

An Update on GABA Analogs for CNS Drug Discovery

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Abstract: GABA (-aminobutyric acid) is one of the major inhibitory transmitters in the central nervous system of mammals. GABA is not transported efficiently into the brain from the bloodstream (i.e. GABA does not effectively cross the blood-brain barrier). Consequently, brain cells provide virtually all of the GABA found in the brain i.e. GABA is biosynthesized by decarboxylation of glutamic acid with pyridoxal phosphate. The implication of low GABA levels in a number of common CNS disease states and/or common medical disorders has stimulated intensive interest in preparing GABA analogs, which have superior pharmaceutical properties in comparison to GABA. Accordingly, a number of GABA analogs, with considerable pharmaceutical activity have been synthesized in the art. This review includes some of the important recent patents on novel GABA analogs and some pharmaceutical compositions thereof.

Keywords: -Aminobutyric acid, blood brain barrier, epilepsy, depression, neuropathic pain, GABA analogs.

1. INTRODUCTION

GABA, -aminobutyric acid (**1**), is the principal inhibitory neurotransmitter in the mammalian brain [1, 2]. It has been estimated that approximately 40% of synapses in the CNS are GABAergic [3]. According to Lipton *et al.* [4] GABA receptors are commonly thought to be divided into two groups: Cl⁻ channel-coupled GABA_A receptors and G-protein-coupled GABA_B receptors. GABA acts at the GABA/benzodiazepine (GABA_A) receptor to increase membrane chloride ion conductance and thereby stabilize or hyperpolarize the resting membrane potential (if extracellular chloride concentration exceeds that of intracellular). Schofield *et al.* [5] in 1987 purified and sequenced the GABA/benzodiazepine receptor complex. The GABA_A receptor complex is a pentameric heterooligomer having a number of subunits designated as 1-6, 1-4, 1-3, and . Bormann in 1988 [6] described GABA_B receptors as coupled to Ca²⁺ and K⁺ channels *via* G-proteins and second messenger systems, activated by Baclofen (4-amino-3-(4-chlorophenyl)butanoic acid, **2**) and resistant to drugs that modulate GABA_A receptors. Later GABA_BR1 and GABA_B R2 were recognized as the two major subunits of the GABA_B receptor.

Early studies by Johnston [7] indicated that the GABA analogue *cis*-4-aminocrotonic acid (**3**) selectively activates a third class of GABA receptors in the mammalian CNS. These receptors designated as GABA_C receptors are relatively simple ligand-gated Cl⁻ channels with a distinctive pharmacology, in that they are not blocked by bicuculline and not modulated by **2**, barbiturates, benzodiazepines or neuroactive steroids [8, 9]. The neuronal GABA_C receptors are formed by heterooligomeric GABA subunits. Compared with GABA_A receptors, GABA_C receptors are

activated at lower concentrations of GABA and are less liable to desensitization. In addition, their channels open for a longer time.

2. NEUROLOGICAL IMPLICATIONS OF GABA

It is well documented that attenuation of GABAergic neurotransmission is involved in the pathophysiology of several CNS disorders in humans, namely anxiety, pain, and epilepsy [10–13]. Evidence also suggests that low GABA levels are linked to depression and possibly mania [14]. Hence over the past twenty-five years, research on therapeutics in the above-mentioned areas has grown by leaps and bounds, with much interest focused on the various potential pharmacological approaches to the enhancement of GABAergic function in humans [15]. Some of the clinically effective approaches being the direct agonism of GABA receptors [16, 17], the inhibition of enzymatic breakdown of GABA [18, 19], and the inhibition of the uptake of GABA into neuronal and glial cell bodies [20, 21]. With regard to epilepsy, it has been shown that convulsions can occur when the level of GABA in the brain diminishes below a critical amount and that direct administration of GABA into the brain terminates the seizures [22–24]. However, GABA does not cross the blood-brain barrier, a protective membrane that prevents xenobiotics from entering the brain. Consequently, GABA is not an effective anticonvulsant agent [25]. This seems to be true for all the other clinical conditions as well.

3. GABA ANALOGS – MARKETED AND CURRENTLY UNDER RESEARCH

One of the pioneering efforts in the area of research on GABA analogs was the discovery that **2**, a GABA analog could be considered a prototype for GABA_B receptor agonists. Baclofen was first synthesized in 1962 by the CIBA chemist Heinrich Keberle and was shown to exert potent muscle-relaxant and analgesic properties [26]. A report from Bowery *et al.* [27] holds **2** as an invaluable pharmacological tool in elucidating the role of GABA_B receptors in several disorders including epilepsy, cognition,

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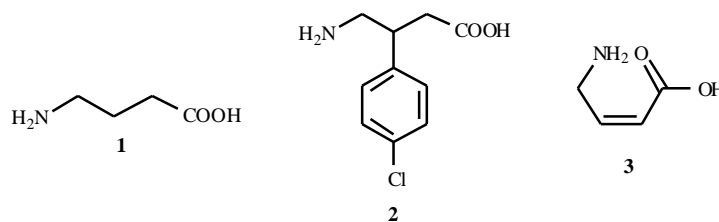


Fig. (1).

pain, and addiction. Furthermore, **2** has been used clinically to treat spasticity for more than 30 years long before the GABA_B receptor was identified [28].

Later, a number of cyclic amino acids such as nipecotic acid (**4**), guvacine (**5**), and homo- γ -proline (**6**) were developed and shown to display *in vitro* activity as inhibitors of [³H]-GABA uptake [29, 30]. These were considered as conformationally-restricted GABA analogs [31].

In 1999 Bryans *et al.* [32] reported gabapentin (**7**) and pregabalin (**8**), two γ -amino acids as having anticonvulsant, anxiolytic-like, and analgesic actions. Gabapentin was originally developed as an add-on therapy for the treatment of partial seizures but showed efficacy in the treatment of postherpetic neuralgia (a type of neuropathic pain) and in several preclinical models of neuropathic pain [33]. On the other hand, **8** has more potent and robust activity than **7** in preclinical models of epilepsy [34-36] neuropathic pain [33], and anxiety [37]. Pregabalin or S-(+)-3-isobutyl GABA was designed as a lipophilic analog of GABA, substituted at the third position to facilitate diffusion across the BBB. According to Lauria *et al.* **8** although structurally related to GABA, is inactive at GABA receptors and doesn't appear to mimic GABA physiologically [38].

Vigabatrin (4-aminohex-5-enoate; γ -vinyl GABA, **9**) is a GABA analog that was developed to increase GABA concentration in the central nervous system. It is one of the most effective antiepileptic drugs introduced in recent years [39]. Vigabatrin irreversibly inhibits γ -aminobutyric acid transaminase (GABA-T), the major metabolizing enzyme of endogenous GABA by acting as a substrate for this enzyme.

Biochemical investigations by Lippert *et al.* into the mode of action of **9** have demonstrated that initial reversible binding to the pyridoxal-5'-phosphate (PLP) cofactor was followed by an irreversible step leading to enzyme inactivation [40]. Engelborghs *et al.* [41] suggested that **9** possessed an additional mechanism of action by reduction of brain excitatory amino acid levels and/or elevation of glycine level.

Receveur *et al.* [42] synthesized a series of conformationally restricted analogues of gabapentin. The pyrrolidine analogue (R)-2-aza-spiro [4, 5] decane-4-carboxylic acid hydrochloride (**10**) had an IC₅₀ of 120 nM, similar to that of gabapentin (IC₅₀ = 140 nM) by acting at the gabapentin binding site on the α_2 subunit of a calcium channel. This compound also reversed carrageenan-induced hyperalgesia in rats.

Cundy *et al.* [43] reported XP13512 [(±)-1-([(1S)-isobutanoyloxyethoxy] carbonyl) aminomethyl]-1-cyclohexane acetic acid (**11**) as a novel prodrug of gabapentin designed to be absorbed throughout the intestine by high capacity nutrient transporters. Based on the observations of the study, this group suggested that administration of the prodrug should result in improved gabapentin bioavailability, dose-proportionality, and colonic absorption compared to administration of gabapentin.

In the same year, Cundy *et al.* [44] disclosed the procedure for the synthesis of GABA analog prodrugs (**12**) that were shown to possess reduced toxicity when administered as oral dosage forms. The main skeleton of the patented prodrugs is given in (Fig. 4).

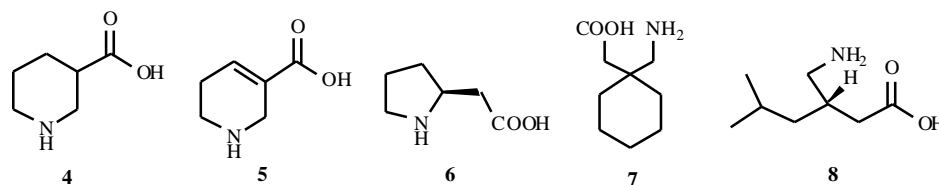


Fig. (2).

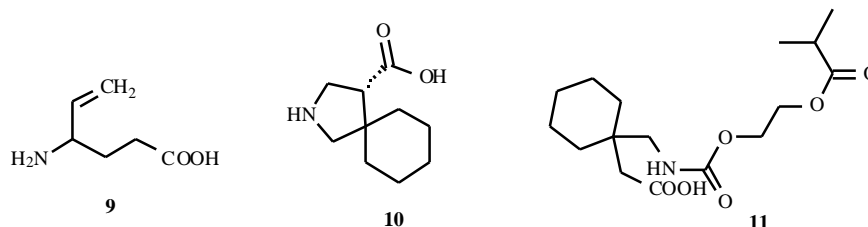


Fig. (3).

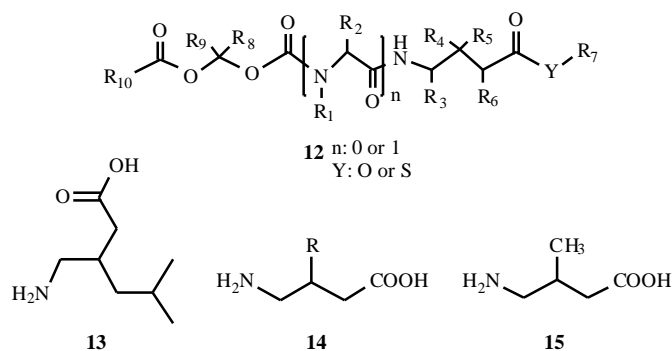


Fig. (4).

Silverman *et al.* [45] patented an invention relating to compounds that are analogs of glutamic acid and GABA. These analogs were proposed as novel compounds for the treatment of various central nervous system disorders such as Huntington's chorea, cerebral ischemia, Parkinson's disease, tardive dyskinesia, spasticity, and more specifically epilepsy. The invention provided a series of 3-alkyl-4-aminobutyric acid or 3-alkyl glutamic acid analogs useful as anticonvulsants. The analogs were further shown to prevent seizure while not causing the side effect of ataxia, which in several anti-seizure pharmaceuticals is a common side effect. The most preferred compounds of the invention were the (S)-(+)- (**13a**) and the (R)-(-)-4-amino-3-(2-methylpropyl) butanoic acid (**13b**) with the **13a** most preferred. From all the pharmacological and radioligand displacement studies, it was disclosed that the **13** was the most potent compound for displacement of tritiated gabapentin and responsible for virtually all blockade of maximal electroshock seizures in mice and rats. The enantiomer **13b** was found to be much less effective in the blockade of maximal electroshock seizures and in displacement of tritiated gabapentin.

Andruszkiewicz *et al.* [46] in 1990 reported 4-amino-3-alkylbutanoic acids (**14**) as substrates for γ -aminobutyric acid aminotransferase. Again in the same year Andruszkiewicz *et al.* [47] disclosed a report on the chemoenzymatic synthesis of (R)- and (S)-4-amino-3-methylbutanoic acids (**15a** and **15b**).

Silverman *et al.* in 2000 [48] patented a method for treating anxiety in a mammal involving the administration of an effective amount of **13a**. The compound of the invention was also found to activate glutamic acid decarboxylase (GAD) *in vitro* and have a dose dependent protective effect on seizure *in vivo*. Silverman *et al.* [49] in 2001, also reported a method of treating a patient having Parkinson's disease by administering an anti-seizure effective amount of the compound **13** and its enantiomer.

In 2004, Gallop *et al.* [50] reported procedures for the synthesis of prodrugs of GABA analogs. The GABA analogs selected for the study were gabapentin and pregabalin. The compounds of the invention, included promoieties attached to both the -amino and carboxyl groups of the GABA analogs with the carboxyl promoiety typically being an ester or thioester group. This research team also described methods for using pharmaceutical compositions of prodrugs of GABA analogs for treating or preventing common diseases. The basic skeleton of the representative structures (**16-18**) are given in (Fig. 5). This work was undertaken in continuation to the past research on GABA analogs [51-54].

In 2003, a patent was published wherein a method for the synthesis of mono and disubstituted 3-propyl γ -aminobutyric acids was disclosed [55]. In addition to the reported anticonvulsant activity the compounds were proposed as effective in the treatment of hypokinesia, cranial disorders, neurodegenerative disorders, depression, anxiety, panic,

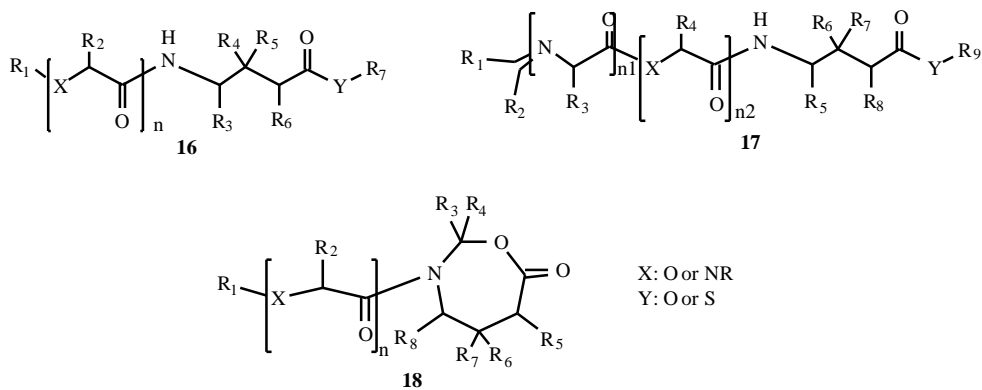


Fig. (5).

pain, neuropathological disorders, arthritis, sleep disorders, and gastric damage. The structures of the patented derivatives (**19-23**) of GABA are given in (Fig. 6).

In the same year, Belliotti *et al.* [56] patented another series of compounds, which are cycloalkyl derivatives of GABA (**24**) and proved them as having improved activity in models of pain and epilepsy. The DBA/2 mouse model was employed to test the protection offered by the compounds against sound-induced seizures.

In 2001, Magnus *et al.* [57] patented the novel use of GABA analogues as a treatment for insomnia. According to their report, the benefit of using GABA analogues to treat insomnia is that they are not addictive.

Owing to an urgent need to develop effective sustained release versions of GABA analogs, in order to minimize increased dosing frequency due to rapid systemic clearance of these compounds and also to synthesize pure GABA analogs that do not spontaneously lactamize upon storage or during formulation, Gallop *et al.* [58] in 2004 patented an invention relating to the design, synthesis and evaluation of sustained release forms of **7** and **8**. This team evaluated the permeability of the synthesized prodrugs *in vitro* by using Caco-2 cell line system. *In vivo*, the prodrugs of **7** and **8** were evaluated for effective intracolonic absorption in rats.

Yuen in 2004 [59] reported the synthetic procedure and the therapeutic benefits of 3-heteroarylalkyl substituted GABA analogs (**25, 26**) the structures of which are given in (Fig. 7). The compounds exhibited protective effects against cramps induced by thiosemicarbazide and cardiazole. The patented compounds were also claimed to have curative effects against various cerebral diseases like epilepsy, faintness attacks, and cranial traumas.

The heteroaryl ring in the patented compounds was one of furan, thiophene or pyrrole. The pyrrole derivative was unsubstituted or substituted with one of branched alkyl, cycloalkyl, phenyl or benzyl. The prodrugs of these compounds included, but not limited to esters, amides, and carbamates. This team tested the novel compounds for their dose-dependent suppression of sound-induced tonic seizures

in DBA/2 mice. The ED₅₀ values were found to be much lower than those determined in the maximal electroshock test. In order to find the mechanism of action, a radioligand-binding assay using [³H] gabapentin and the α_2 subunit derived from porcine brain tissue was conducted. The compounds of the invention showed good binding affinity to the α_2 subunit. It was then hypothesized that the compounds are expected to exhibit pharmacologic properties comparable to gabapentin.

Scriba *et al.* [60] reported the synthesis and anticonvulsant activity of *N, N*-phthaloyl derivatives of central nervous system inhibitory amino acids. The compounds were tested for anticonvulsant activity according to standard procedures, which included the maximal electroshock seizure test and the seizure threshold test with subcutaneous pentylenetetrazole. The *N, N*-phthaloyl GABA derivative (**27**) was found to have no anticonvulsant activity. In contrast, another research team reported seizure-antagonizing effect of **27** in several models including the MES test [61]. Compared to the *N, N*-phthaloyl glycine amides, the *N, N*-phthaloyl GABA amides (**28a-h**) had lesser anticonvulsant effects in both the MES and the scPTZ models of seizure.

Librowski *et al.* [62] in 2001, studied the influence of new γ -aminobutyric acid amide derivatives and its phthalimide precursors on the central nervous system activity in mice. This research team investigated four new γ -aminobutyric acid amide derivatives, namely *N*-(4-fluorobenzylamide)-2-(4-phenylpiperazin-1-yl)-4-aminobutyric acid (**29a**), *N*-(4-methylbenzylamide)-2-(4-phenylpiperazin-1-yl)-4-aminobutyric acid (**29b**) and its phthalimide precursors, in an attempt to study their pharmacological effects on the CNS. The effects of all the above-mentioned compounds on the spontaneous locomotor activity of mice were measured using photoresistor actometers and the anticonvulsant efficacy determined in the Picrotoxin-induced convulsions model. The results of *in vivo* pharmacological examination of the effects of all the compounds showed that there was a different but clear influence on CNS in mice.

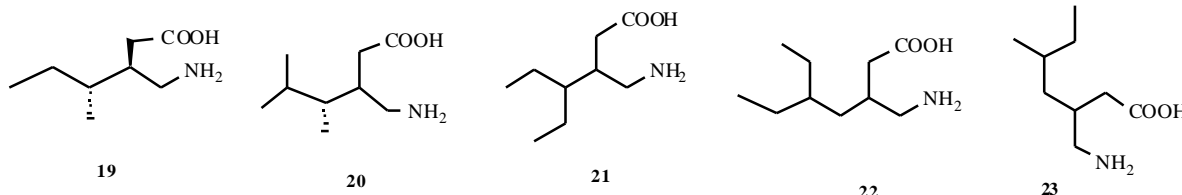


Fig. (6).

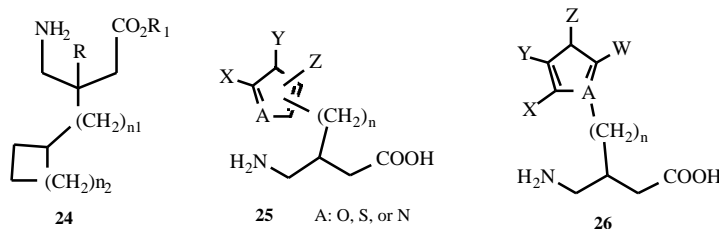


Fig. (7).

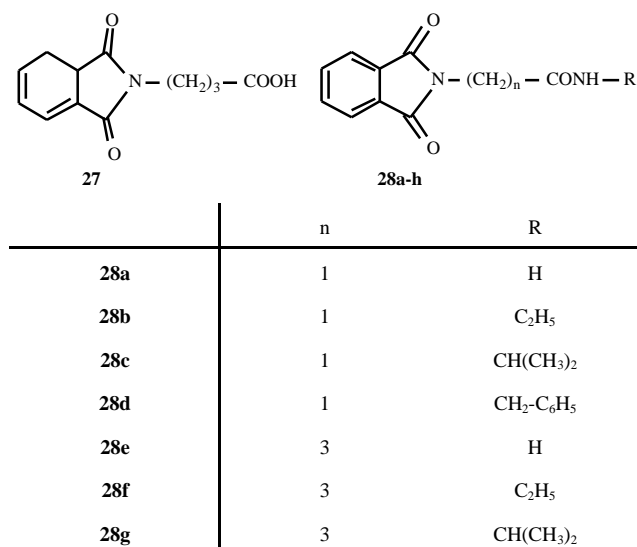


Fig. (8).

Schwarz *et al.* [63] in 2005, reported some novel cyclopropyl -amino acid analogs of **7** and **8** that target the α_2 protein. The antiepileptic activity of the synthesized compounds was measured by their ability to prevent audiogenically induced seizures in the DBA/2 strain of mice. The dipropyl- (**30a**), cyclopentyl- (**30b**), and cyclohexyl-substituted (**30c**) cyclopropyl -amino acids all bound with K_i values (equilibrium dissociation constants) less than or equal to 0.2 μ M, demonstrating high potency. The structures are given in (Fig. 9).

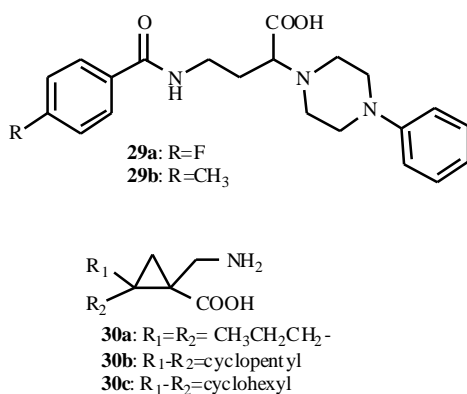


Fig. (9).

In the same year, Belliotti *et al.* [64] studied the structure-activity relationships of pregabalin and its analogues that target the α_2 protein of the voltage-gated calcium channels.

Restless legs syndrome (RLS) is an intensely uncomfortable sensory -motor disorder. The current treatment of RLS is with dopaminergic drugs, such as L-dopa, bromocriptine, pergolide, pramipexole or ropinirole. However, dopaminergic drugs have various side effects notably nausea. In addition, many dopaminergic drugs

exhibit a rebound phenomenon, in which symptoms tend to increase as a dose diminishes. Hence search for an effective treatment of RLS progressed at a much faster pace leading to the discovery that the well-established antiepileptic drug gabapentin, which showed efficacy in controlled studies for treating neuropathic pain of varying etiologies, could also be used in treating restless legs syndrome [65, 66]. Bryans *et al.* [67] in 1999 reported a requirement for frequent dosing of **7** to maintain a therapeutic or prophylactic concentration in the systemic circulation, as **7** has a clinical problem of rapid systemic clearance.

4. CURRENT AND FUTURE DEVELOPMENTS

The main goal of this paper was to show the importance of GABA analogs by covalently coupling the neurotransmitter to an appropriate transport moiety (carrier group) represented by a lipophilic moiety. This may lead to an improved access to the CNS by passive transport through the BBB. Taken together the literature results, it proves to be highly promising and feasible to synthesize useful anticonvulsants either by coupling the amine function of GABA with various neuropharmaceuticals leading to a dual/mutual prodrug or by modifying the carboxylic end. With GABA structure as a template, many modifications can still be carried out and there is scope for further modification and a systematic structure-activity relationship could be derived out.

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