1

Drug Discovery in Epilepsy: A Synthetic Review

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1. Introduction

Although recurrent unprovoked seizures or epilepsy has been known for more than three thousand years, and even considering pivotal contributions like that of Hypocrates (*circa* 400 BC) establishing epilepsy as a brain disease instead of a religious or evil phenomenon, it was not until the 20th century that the first relatively effective antiepileptic drugs were discovered. Starting from phenobarbital and phenytoin almost 100 years ago, much research has been devoted to the development of new, more active drugs to treat such a broad category of symptom complexes (Krasowski, 2010). A chronological overview of the aforementioned development would provide interesting information about trial and errors in antiepileptic therapy, but from a chemical point of view (drug discovery) a classification according to structure is by far more useful. That is the aim of this review, thus covering the most relevant literature concerning synthetic approaches to the main anticonvulsant drugs. More detailed, comprehensive reviews on some of the main anti-epileptic drugs (AEDs) have been reported so far (Carril et al., 2007; Kraus et al., 2010), in some cases describing also aspects like pharmacokinetics, medicinal uses, approval for commercialization, etc. The present review intends to give a concise outlook at the most significant strategies employed in the synthesis of a good number of AEDs. Currently marketed drugs and some others in development will be briefly examined. Finally, a slightly more profound coverage has been given to some sections (i.e. carbamazepine, oxcarbazepine and eslicarbazepine acetate) on the basis of the relevance, therapeutic importance or promising applications of some AEDs over other ones occasionally employed or with a narrower application spectrum.

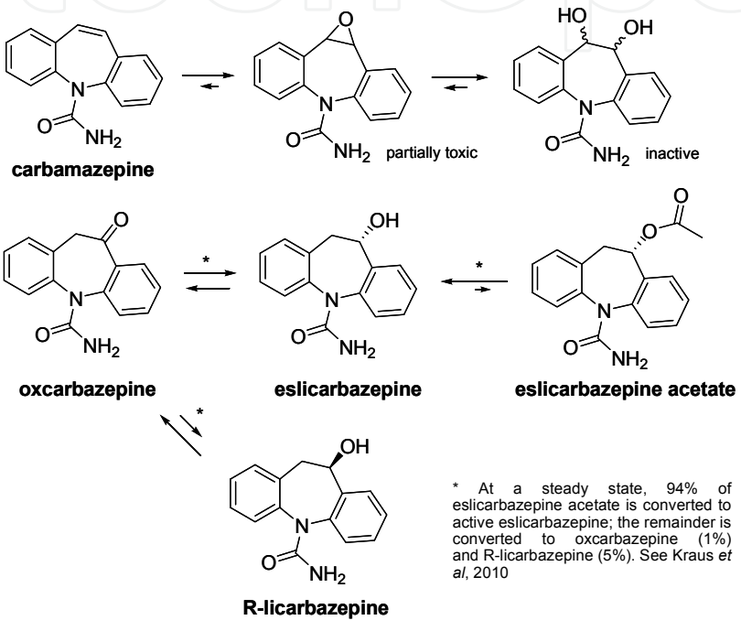
2. Results

2.1 First generation AEDs and related

2.1.1 Carbamazepine, oxcarbazepine and eslicarbazepine acetate

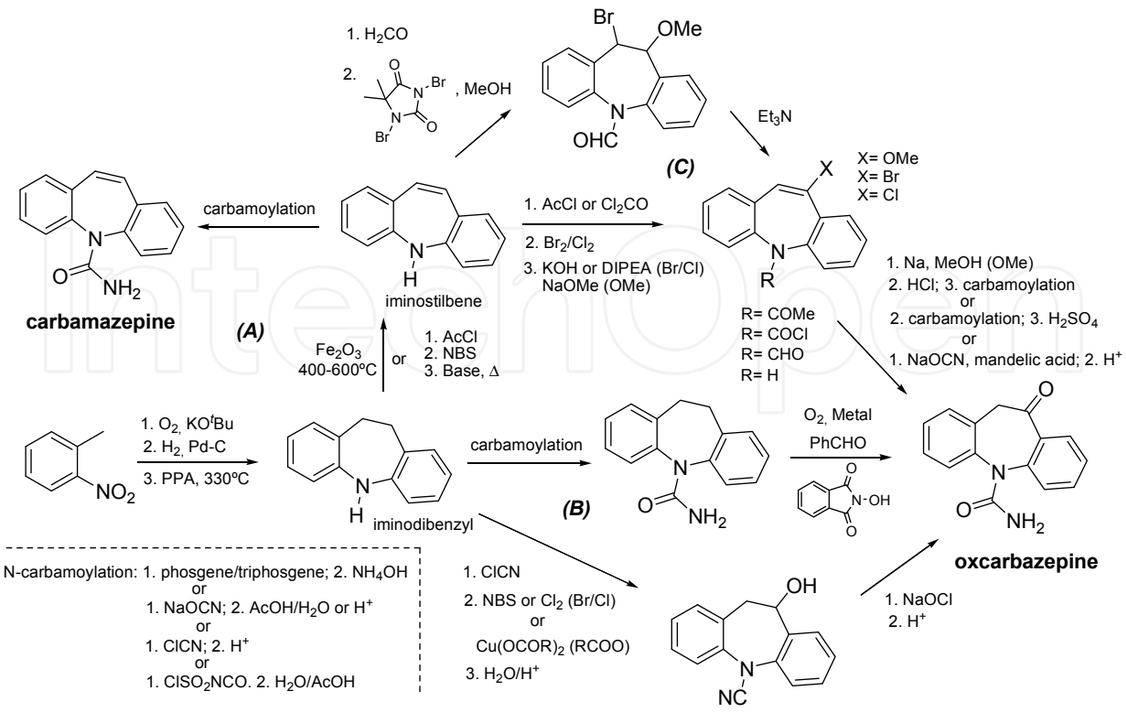
Despite the obvious similarity between these three compounds, which share a *N*-carbamoyldibenzo[*b,f*]azepine framework, their chronological appearance as antiepileptic drugs has been delayed for more than 30 years. Indeed, carbamazepine was first marketed as a drug to treat trigeminal neuralgia in 1962 and then started to be used as an

anticonvulsant in the UK in 1965 and approved in the US by 1967 (Schlinder, 1958). Oxcarbazepine was first synthesized in 1965, just a few years after its precursor carbamazepine, but it was not until 1990 that it was approved to treat epileptic seizures in Denmark, the rest of the EU (1999) and US (2000). Geigy (now part of Novartis) was the company that discovered both carbamazepine and oxcarbazepine drugs and commercialized them under the trade names of Tegretol® and Trileptal® respectively. The last member of this family, eslicarbazepine acetate, which has been developed by Bial, has been approved in Europe as an adjunctive therapy for adults with refractory partial-onset seizures and is in review for US approval (Chung, 2010).



Scheme 1. Summary of metabolic paths concerning carbamazepine, oxcarbazepine and eslicarbazepine acetate.

Scheme 1 shows a summary of the metabolic paths and connections between these drugs. Both oxcarbazepine and eslicarbazepine acetate are considered prodrugs of eslicarbazepine or S-licarbazepine, the most active and selective (towards preferential modulation of inactivated voltage-dependent sodium channels more than sodium channels in the resting state) metabolite. The also active (and toxic) carbamazepine-10,11-epoxide is generated by metabolic oxidation of carbamazepine, but this compound and the *R*-isomer of licarbazepine (R-licarbazepine, generated in a approximate 5% proportion from eslicarbazepine acetate and 25% from oxcarbazepine) result to be less active and selective. Finally, trans-10,11-dihydroxy-10,11-dihydrocarbamazepine is an inactive metabolite which is excreted in the urine mainly in an unconjugated form. One of the advantages of oxcarbazepine over carbamazepine is a clear reduction of the impact on the liver and prevention of the serious forms of anemia or agranulocytosis occasionally associated with carbamazepine. A tolerability improvement has been also observed when comparing oxacarbazepine with the third generation drug eslicarbazepine acetate. (Kraus et al., 2010).

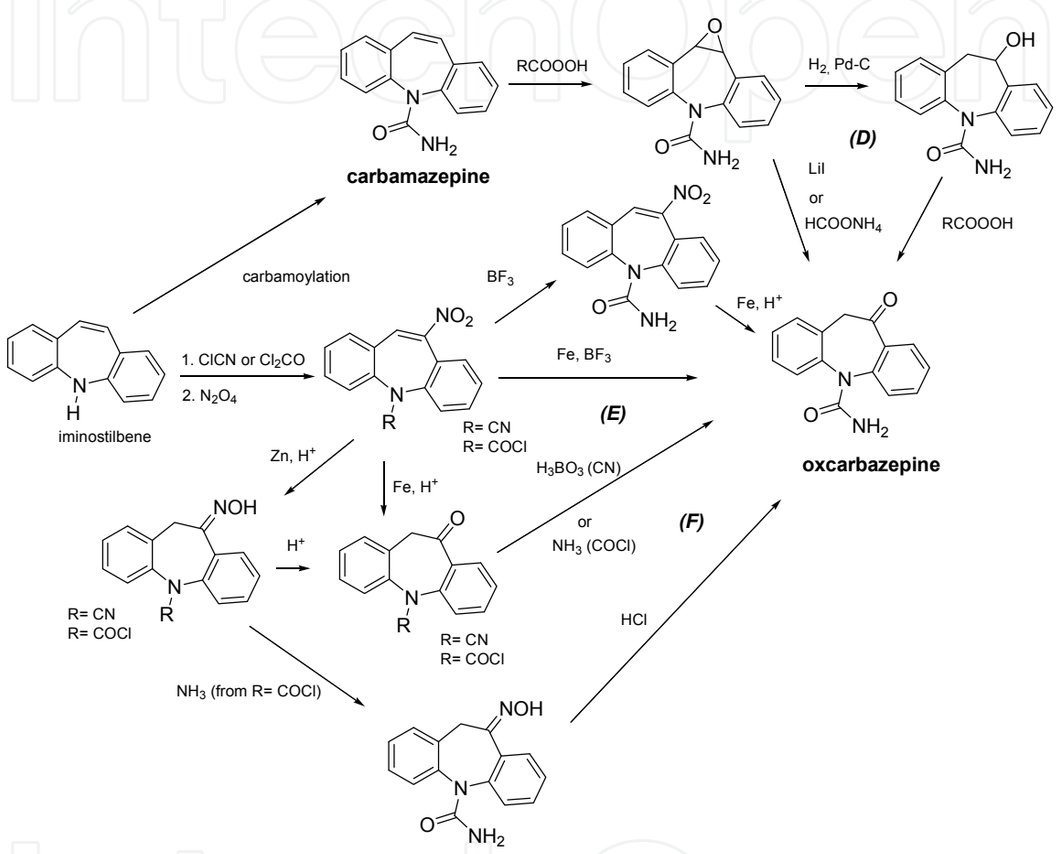


Scheme 2. A first selection of the reported approaches to carbamazepine and oxcarbazepine.

Both carbamazepine and oxcarbazepine have been crucial milestones, reference drugs in the therapy of epilepsy for a long time, and eslicarbazepine acetate looks like a suitable candidate for the future. Due to the aforementioned importance of carbamazepine and oxcarbazepine, a good number of synthetic strategies have been developed for the access to both dibenzoazepine drugs. Moreover, most of the existing methodologies share common substrates and intermediates in such a way that it can be said they are interconnected, as shown in schemes 2 and 3, and many alternative protocols have been developed for the same step or transformation. In fact, some of the publications or patents claim overall yield improvements by slight modifications in the procedures for just one or two steps of the whole sequence. One of those common intermediates is 10,11-dihydro-5*H*-dibenzo[*b,f*]azepine, also known as iminodibenzyl, obtained by an initial oxidative coupling of *o*-nitrotoluene, reduction of the nitro groups and PPA-promoted cyclization (Method A). After oxidation to dibenzoazepine ring, a carbamoylation step (see alternative procedures for this transformation) renders carbamazepine (Aufderhaar et al., 1980). A relatively straightforward approach to oxcarbazepine from iminodibenzyl involves benzylic direct or stepwise (Method B) oxidation after a suitable *N*-functionalization (carbamoylation, cyanation, etc.). Another well-established strategy relies on the preparation of 10-methoxy or 10-haloiminostilbene derivatives by a *N*-protection/halogenation/elimination sequence (Karusala et al., 2009) or alternatively by a dehydrohalogenation of a halomethoxy intermediate obtained by using 1,3-dihalodimethylhydantoin (Method C). Demethylation or hydrolysis and carbamoylation steps provide target oxcarbazepine (Gupta et al., 2007).

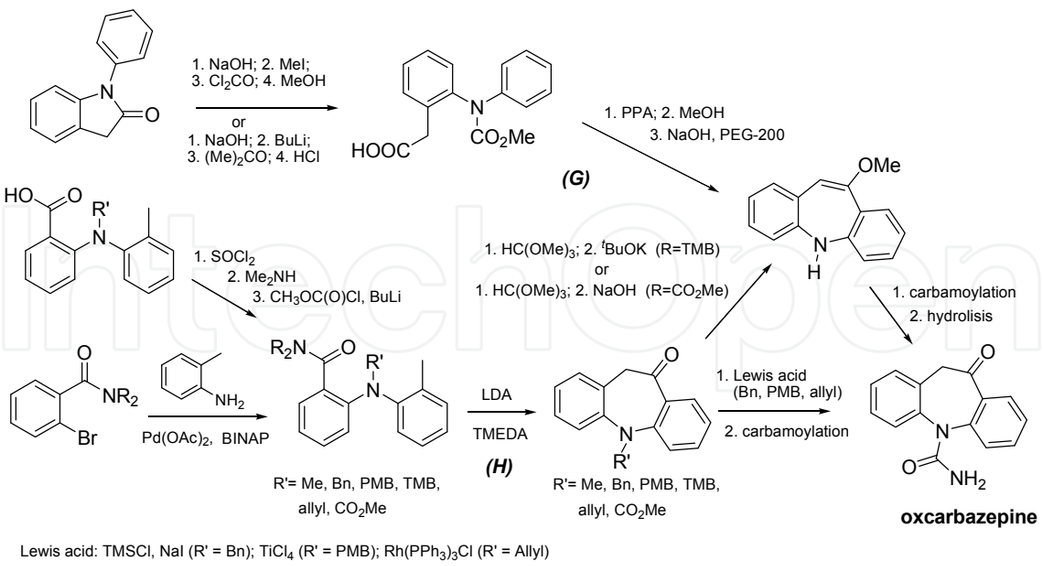
Scheme 3 displays another set of synthetic strategies towards oxcarbazepine. Carbamazepine, though a final product itself, has been employed as intermediate for the

synthesis of oxcarbazepine. Epoxidation of the former and rearrangement by iodide salts or hydrogenation/oxidation (Method D) provided target compound (Heckendorn et al., 1982). Other interesting approaches from iminostilbene involved the use of 10-nitro derivative intermediates and, in some cases, of the corresponding oximes. Iron-catalyzed reduction and acidic hydrolysis (Methods E and F) were the key steps in these synthetic sequences (Aufderhaar, 1981; Eidenhammer et al., 2000). The latter approaches are related to the originally employed industrial procedure at Novartis (Fuenfschilling et al., 2005).

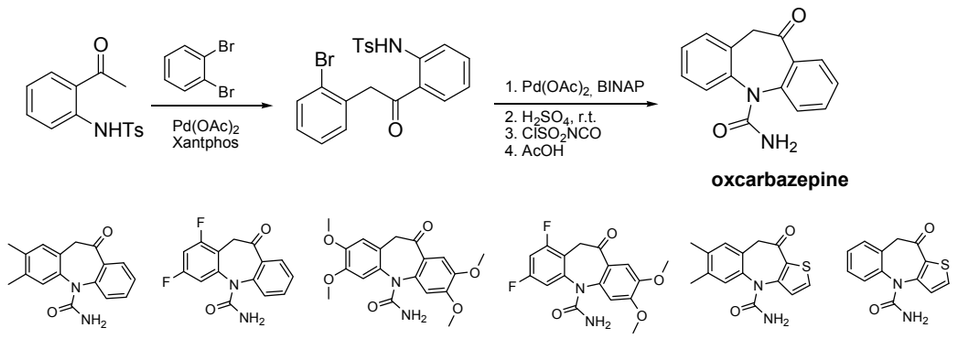


Scheme 3. Other synthetic sequences leading to carbamazepine and oxcarbazepine.

In the last years more innovative entries to oxcarbazepine have been reported. As shown in Scheme 4, an intramolecular Friedel-Crafts acylation performed at a 2-carboxymethyldiarylamine intermediate provides 10-methoxyiminostilbene, which upon carbamoylation and hydrolysis (Method G) provides target compound (Kaufmann et al., 2004). A tandem remote metalation/cyclization was applied to 2-carboxamido-2'-methyldiarylamines (Method H), thus affording the corresponding dibenzoazepinones which were finally *N*-deprotected and carbamoylated, or alternatively transformed into the aforementioned 10-methoxyiminostilbene and carbamoylated/hydrolysed (Lohse et al., 2001). A straightforward, efficient approach to oxcarbazepine, based two palladium-catalyzed *N*-arylation reactions, was recently reported (Scheme 5). The scope of the latter strategy was expanded by the synthesis of a series of analogs which incorporated different substituents in the arene or heteroarene rings (Carril eta al., 2005, 2007).

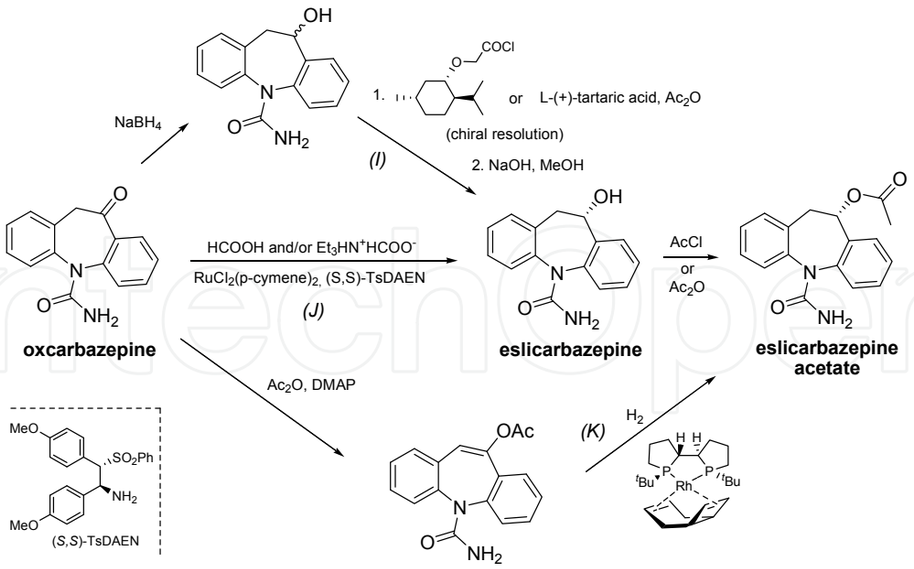


Scheme 4. Remote metalation/cyclization and intramolecular F-C acylation as key steps for the synthesis of oxcarbazepine.



Scheme 5. Palladium-catalyzed sequential *N*-arylations for the synthesis of oxcarbazepine and several structural analogs.

Considering the above metabolic paths and the commercial availability of oxcarbazepine, all the synthetic approaches to eslicarbazepine acetate start from the former AED, as displayed in Scheme 6. A chiral resolution of the reduction products of oxcarbazepine under standard conditions, the racemic mixture of 10-hydroxyderivatives, can be performed by means of either menthoxyacetic acid chloride or L-(+)-tartaric acid acetic anhydride (Method I). Eslicarbazepine would be obtained in this way and then transformed into eslicarbazepine acetate by acetylation (Benes et al., 1999; Learmonth, 2002). A more efficient approach to eslicarbazepine implies an stereoselective reduction of oxcarbazepine (Method J) using formic acid derivatives and a chiral ruthenium catalyst with *p*-cymene and sulfonamide (S,S)-TsDAEN ligands (Learmonth et al., 2007). Finally, an asymmetric catalytic hydrogenation catalyzed by Rh((*SSRR*)-TangPhos)(COD)BF4 complex also afforded highly enantiopure eslicarbazepine acetate (Method K), this time from achiral 10-acetoxyiminostilbene, readily prepared from oxcarbazepine (Yu et al., 2007).



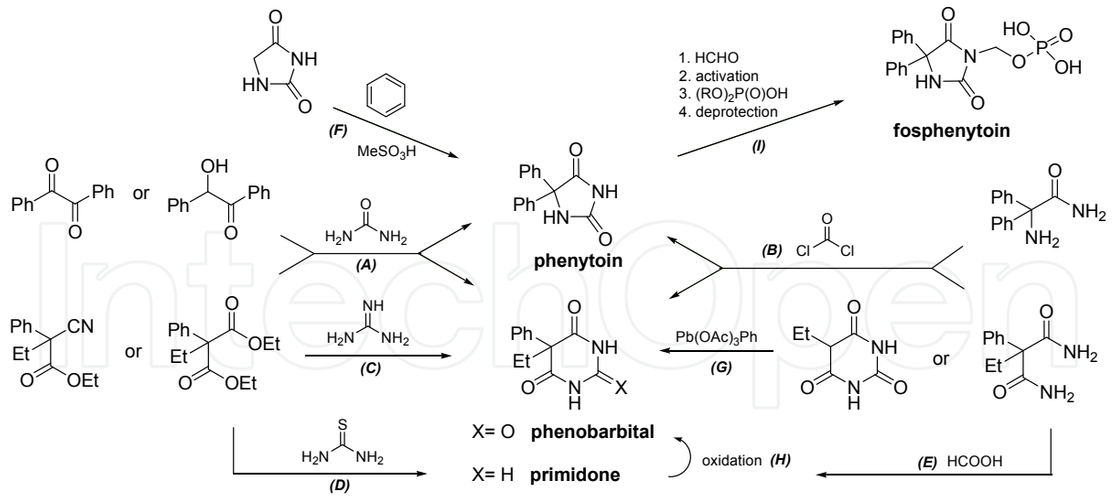
Scheme 6. Synthesis of eslicarbazepine acetate from oxcarbazepine.

2.1.2 Phenobarbital, primidone, phenytoin and phosphenytoin

Phenobarbital (PHB, Luminal®) is one of the first discovered AEDs and still remains as effective as more modern drugs in a wide variety of seizures (Kwan & Brodie, 2004). PHB acts directly on $GABA_A$ receptors by modulating chloride currents through receptor channels, as well as inhibits glutamate induced depolarizations. Similar mechanism of action is shared by primidone (Mysoline®), another AED related to the barbiturates, which is partly metabolized to PHB in the body (Gallagher et al., 1972). Currently they use is limited because of their adverse effects but in developing countries, PHB is still widely employed for the treatment of all types of seizures except absence due to its low cost.

Since its early discovery and introduction in 1938, phenytoin (PHT, 5,5-diphenylhydantoin, Dilantin®) has become one of the most commonly used drug in adjunctive treatments for partial and generalized seizures as well as various epileptic syndromes (Tunnicliff, 1997). The primary site of action appears to be the motor cortex where, by blocking voltage-sensitive sodium channels in neurons, the spread of seizures is reduced and the development of maximal seizure activity is limited. PHT is a highly effective and economical AED but the complications in its administration associated to its physicochemical properties led to the development of a better tolerated and safer derivative, fosphenytoin (Cerebyx®), a phosphate ester containing PHT prodrug (Luer, 1998).

Despite their differences, the chemical structure of these four derivatives is related. Among the variety of approaches reported in literature for their synthesis (Roth & Kleeman, 1988), there are two general and common methods for the preparation of the heterocyclic cores (Scheme 1): the condensation of dicarbonyl derivates with urea under basic conditions (method A) and the treatment of β-diamido/β-aminoamido compounds with phosgene (method B). Several related approaches have been developed in which alternative reagents to urea and phosgene are employed, such as guanidine (method C) and thiourea (method D), or formic acid (method E), respectively. In addition to these methods, modifications on the heterocyclic ring include the phenyl insertion, both under superacidic conditions (method F) (Klummp et al., 1998) and/or by using phenyllead(IV) compounds (method G)

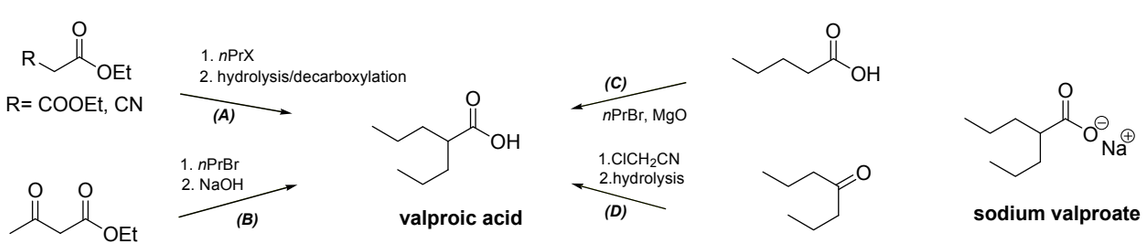


Scheme 7. General methods for the synthesis of phenobarbital, primidone, phenytoin and fosphenytoin.

(Pinhey & Rowe, 1980), and oxidation reactions (method H) (Mac Leod et al., 2008). Most of these classical methods suffer from general drawbacks, including long reaction times, low yield, and difficult operating conditions. However, by the application of new technologies or the use of newly developed heterogeneous reagents, their scope has been considerably extended. Thus, for example, the synthesis of PHT in almost quantitatively yield is accomplished using method A assisted by microwave irradiation (Safari et al., 2009).
Finally, fosphenytoin is readily available from PHT by its sequential treatment with formaldehyde and, after activation of the so-obtained aminoalcohol, with the corresponding phosphoric acid. The recently reported use of an *in situ* prepared tertiary ammonium phosphate as phosphorylating reagent has resulted in a considerably improvement regarding reaction yield and steps, affording fosphenytoin in an overall 82% yield (Grassi & Volante, 2005).

2.1.3 Valproate and valproic acid

Valproic acid (VPA, Depakote®, Depakene®) and sodium valproate (Depacon®, Epilim®), are a broad spectrum AEDs very effective for generalized seizure types. With an unknown mechanism of action, VPA has the shortest half life (10-15 h) among the all existing AEDs (Badir et al., 1991), which results on a multiple daily dosing administration. Although clinically effective, its use is restricted because of rare but potentially severe life threatening side effects, such as teratogenicity and hepatotoxicity.



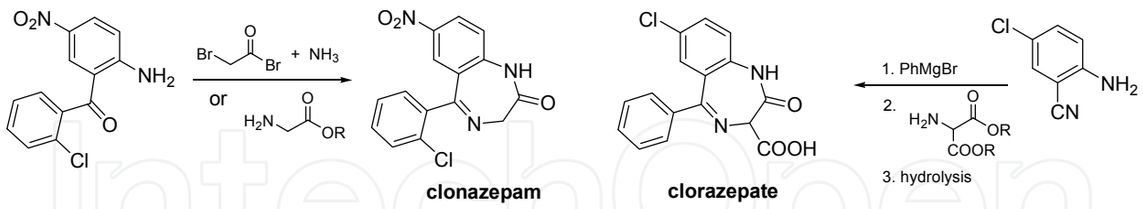
Scheme 8. General methods for the synthesis of valproic acid.

The alkylation of carboxy acid derivatives with *n*-propyl halides is the most general approach reported in literature for the synthesis of VPA and so far the most effective (Santaniello et al., 1998). Starting from diverse substrates, different variations of the method have been carried out, as the elimination-hydrolysis of 2,2-dipropyl acetoacetic ethyl ester via retroclaisen reaction promoted by NaOH (method B) or the monoalkylation of a soluble metalated magnesium carboxylate derived from valeric acid (method C). Among all, the classical alkylation β-activated carboxylic esters (method A) is still the better studied method. The optimization of the hydrolysis and decarboxylation steps had provided a one-pot, easy to operate and high yielding (84%) synthesis of VPA using methanesulfonic acid (Zeiler, 1994). Alternatively, the transformation of 4-heptanone into VPA has also received much attention. Recently, a novel approach has been described in which after addition of 2-chloroacetonitrile, the hydrolysis of the so-obtained epoxynitrile is successfully accomplished in presence of a phase transfer catalyst (method D), yielding VPA in an overall 71% (Nagarajan et al., 2009).

2.2 Second generation AEDs

2.2.1 Clorazepate and clonazepam

Benzodiazepines (BDZs) are a class of drugs that have long been employed to treat convulsive seizures as well as used as tranquilizers, sedatives and muscle relaxants (Ashton, 1994). Clonacepam (Klonopin®) was the first BDZ used for epilepsy and nowadays is a potent AED for the treatment of myoclonic seizures and subcortical myoclonus. Another important member of this family is Clorazepate (Traxene®), a prodrug for desmethyl diazepam and very rapidly produced as active metabolite. BDZs are partial agonist of the $GABA_A$ receptor which leads to increase the frequency of chloride ion channel opening and therefore to the inhibition of the synaptic transmissions across the CNS. Due to the development of tolerance and their sedative effect, BDZs are not appropriate for a long-term and adjunctive treatment of refractory epilepsy (Riss et al., 2008).



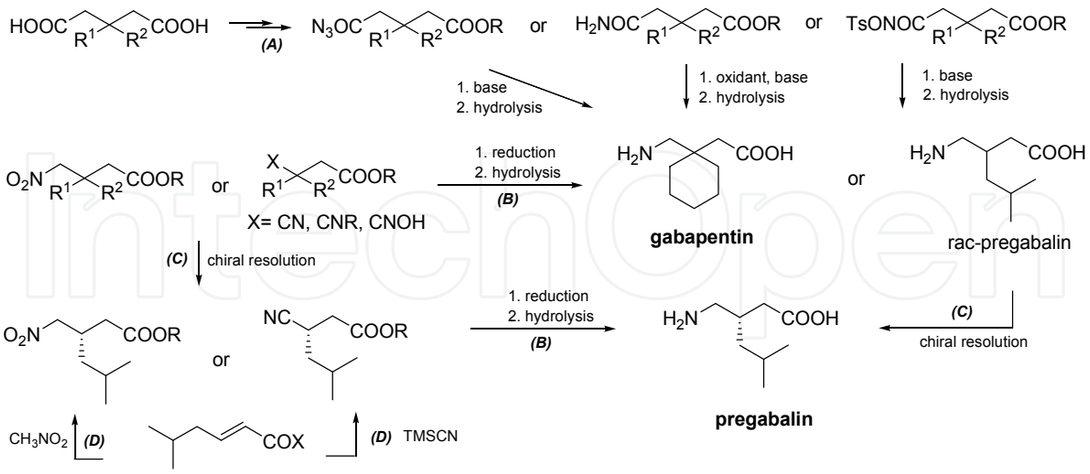
Scheme 9. Synthesis of clorazepate and clonazepam.

Two general approaches have been reported for the access of 5-aryl-1-4-benzodiazepines. The first method, which is the condensation of 2-amino benzophenone derivatives with bromoacetyl bromide and ammonia or glycine alkyl esters, has been successfully applied to the synthesis of clonazepam (Vardanyan & Hruby, 2006). The alternative method includes an additional step which consists of the Grignard addition to benzonitriles to afford benzophenone imine intermediate before condensation with the corresponding 2-aminomalonic ester derivate. Both approaches are high yielding and effective in the synthesis of benzodiazepines, therefore, the scope of their application has relied on the availability of starting materials. Thus, this second approach has been the method of choice for a straightforward and efficient access to clorazepate (Schmitt, 1970).

2.2.2 Gabapentin and pregabalin

Despite being GABA analogues and having been designed as GABA agonists, both gabapentin (GBP, Neurontin®) and its more potent successor pregabalin (Lyrica®) have shown to be inactive at GABA receptors. Nevertheless, they are effective in several neurological and psychiatric conditions and they are conventionally used in the treatment of partial epilepsies. GBP´s mechanism of action was recently discovered (Eroglu et al., 2009) and demonstrates that by binding to the alpha2delta-1 receptor on neurons, GBP avoids synapse formation. The main advantage of these AEDs is that both are relatively well tolerated although they have some adverse effects, particularly in high doses, but these usually are relatively minor. Compared to GBP, pregabalin is more potent, absorbs faster and has greater bioavailability (Bryans & Wustrow, 1999).

Two general approaches for the synthesis of geminally substituted aminomethyl acetic acid compounds are known (Johnson & Li, 2007): the transformation of geminal diacetic acids into suitable amido intermediates which rearrange to desired target (method A) and the reduction of saturated aminomethyl derivatives such as nitro-, cyano-, imino-, or oxime-containing geminal acetic acetates (method B). Method A constitutes the most straightforward procedure for the synthesis of GBP, which is efficiently accomplished in just 3 steps in a 80% yield through the Hofmann rearrangement of 3,3-pentamethylene glutarimide intermediate (Ferrari et al., 2004). Pregabalin, for other hand, contains a chiral centre and requires an asymmetric approach for its synthesis. Typically, a racemic mixture of pregabalin or its intermediates is synthesized and then processes involving racemic chiral or enzymatic resolution are applied (method C), but the effective throughput of the process is reduced by 50%. Much effort has been focused on the development of enantioselective routes. The employment of chiral auxiliaries and ligands has proven to be effective but also unsuitable for the high cost of the reagents. However, asymmetric organocatalysis has emerged as a very efficient and sustainable alternative for the synthesis of enantiopure intermediates via conjugated addition of cyanide or nitromethane to the corresponding α,β-unsaturated precursors (method D) (Bassas et al., 2009).

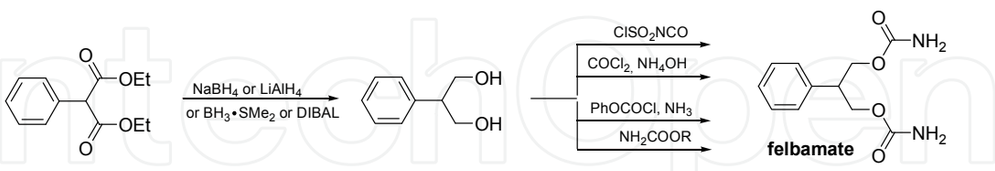


Scheme 10. General methods for the synthesis of gabapentin and pregabalin.

2.2.3 Felbamate

Felbamate (Felbatol®) was first marketed in the early 90s and reported as a potent anticonvulsant very effective against multiple seizure types (Pellock & Boggs, 1995). It is

usually well tolerated but due to very serious side effects such as aplastic anemia and hepatic failure, its use is restricted to patients with severe refractory epilepsy or Lennox-Gastaut syndrome. Felbamate´s mechanism of action is not known, but it has been reported as an allosteric antagonist at the NR2B subunit of the NMDA glutamate receptor and also as $GABA_A$ receptor agonist.

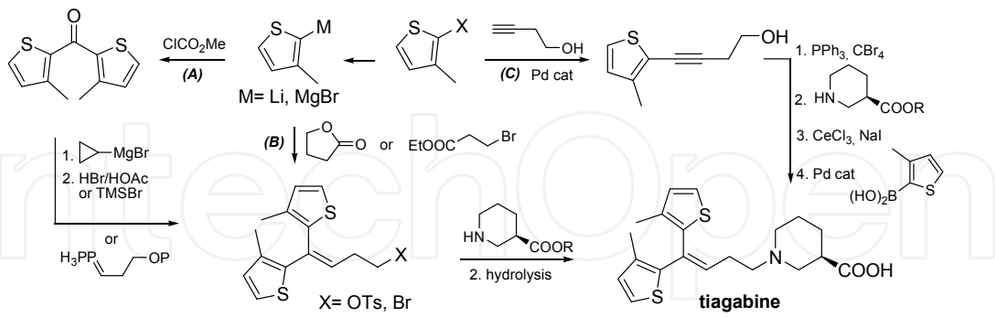


Scheme 11. General methods for the synthesis of felbamate.

The synthesis of felbamate involves a two step procedure, for which during these years, different reaction conditions have been developed. The reduction of commercially available diethyl phenyl malonate to diol intermediate has been carried out with several reagents, among which sodium borohydride has performed the best results regarding effectiveness and handeling-purification (Walker et al., 1994). Its subsequent transformation into the corresponding carbamate has been studied using phosgene, chloroformate as well as cyanate derivates, but still urethane exchange constitutes the best method for preparing felbamate (Walker et al., 1994).

2.2.4 Tiagabine

Tiagabine (TBG, Gabitril®) is a GABA uptake inhibitor primarily used in combination with other AEDs for the treatment of partial seizures (Schachter, 1999). The precise mechanism of action is not known but it modulates the excitatory synaptic currents by retarding the neuronal reuptake of GABA into the presynaptic terminal, which leads to the maintenance of the extra cellular concentration of GABA.



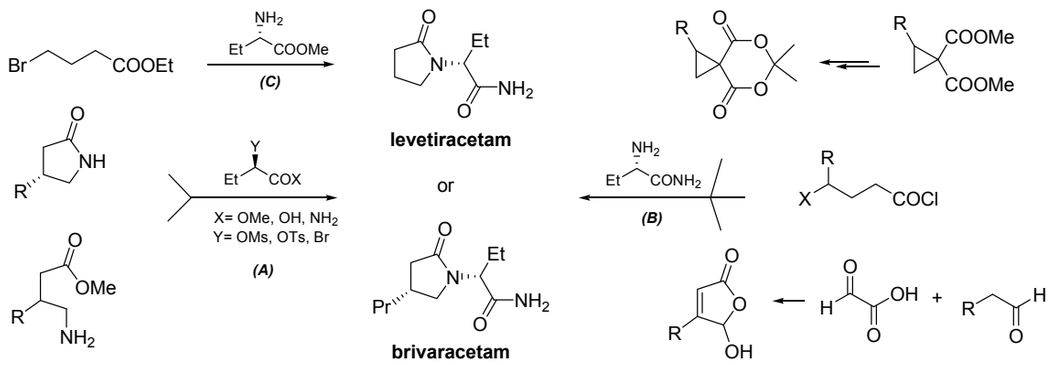
Scheme 12. General methods for the synthesis of tiagabine.

There is one general approach for the synthesis of TGB, which includes the Grignard addition of 2-metallo-3-methylthiofuran to different carbonyl electrophiles as common step (Andersen et al., 1993). When methylchloroformate is employed (method A), the resulting diarylketone can be transformed into the alkenyl precursor of TGB by reaction with cyclopropylmagnesium bromide and subsequent opening under acidic conditions or *via* Wittig olefination. However, the reaction of the Grignard with γ-butyrolactone or ethyl 3-bromopropanoate (method B) has resulted as a much more straightforward and effective

method. Then, the synthesis of TGB is completed by the N-alkylation of the 4-bromo or 4-tosylbutene intermediate with the corresponding protected cyclic amino acid. Recently, an alternative method (C) based on palladium catalyzed Sonogashira and Suzuki reactions for new carbon-carbon connections and $CeCl_3$-NaI mediated diastereoselective hydroiodination of alkynes as key step has been published (Bartoli et al., 2010). Nevertheless, despite the synthetic importance of this newly developed methodology applied to the synthesis of TGB, still it lacks of practical and industrial extend.

2.2.5 Levetiracetam and brivaracetam

Levetiracetam (LEV, Keppra®) is a newly developed potent AED for the adjunctive therapy in the treatment of partial onset seizures in both adults and children. Even if its mechanism of action is not fully elucidated, it is known to target the synaptic vesicle protein 2A (SV2A) as well as high-voltage, N-type calcium channels. With a nearly ideal pharmacokinetics, LEV reveal a very good safety profile which makes it a very well tolerated AED and also efficient for different patient populations (Grosso et al., 2005). Brivaracetam (UCB 34714), the *n*-propyl derivate of LEV, possesses a ten-fold higher binding affinity for SV2A compared to LEV and it shows as a very promising new AED but still is under development (Malawka & Kulig, 2008).



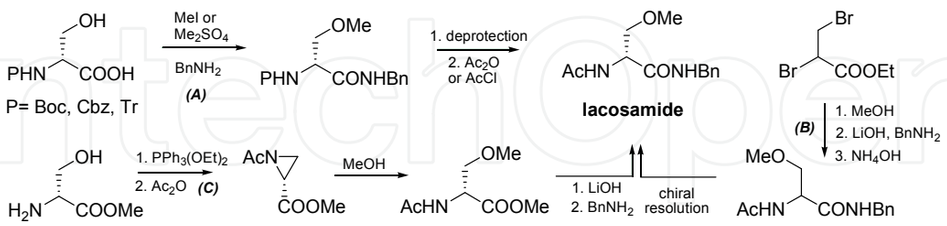
Scheme 13. General methods for the synthesis of levetiracetam and brivaracetam.

The main chemical disconnection of both LEV and brivaracetam occurs at the C-N-pyrrolidinone bond, which can be accomplished by the alkylation of N-pyrrolidinone or N-alkyl intermediate with an activated butyric acid derivative (method A) as well as by the construction of the pyrrolidinone ring from (s)-aminobutyramide or the methyl ester of (s)-aminobutyric acid as nitrogen source (method B and C, respectively) (Kenda et al., 2004). Enantiomerically pure (s)-aminobutyric acid derivatives are readily available from L-methionine and easier to obtain than the required butyric acid derivate in method A. Thus, by using method C, LEV has been successfully prepared in an overall 71% (Ates et al., 2003). However, the most efficient approach for the synthesis of brivaracetam consist of the palladium catalyzed diastereoselective reductive amination of aminobutyramide with a furan intermediate suitably prepared from butyric acid and glyoxalic acid (method B)(Surtees et al., 2005).

2.2.6 Lacosamide

The continuous search for new AEDs has lead to the discovery of a novel category of drugs labeled as Functionalized Amino Acids, among which lacosamide (LCM, Vimpat®) is the

first-in-class. LCM is effective for the adjunctive treatment of partial-onset seizures in adults and it has a novel mode of action: a "novel dual mechanism" consisting of selective enhancement of sodium channel slow inactivation and modulation of CRMP-2 activity (Chung, 2009). It is generally well tolerated but still presents regular side effects such as dizziness, nausea and vomiting.



Scheme 14. General methods for the synthesis of lacosamide.

The synthesis of LCM is primarily based on the stepwise functionalization of L-serine, which starts in most of the cases with the protection of the free amine (method A). Then, after methylation of the hydroxyl group and amidation, the N-protecting group is removed and the amine acylated to afford LCM with high enantioselectivity and in good overall yield (Riedner & Dunne, 2008). Alternatively, and also starting from serine an elegant approach has been reported based on the selective ring opening of N-acetylazirine methylester (method C) (Morieux et al., 2008). For other hand, a new route beginning with ethyl 2,3-dibromopropionate has been published recently in which additional chiral resolution step is necessary to obtained enantiomerically pure LCM (method B) (Bouvi et al., 2010).

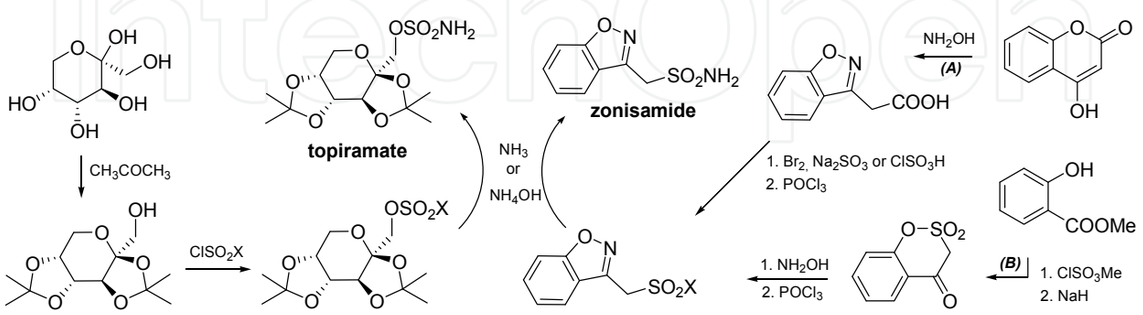
2.2.7 Topiramate and zonisamide

Topiramate (Topamax®) is a highly effective anticonvulsant for the treatment of primary and secondary generalized tonic-clonic seizures as well as the Lennox Gastaut syndrome (Perucca, 1997). It differs from other AED in its structure, which is derived from D-fructose and also contains an unusual sulfamate functional group. Topiramate´s mechanism of action is not fully elucidated, but it shows inhibitory effect on voltage-dependent sodium channels and AMPA subtype glutamate receptor, and enhances some of $GABA_A$ receptors.

Zonisamide (ZNS, Zonegran®, Excegran ®) is another sulfonamide containing AED, effective as adjunctive therapy in adults with partial onset seizures (Schulze-Bonhage, 2010). With an unknown mechanism of action, it is reported to block voltage-dependent sodium channels, which would lead to inhibit the spread of epileptiform activity, and the reduction of T-type calcium channel currents, or to inhibit the uptake of the inhibitory neurotransmitter GABA while enhancing the uptake of the excitatory neurotransmitter glutamate. ZNS is generally well-tolerated but also associated to various side effects such as drowsiness, loss of appetite, gastrointestinal problems and CNS toxicity. However, the rare occurrence of nephrolithiasis suggests a careful monitorization of patients.

Sulfonamide containing AEDs are prepared *via* amidation of the corresponding sulfonyl derivative as last step. Thus, topiramate is readily available from D-fructose by condensation with acetone and transformation of the pendant hydroxyl group into a sulfonate derivative before amidation. Among the different reagents described for the sulfamoylation step, chlorosulfonyl isocyanate is the one providing better results regarding safety and effectiveness (Arvai eta al., 2006). For other hand, the synthesis of ZNS has been

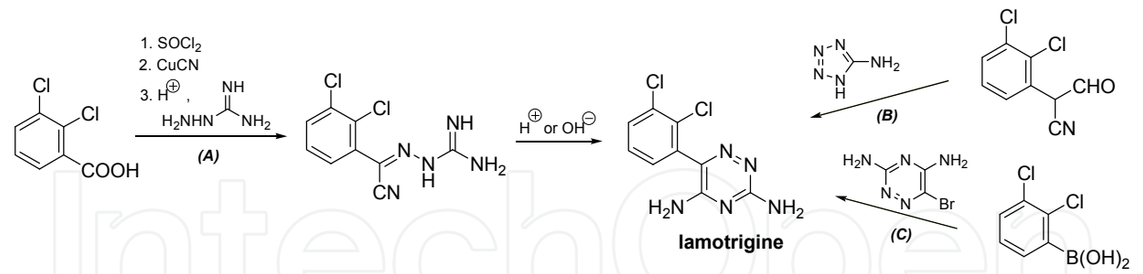
accomplished following two general and complementary approaches: through a 1,2-benzisoxazole-3-acetic acid intermediate derived from 4-hydroxycoumarin (method A) and the conversion of methyl salicylate into 1,2-benzoxathiin-4(3*H*)-one-2,2-dioxide, which is reacted with hydroxylamine to afford the corresponding sulfonyl 1,2-benzisoxazole in a later step (method B)(Arava et al., 2007). Despite the similarities between these two routes, the application of method A using chlorosulfonic acid as sulfonylating reagent has offered a higher-yielding (65% overall yield) and cost-effective process (Nageib et al., 2008)



Scheme 15. General methods for the synthesis of topiramate and zonisamide.

2.2.8 Lamotrigine

In addition to being approved in 1994 as an adjunctive treatment of partial seizures in adults, lamotrigine (LTG, Lamictal®) has shown since then a broad spectrum of antiepileptic activity (Malik et al., 2006). It may stabilize neuronal membranes by inhibition of voltage-sensitive sodium channel, but still the mechanism of action is unknown. Alternative to VPA, LTG shows a better side effect profile and also an important safety record in pregnancy, which makes it as the AED of choice in pregnant women with epilepsy (Sabers & Tomson, 2009).

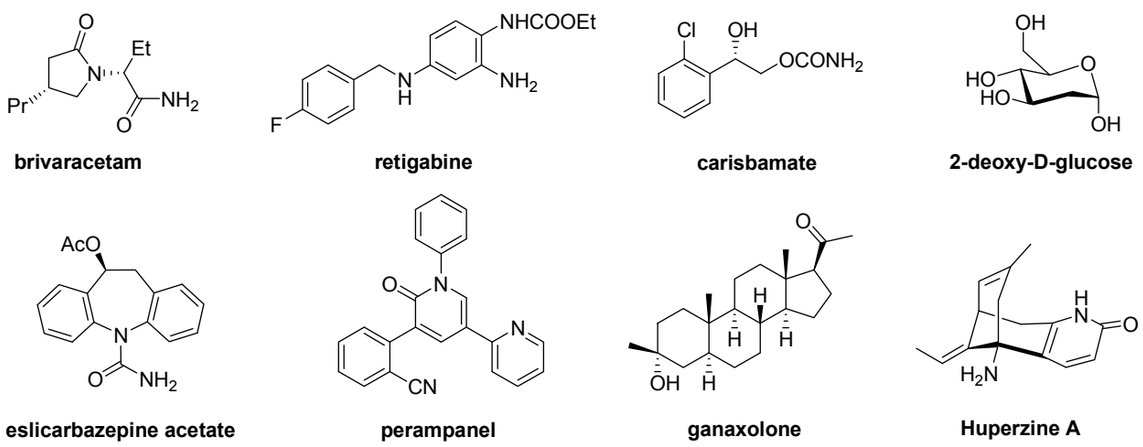


Scheme 16. General methods for the synthesis of lamotrigine.

The different methods for preparation of LTG can be classified according to the existing approaches for the formation of the triazine heterocyclic ring. The acid or base promoted intramolecular cyclization of aminoguanidine intermediates (method A) consists of the most studied and effective route so far, providing desired LTG product in moderate yield (52%) (Dalmasses Barjoan & Bessa Bellmunt, 2004). Alternatively, the synthesis of LTG has been also accomplished by using tetrazolamine instead of aminoguanidine (method B)(Ulomskii et al., 2005) or by the direct Suzuki coupling of a preformed diamino triazine halide with the corresponding boronic acid (method C) (Titirmare, 2007). But despite the potential applicability of these two approaches, the preparation of required intermediates as well as the poor reaction yields obtained limits considerably their scope.

2.3 New generation AEDs

Despite the continuous research and advances in the field, none of the currently available treatments for epilepsy accomplishes satisfactory control of seizures without causing important side effects. Therefore, ongoing studies towards the development of new AEDs regarding efficiency, tolerability and safety have been carried out and have lead to a new generation of AEDs, most of which have already undergone preclinical and clinical studies (Bialer et al., 2010; Stephen & Brodie, 2011). Some of these new candidates are optimized analogues of known AEDs, such as eslicarbazepine acetate (see section 2.11 for more details) or brivaracetam, but most of them are being developed with novel mechanisms and clinical characteristics compared with previous AEDs: Perampanel was designed as an AMPA-type glutamate receptor antagonist, retigabine modulates neuronal $K_V7.2–7.5$ voltage-activated K^+ channels while 2-deoxy-D-glucose acts on the NRSF-CtBP–dependent metabolic regulation of chromatin structure.



Scheme 17. Chemical structures of the new generation of AEDs.

Given the heterogeneity of their functions, they show big differences on their chemical structures as well as their occurrence. Thus, Huperzine A is a natural sesquiterpene alkaloid and both 2-deoxy-D-glucose and ganaxolone are analogues and therefore easily available from D-glucose and progesterone respectively. Most of the new AEDs, nevertheless, are synthetic small molecules whose preparation processes are not yet reported or even with unknown structures as for ICA-105665, NAX 5055 or YKP3089 candidates.

3. Conclusion

To sum up, there is a broad spectrum of compounds active against several seizure types. In addition to the synthetic approaches patented by the pharmaceutical companies that discovered or marketed them, an acceptable (and in some cases overwhelming) number of preparation strategies to these AEDs have been reported, thus overcoming in some cases problems (low overall yields, long sequences, harsh conditions, etc.) encountered in the initial protocols. Since a variety of structural motifs (dibenzoazepines, imidazodiones, benzodiazepines, piperidines, triazines, isoxazoles, pyrrolidinones, etc.) has proved activity in antiepileptic therapy, a complete arsenal of synthetic tools has been required for their

preparation. It becomes clear to the reader that a valuable evolution from classical transformations to modern (stereoselective, catalytic, more sustainable) procedures has occurred also in this field. However, only in a limited number of cases can be found whole approaches with an extensive scope, that is, applicable to the preparation of a reasonably diverse series of structural analogs that could provide more effective drugs and/or reduced side-effects. One of the main features of the aforementioned evolution in the future will be probably related to filling the latter gap.

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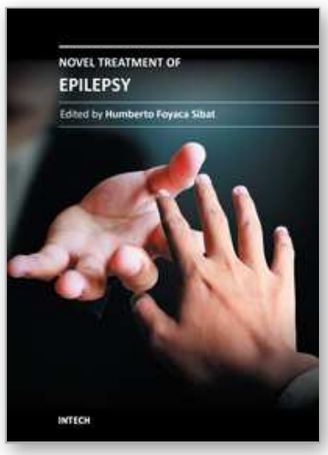

Novel Treatment of Epilepsy

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Epilepsy continues to be a major health problem throughout the planet, affecting millions of people, mainly in developing countries where parasitic zoonoses are more common and cysticercosis, as a leading cause, is endemic. There is epidemiological evidence for an increasing prevalence of epilepsy throughout the world, and evidence of increasing morbidity and mortality in many countries as a consequence of higher incidence of infectious diseases, head injury and stroke. We decided to edit this book because we identified another way to approach this problem, covering aspects of the treatment of epilepsy based on the most recent technological results â€œin vitroâ€ from developed countries, and the basic treatment of epilepsy at the primary care level in rural areas of South Africa. Therefore, apart from the classic issues that cannot be missing in any book about epilepsy, we introduced novel aspects related with epilepsy and neurocysticercosis, as a leading cause of epilepsy in developing countries. Many experts from the field of epilepsy worked hard on this publication to provide valuable updated information about the treatment of epilepsy and other related problems.

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