)hexanoic acid (61). The crude mass of intermediate 61 was used without separation for cyclization to provide (R)-4-propylfuran-2(5H)-one (113). The obtained compound 113 undergoes reduction in the presence of copper salt, sodium tert-butoxide, and S-BINAP to yield intermediate 8. The compound undergoes lactone-opening by the nucleophilic attack of S-phenylethylamine (110) to afford intermediate 120. The yielded compound 120 was recrystallized by using isopropyl acetate and di-isopropyl ether (5:95) mixture to provide enantiopure (R)-3-((S)-1-phenyl-ethyl) hexanamide (121). Enantiomerically pure 121 was

2.4.1.3. Synthesis of Brivaracetam (1) by Using Stereochemical Resolution. In 2019, Shanghai Park Yi Chemical Technology Co. Ltd. revealed a new synthetic route for the preparation of brivaracetam (1) by using the stereogenic chiral separation method, which is disclosed in WO201924219274 (Scheme 20). The synthesis begins with the morpholine-catalyzed condensation to obtain intermediate 4. Further, dehydroxylation of intermediate 4 was carried out to afford 4-propylfuran-2(3H)-one (113). The obtained compound 113 undergoes reduction in the presence of copper salt, sodium tert-butoxide, and S-BINAP to yield intermediate 8. The compound undergoes lactone-opening by the nucleophilic attack of S-phenylethylamine (110) to afford intermediate 120. The yielded compound 120 was recrystallized by using isopropyl acetate and di-isopropyl ether (5:95) mixture to provide enantiopure (R)-3-(hydroxymethyl)-N-((S)-phenylethyl) hexanamide (121).
neutralized with 30% aq. H$_2$SO$_4$ to generate compound 45. Later, the ring-opening of compound 45 via the nucleophilic substitution reaction afforded compound 122. The obtained compound 122 was esterified with ethyl alcohol to produce ethyl-(R)-3-(bromomethyl)-hexanoate (123). Ultimately, the aimed brivaracetam (1) was accomplished by coupling of intermediate 123 with (S)-2-aminobutanamide (5).

2.4.2. Enzymatic Resolution. Enzymes employing an extremely selective method were used to produce enantiomerically pure and diastereoselective impact on both natural and unnatural substrates under very mild conditions. The main drawback of this method is the limitation of the substrate with a limited functionality.

2.4.2.1. Synthesis of Butyrolactam (18) by Chemoenzymatic Resolution. In 2016, the synthesis of butyrolactone (18) via racemization and stereoselective reductive amination was patented by Sandoz Ag Pharmaceuticals in WO2016075082A1 (Scheme 22). The proposed synthetic route outlines the utility of $\omega$-transaminase (TA) as a catalyst in the transformation of aldehyde to amine via stereoselective reductive amination. The illustrated synthesis starts with the formation of enamine 124 using valeraldehyde (2) and diisopropyl amine. The obtained enamine 124 was treated with ethyl bromoacetate (12) to generate ethyl 3-formylhexanoate (13). Racemization of aldehyde 13 with $\omega$-transaminase in buffer at pH 7 and L-alanine obtained the intermediate (R)-3-(aminomethyl)hexanoate (20). Targeted butyrolactam (18) was obtained via the treatment of intermediate 20 with NaOH. Selective method allows researchers to produce an enantiomerically pure substrate with the potential recyclable process; however, the overall yield is poor. Similarly, Christine S. Fuchs et al. also reported a chemoenzymatic stereoselective reductive amination of an aldehyde into an amine by using (R)-selective HN-TA extracted from marine bacteria Hyphomonas neptunium to synthesize butyrolactam (18) as a precursor of brivaracetam (1).

2.4.2.2. Synthesis of Butyrolactone (45) by Chemoenzymatic Resolution. In 2019, Shanghai Yikelai Biomedical Technology Co. Ltd. reported a process for the preparation of (R)-4-propyldihydrofuran-2(3H)-one (45) by using alcohol dehydrogenase (ADH) with enzyme patented in CN109852644A (Scheme 23). The synthetic route begins with the condensation of valeraldehyde (2) and glyoxylic acid (3) in morpholine to obtain intermediate 4. The obtained compound 4 was subjected to hydrogenolysis by H$_2$, Pd/C to...
obtain 5-hydroxy-4-propyl-dihydrofuran-2(3H)-one (125). In the last step, intermediate 125 was reduced by the heterologous ADH enzyme extracted from *Bacillus subtilis* to afford (R)-4-propyldihydrofuran-2(3H)-one (45).

2.4.2.3. Synthesis of Brivaracetam (1) by Using the Biocatalytic Route with Lipase Enzyme. In 2016, Schule et al.\(^\text{77}\) reported a new synthetic approach for the preparation of brivaracetam (1) by using biocatalytic resolution with fine screening of different enzymes (Scheme 24). At first, alkylation of dimethyl 2-propyl malonate (126) with tert-butyl 2-bromoacetate (98) afforded intermediate 127. Further, intermediate 127 undergoes Krapcho decarboxylation to form 2,2-(tert-butoxy)-2-oxoethylpentanoic acid (128). The aimed (R)-2-(2-(tert-butoxy)-2-oxoethyl)pentanoic acid (100) was synthesized by using enzymatic resolution of racemic compound 128, for which they screened four families of enzymes and found protease B and C from *B. subtilis* that exhibit excellent enzymatic performance. Shanghai Yikelai Biomedical Technology Co. Ltd. also reported enzyme-catalyzed reaction by hydrolysis of ester to acid in the patent CN109266630A.\(^\text{79}\) The enantiomerically pure (R)-succinic acid 100 was selectively reduced to alcohol 57, followed by the addition of TFA to afford butyro lactone (45). Compound 45 further undergoes ring-opening by the nucleophilic substitution reaction in the presence of bromine in acetic acid to afford acid intermediate 122. Intermediate 122 was introduced by esterification to obtain (R)-ethyl 3-(bromomethyl)hexanoate (123). Finally, compound 123 coupled with (S)-2-amino butanamide (5) yielded aimed at brivaracetam (1).

3. CONCLUSIONS

In this review, we summarized all the available synthetic strategies reported in the literature. Especially in the last few years, by an enantiomeric scaffold, chiral pool, chiral organocatalysts, and metal complex catalysts, chemical resolution and enzymatic resolution are developed for synthetic approaches used in the method by which chirality is introduced in the brivaracetam molecule. Therefore, with the advancement in catalytic approaches, an impressive progress has been made in the synthesis of brivaracetam.

4. FUTURE RESEARCH PERSPECTIVE

In the class of AEDs, brivaracetam exhibits 13-fold more affinity toward SV2A than levetiracetam and 400-fold more affinity than piracetam. This rationale converted the interest of the scientific community toward a potent drug, brivaracetam, which boosted the synthesis of brivaracetam involving 24 different routes by using racemic and asymmetric moieties. The explained four different categorizations of synthetic approaches will surely encourage medicinal chemists to develop novel synthetic approaches with higher yields for synthesizing brivaracetam. It has been shown that for brivaracetam, the chiral pool/enantiomeric scaffold method proved to be the best approach in making this drug molecule conveniently. These approaches are even proven to be modest and efficient for brivaracetam synthesis. Using commercially available chiral starting materials to achieve excellent regioselectivity, excellent yield, and minimum chemical waste, further future improvements and modifications in the existing routes or development of novel synthetic routes are required. This review must be obliging for the future development of brivaracetam synthetic novel methodologies and for industrial process chemistry.

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### Notes

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