

# GABA receptors

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## GABA

GABA ( $\gamma$ -aminobutyric acid; Figure 1) is the most important and most abundant inhibitory neurotransmitter in the mammalian brain<sup>1,2</sup>, where it was first discovered in 1950<sup>3-5</sup>. It is a small achiral molecule with molecular weight of 103 g/mol and high water solubility. At 25 °C one gram of water can dissolve 1.3 grams of GABA. Such a hydrophilic molecule ( $\log P = -2.13$ ,  $PSA = 63.3 \text{ \AA}^2$ ) cannot cross the blood brain barrier. It is produced in the brain by decarboxylation of L-glutamic acid by the enzyme glutamic acid decarboxylase (GAD, EC 4.1.1.15). It is a neutral amino acid with  $pK_1 = 4.23$  and  $pK_2 = 10.43$ . GABA interacts with three receptors: GABA<sub>A</sub>, GABA<sub>B</sub> and GABA<sub>C</sub>.

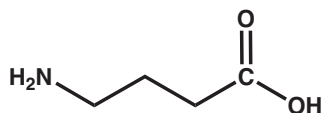


Figure 1.  $\gamma$ -Aminobutyric acid (GABA).

## GABA<sub>A</sub> Receptors

GABA<sub>A</sub> receptor is an ion channel receptor of the Cys-loop receptor superfamily together with the nicotinic acetylcholine receptor, the 5-HT<sub>3</sub> receptor and the strychnine-sensitive glycine receptor<sup>6</sup>. It was cloned in collaboration between the groups of Eric A. Barnard of the MRC in Cambridge, UK and Peter H. Seeburg of Genentech in 1987<sup>7</sup>. It is a pentamer consisting of five subunits with a large extracellular N-term, 4 transmembrane domains and a short extracellular C-term arranged in such a way that the transmembrane domains 2 form the inner walls of a chloride channel (Figure 2).

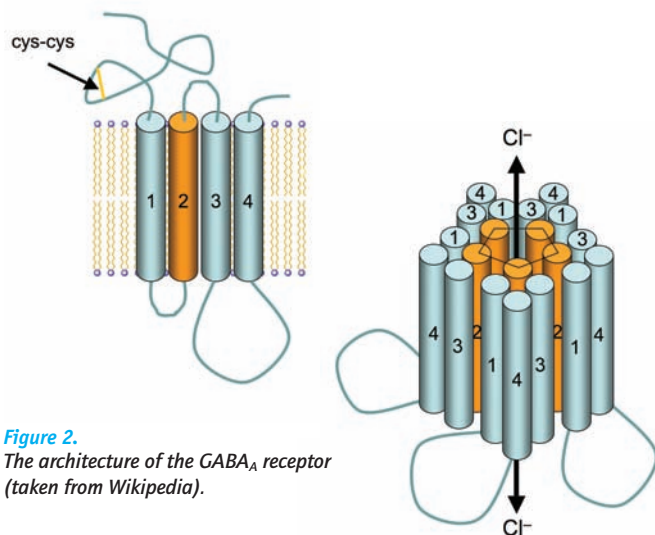


Figure 2. The architecture of the GABA<sub>A</sub> receptor (taken from Wikipedia).

Activation of the GABA<sub>A</sub> receptor leads to an influx of chloride ions and to a hyperpolarization of the membrane. 16 subunits with molecular weights between 50 and 65 kD have been identified so far, 6  $\alpha$  subunits, 3  $\beta$  subunits, 3  $\gamma$  subunits, and the  $\delta$ ,  $\epsilon$ ,  $\theta$  and  $\pi$  subunits<sup>8,9</sup>.

In the meantime all GABA<sub>A</sub> receptor binding sites have been elucidated in great detail. The GABA site is located at the interface between  $\alpha$  and  $\beta$  subunits. Benzodiazepines interact with subunit combinations ( $\alpha_1$ )<sub>2</sub> ( $\beta_2$ )<sub>2</sub>  $\gamma_2$ , which is the most abundant combination to form a pentamer, or with combinations of  $\alpha_2\beta\gamma_2$ ,  $\alpha_3\beta\gamma_2$  and  $\alpha_5\beta\gamma_2$ . They bind at the interface between  $\alpha$  and  $\gamma$  subunits<sup>10</sup>.

Other allosteric binding sites are the barbiturate site, the site of general anesthetics and the site for the channel blocking agents TBPS and picrotoxin(in) (Figure 3).

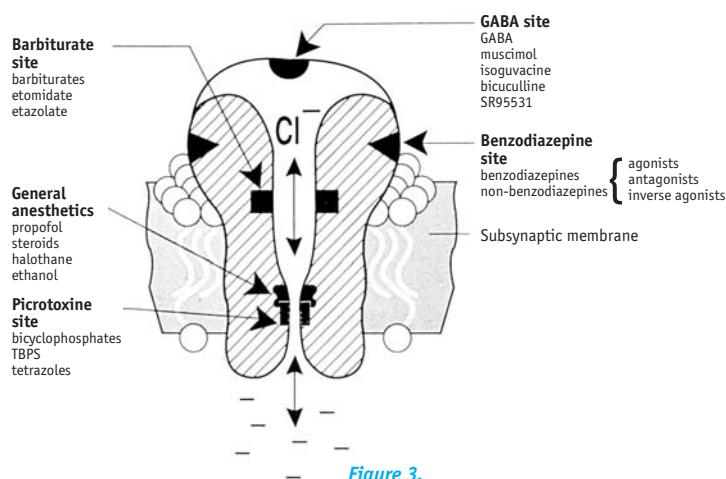
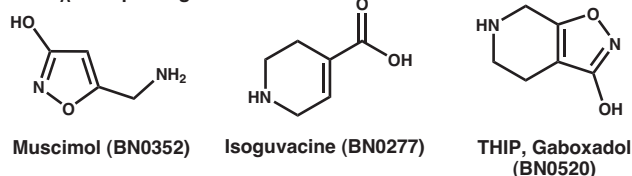


Figure 3. Different binding sites at the GABA<sub>A</sub> receptor (courtesy of Prof. N. G. Bowery).

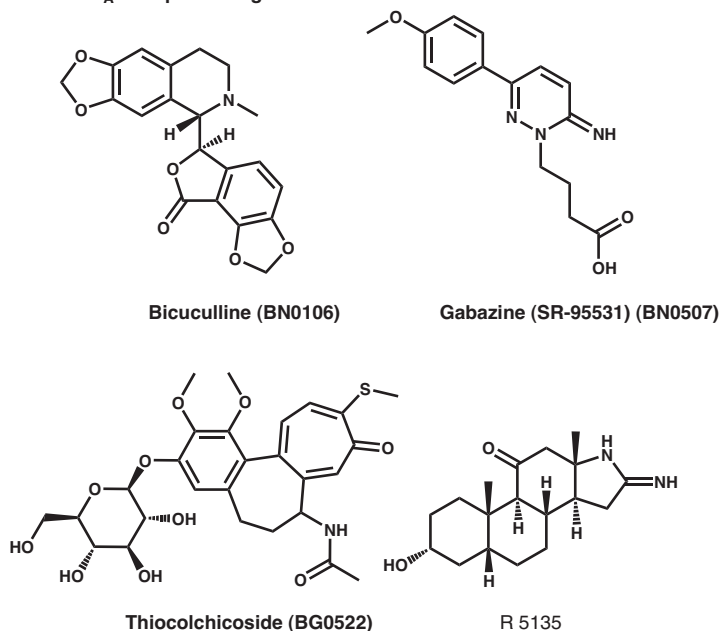
The best known GABA agonists are GABA (Figure 1), muscimol, and isoguvacine (Figure 4). THIP (Gaboxadol)<sup>11,12</sup>, a hypnotic drug, however, is interacting with  $\alpha_4\beta_3\delta$  subunits at extrasynaptic sites (as do the general anesthetics and ethanol).

# GABA receptors

## GABA<sub>A</sub> Receptor Agonists



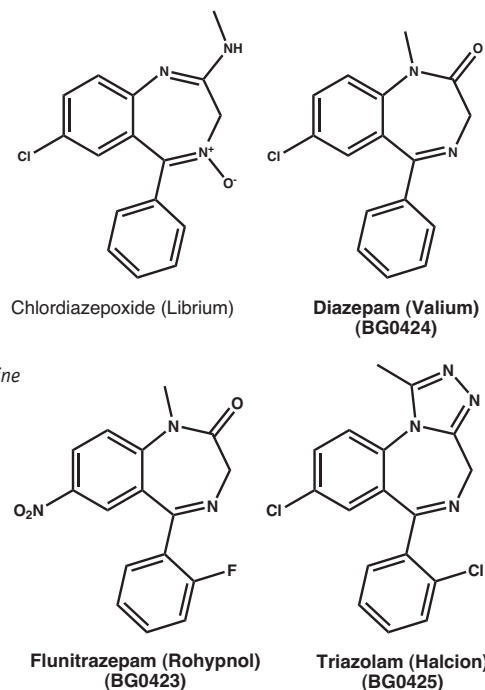
## GABA<sub>A</sub> Receptor Antagonists



**Figure 4.**  
GABA<sub>A</sub> receptor agonists and antagonists  
(Bold text denotes compound available from BIOTREND with catalogue number).

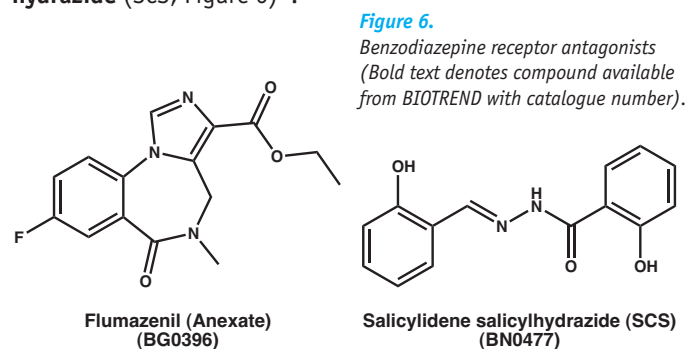
The best known GABA antagonists are bicuculline<sup>13</sup>, gabazine (SR-95531)<sup>14</sup>, thiolcolchicoside, a semisynthetic derivative of colchicoside used as muscle relaxant with anti-inflammatory and analgesic action<sup>15</sup> and the steroid derivative 3 $\alpha$ -hydroxy-16-imino-5 $\beta$ -17-aza-androstan-11-one (R-5135)<sup>16</sup> (Figure 4).

The biggest boost to GABA<sub>A</sub> receptor research came in 1957 with the discovery of the benzodiazepines by Leo H. Sternbach and colleagues of Roche, Nutley<sup>17</sup>. In fact, **chlordiazepoxide** had been synthesized already in 1955, was somehow forgotten and sent to biological testing in 1957 after a clean-up of the lab. Three years later the drug was on the US market launched as Librium (Figure 5). Roche Basel biologists established that the benzodiazepines act as positive allosteric modulators (PAMs) of GABA receptors<sup>18</sup>. **Diazepam** (Valium) was launched in 1963 and became the top-selling drug in the USA from 1969 to 1982 (Figure 5). Other "classical" benzodiazepine receptor agonists are **Flunitrazepam** (Rohypnol; Figure 5) and **Triazolam** (Halcion; Figure 5).



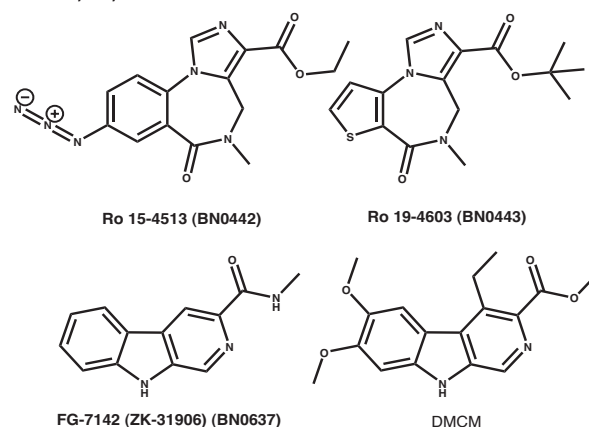
**Figure 5.**  
Classical benzodiazepine receptor agonists  
(Bold text denotes compound available from BIOTREND with catalogue number).

The benzodiazepine receptor antagonist **Flumazenil** (Anexate; Ro 15-1788) was discovered at Roche and marketed in 1987<sup>19</sup> (Figure 6). It is used as an antidote for overdoses of benzodiazepines. A selective inhibitor of  $\beta_1$ -containing GABA<sub>A</sub> receptors was discovered by Merck UK scientists, **salicylidene salicylhydrazide** (SCS; Figure 6)<sup>20</sup>.



**Figure 6.**  
Benzodiazepine receptor antagonists  
(Bold text denotes compound available from BIOTREND with catalogue number).

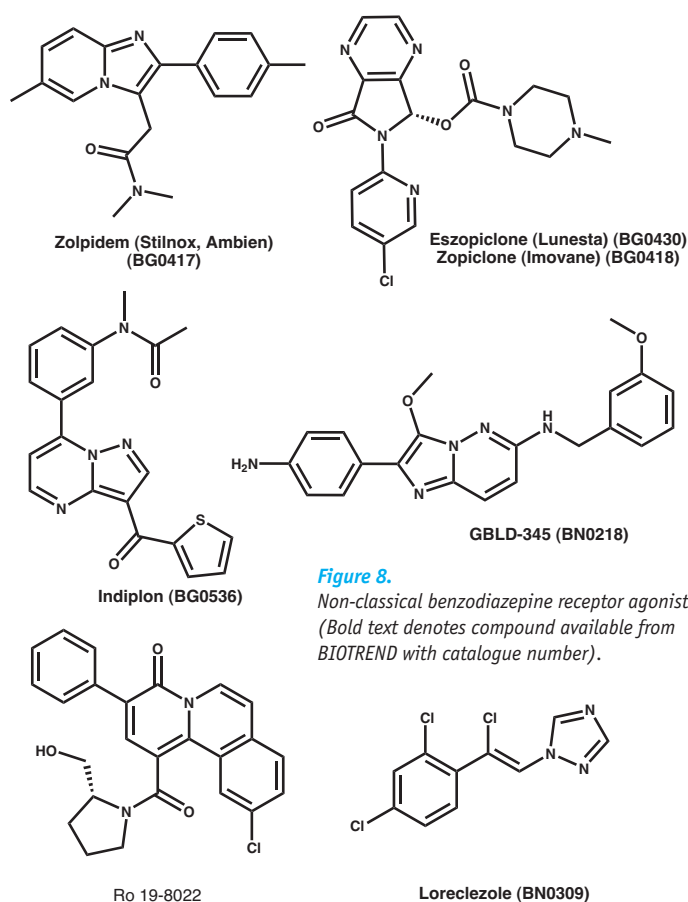
Partial inverse agonists, such as **Ro 15-4513** and **Ro 19-4603** are structurally related to flumazenil. They selectively block the effects of ethanol on locomotor behavior and suppress ethanol intake<sup>21,22</sup> (Figure 7). Other partial inverse agonists are the  $\beta$ -carboline derivatives **FG-7142** (ZK-31906), which improves memory retention in animal studies<sup>23</sup> and **DMCM** (methyl 6,7-dimethoxy-4-ethyl- $\beta$ -carboline-3-carboxylate), which displays anxiogenic and convulsant properties<sup>24</sup>.



**Figure 7.**  
Non-subtype selective benzodiazepine receptor inverse agonists  
(Bold text denotes compound available from BIOTREND with catalogue number).

Many valuable compounds without a 1,4-benzodiazepine structure (“non-classical” benzodiazepines”) bind also to benzodiazepine receptors, such as the imidazo[1,2-a]pyridine **Zolpidem** (Stilnox, Ambien), a widely prescribed hypnotic drug<sup>25</sup> (Figure 8). **Zopiclone** (Imovane), now replaced by **Eszopiclone** (Lunesta), is a short acting non-benzodiazepine sedative hypnotic<sup>26,39</sup>. **Indiplon** (Figure 8) displays a ten-fold selectivity for the  $\alpha_1$  subunit-containing GABA<sub>A</sub> receptors<sup>27</sup>. **GBLD-345** is an imidazo-pyridazine anxiolytic<sup>28</sup>.

**Ro 19-8022** (Figure 8) is a partial agonist at benzodiazepine receptors with no sedative or motor-impairing effects<sup>29</sup>. **Loreclezole** (Figure 8) is a sedative and anticonvulsant drug, which interacts selectively with  $\beta_2$  and  $\beta_3$  subunit containing GABA<sub>A</sub> receptors<sup>30</sup>.



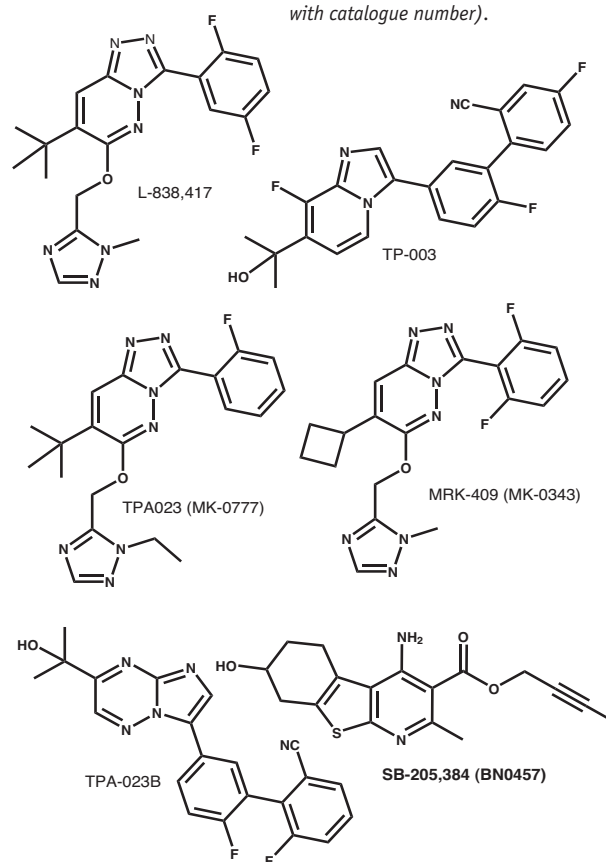
**Figure 8.** Non-classical benzodiazepine receptor agonists (Bold text denotes compound available from BIOTREND with catalogue number).

Benzodiazepines act as anxiolytics, hypnotics, anesthetics, muscle relaxants, analgetic and antiepileptic drugs. Currently there are 50 drugs on the market<sup>31</sup> (alpidem, alprazolam, bentazepam, bromazepam, brotizolam, camazepam, chlordiazepoxide, cinolazepam, clobazam, clonazepam, clorazepate, clotiazepam, cloxazolam, delorazepam, diazepam, estazolam, eszopiclon, ethyl-loflazepate, etizolam, fludiazepam, flumazenil (a benzodiazepine receptor antagonist), flunitrazepam, flurazepam, flutoprazepam, halozepam, haloxazolam, <sup>123</sup>I-iomazenil (a single photon emission tomography [SPECT] ligand), ketazolam, loprazolam, lorazepam, lormetazepam, medazepam, metaclazepam, mexazolam, midazolam, nimetazepam, nitrazepam, nordazepam, oxazepam, oxazolam, pinazepam, prazepam, quazepam, temazepam, tetrazepam, tofisopam, triazolam, zaleplon, zolpidem and zopiclon) making benzodiazepines the financially most lucrative class of drugs of all times (despite the inevitable failures of e.g. abecarnil, bretazenil, divaplon, imidazenil, indiplon, ocinaplon, pagoclone, panadiplon or pazinaclone).

Although benzodiazepines are very valuable drugs, they also have several severe side effects such as tolerance, addiction and potentiation of its effects by ethanol<sup>32-35</sup>. Christian Lüscher and colleagues in Geneva found out, that the addictive effects of benzodiazepines can be attributed to  $\alpha_1$ -containing GABA<sub>A</sub> receptors in the ventral tegmental area of mice<sup>36</sup>. For the use as anxiolytics as well as for cognition enhancing drugs, it would be desirable to eliminate the sedative effects of benzodiazepines.

Sustained efforts, in particular by Hanns Möhler and colleagues in Zürich<sup>37</sup> and by Ruth M. McKernan and her team at Merck UK<sup>38</sup>, made it possible to elucidate the pharmacology of the different subtype combinations. Point mutations on  $\alpha_1$  (H101R),  $\alpha_2$  (H101R),  $\alpha_3$  (H126R) and  $\alpha_5$  (H105R) in knock-in mice allowed the study of the effects of benzodiazepines on isolated GABA<sub>A</sub> receptor subtypes showing that agonists at  $\alpha_1\beta\gamma_2$  GABA<sub>A</sub> receptors mediate sedation, amnesia and anticonvulsive effects, agonists at  $\alpha_2\beta\gamma_2$  GABA<sub>A</sub> receptors mediate anxiolytic and myorelaxant effects, agonists at  $\alpha_3\beta\gamma_2$  GABA<sub>A</sub> receptors mediate anxiolytic and analgetic actions and inverse agonists at  $\alpha_5\beta\gamma_2$  GABA<sub>A</sub> receptors improve learning and memory.

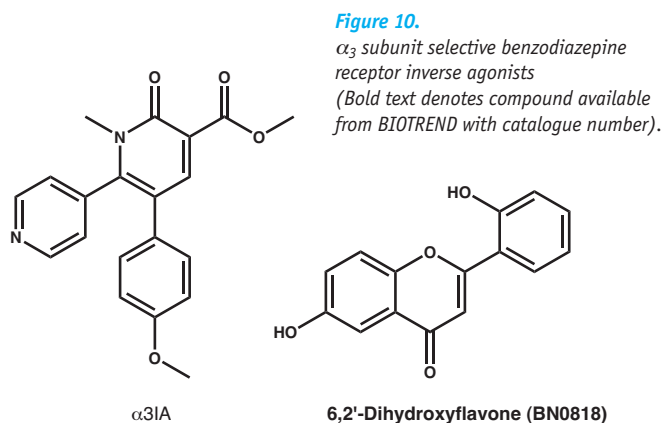
**Figure 9**  $\alpha_2\beta\gamma_2$  and  $\alpha_3\beta\gamma_2$  subtype selective benzodiazepine receptor agonists. (Bold text denotes compound available from BIOTREND with catalogue number).



Big efforts were made by several companies to find selective agonists for  $\alpha_2\beta\gamma_2$  GABA<sub>A</sub> receptors mediating anxiolytic effects without sedation. Scientists at Merck UK discovered **L-838,417** (Figure 9), a subtype selective GABA<sub>A</sub> agonist, acting as partial agonist at  $\alpha_2$ ,  $\alpha_3$  and  $\alpha_5$  subtypes, but as an antagonist at the  $\alpha_1$  subtype<sup>38,39</sup>. **TP-003** (Figure 9) showed significant efficacy at  $\alpha_3$  subtypes only<sup>40</sup>. The triazolo[4,3-b]pyridazine **TPA023** (also

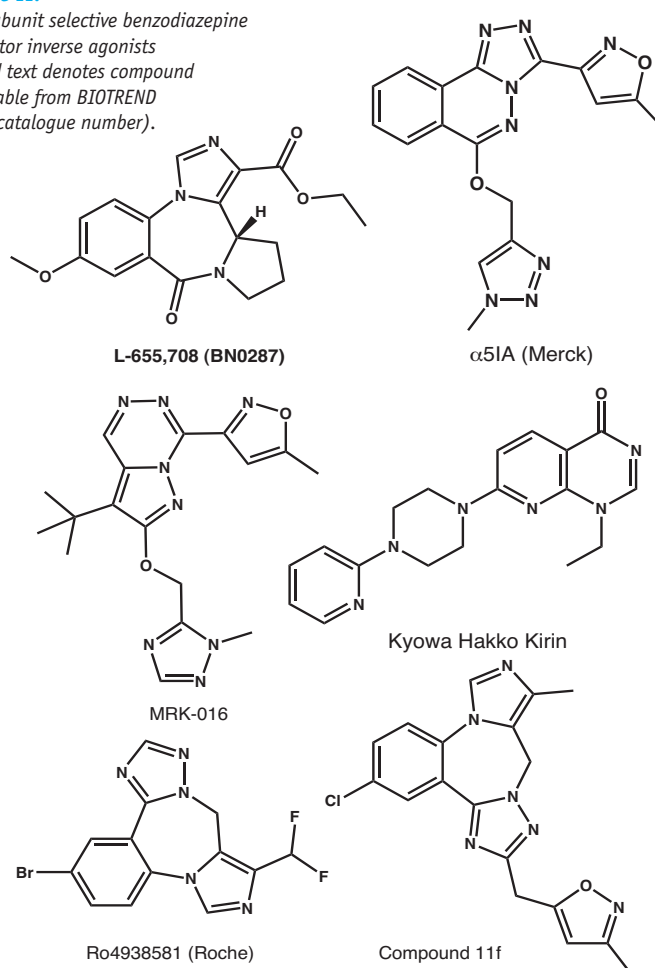
known as MK-0777; Figure 9) has partial agonist efficacy at the  $\alpha_2$  and  $\alpha_3$ , but not at the  $\alpha_1$  and  $\alpha_5$  subtypes. It is a selective non-sedating anxiolytic with a half life of 6–7 hours in humans<sup>41,42</sup>. The high-affinity imidazo[1,2-b][1,2,4]triazine **TPA023B** (Figure 9), has partial agonist efficacy at the  $\alpha_2$  and  $\alpha_3$  subtype, but is an antagonist at the  $\alpha_1$  subtype<sup>43</sup>. The triazolo[4,3-b]pyridazine **MRK-409** (MK-0343; Figure 9) is a non-sedating anxiolytic in preclinical species, but causes sedation in humans due to a small residual efficacy at  $\alpha_1$  subtypes<sup>44</sup>. Scientists at GSK found **SB-205,384** (Figure 9), which binds preferentially to the  $\alpha_3\beta_2\gamma_2$  subunit combination<sup>45</sup>

Anxiogenic properties were reported for an inverse agonist selective for  $\alpha_3$  subunit-containing GABA<sub>A</sub> receptors. The compound  **$\alpha$ 3IA** (Figure 10) showed good CNS penetration in rats and mice and was anxiogenic in the elevated plus maze<sup>46</sup>. Similar effects were described for **6,2'-Dihydroxyflavone** (DHF; Figure 10)<sup>47</sup>.

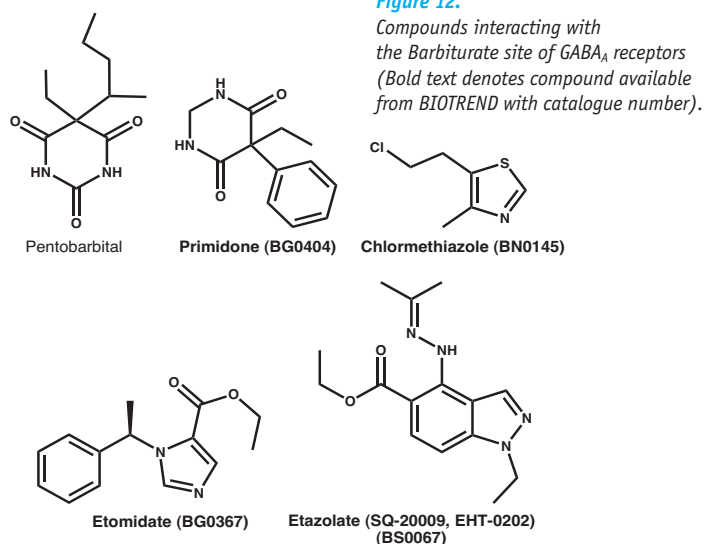


The search for inverse agonists at  $\alpha_5\beta\gamma_2$  GABA<sub>A</sub> receptors to improve learning and memory is ongoing at Merck, Kyowa Hakko and Roche (Figure 11). [<sup>3</sup>H]**L-655,708** was already published in 1996<sup>48</sup>. It enhances cognition in rats and is not proconvulsive at a dose selective for  $\alpha_5$ -containing GABA<sub>A</sub> receptors<sup>49</sup>. The triazolophthalazine  **$\alpha$ 5IA** (Figure 11) improves cognitive performance in normal rats without any anxiogenic or proconvulsant liabilities. Unfortunately, the hydroxymethyl isoxazole metabolite has a very low water solubility resulting in renal toxicity at high doses. The drug reversed the ethanol-induced impairment in performance in healthy young volunteers<sup>50</sup>. The pyrazolo[1,5-d][1,2,4] triazine **MRK-016** (Figure 11) showed an even bigger efficacy selective for the  $\alpha_5$  subtype than  $\alpha$ 5IA. It increased LTP in mouse hippocampal slices to a greater extent than  $\alpha$ 5IA. It was well tolerated in young male volunteers, but was poorly tolerated in elderly subjects<sup>51</sup>. Scientists of Kyowa Hakko Kirin presented a pyrido[2,3-d]pyrimidine-4-one as a novel class of GABA<sub>A</sub>  $\alpha_5$  receptor inverse agonist with a  $K_i$  at  $\alpha_5$  of 37 nM and an efficacy of -75% at  $10^{-5}$  and -11% at  $10^{-6}$  mol/l<sup>52</sup>. The  $K_i$  of Ro4938581 (Figure 11) to  $\alpha_5\beta_3\gamma_2$  receptors is 4.6 nM. The compound reversed scopolamine-induced working memory impairment in the delayed match to position task in rats with doses of 0.3 to 1 mg/kg p.o.<sup>53</sup>. Also **compound 11f** (Figure 11) showed excellent *in vivo* results in the delayed match to position test in rats<sup>54</sup>.

**Figure 11.**  
 *$\alpha_5$  subunit selective benzodiazepine receptor inverse agonists*  
(Bold text denotes compound available from BIOTREND with catalogue number).

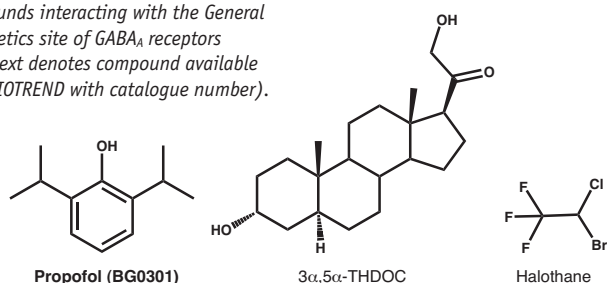


The barbiturates have lost their significance as medication for insomnia with the discovery of the benzodiazepines. **Pentobarbital** (Figure 12) is now used for physician assisted suicides and for executions in the USA and China. Marilyn Monroe died of an overdose of pentobarbital on August 5, 1962. **Primidone** is an anticonvulsant to treat complex partial and generalized tonic-clonic seizures, myoclonic akinetic seizures and essential tremor<sup>55</sup>. **Clomethiazole** is a sedative and hypnotic widely used in treating symptoms of acute alcohol withdrawal. It interacts with GABA<sub>A</sub> receptors containing an  $\alpha_4$  or  $\alpha_6$  subunit. It elicited a greater potentiation on receptors lacking the  $\gamma_2$  subunit<sup>56</sup>. **Etomidate** (Figure 12) is a short acting intravenous anesthetic agent, which does not cause hypotension. It is a modulator at GABA<sub>A</sub>  $\alpha_4(\alpha_6)\beta_3\delta$  receptor subtypes<sup>57</sup>. **Etazolate** (SQ-2009; Figure 12) is an anxiolytic drug discovered at Squibb. It acts as a positive allosteric modulator of the GABA<sub>A</sub> receptor at the barbiturate binding site, as an adenosine antagonist of the A<sub>1</sub> and A<sub>2</sub> subtypes, and as a phosphodiesterase inhibitor selective for the PDE4 isoform<sup>58</sup>. ExonHit Pharmaceuticals is currently testing EHT-0202 in Phase 2 clinical trials for the treatment of Alzheimer's disease<sup>59</sup>.



**Propofol** (Figure 13) is a short-acting, intravenously administered hypnotic agent. Its uses include the induction and maintenance of general anesthesia, sedation for mechanically ventilated adults, and procedural sedation. It binds near the extracellular end of the  $\beta$  subunit M3 segment<sup>60</sup>. Propofol caused the death of Michael Jackson on June 25, 2009. The endogenous neurosteroid  $3\alpha$ -hydroxy- $5\alpha$ -tetrahydro-deoxy-corticosterone ( $3\alpha,5\alpha$ -THDOC; Figure 13) shows very pronounced sedative, anxiolytic and anti-convulsant effects<sup>61,62</sup>. The greatest effect was observed for THDOC at  $\alpha_4\beta_3\delta$  receptors<sup>12</sup>. **Halothane** (Figure 13) is an inhalational general anesthetic<sup>63</sup>, which is nowadays replaced by isoflurane, desflurane and sevoflurane.

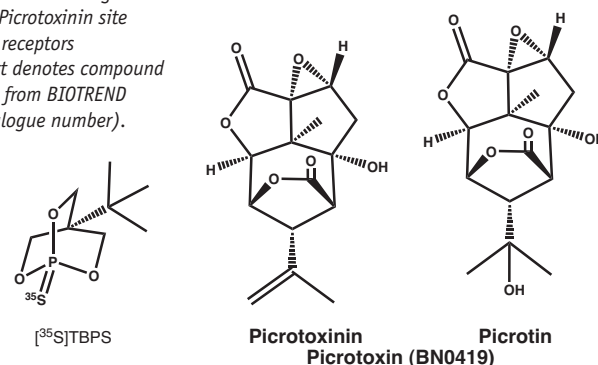
**Figure 13.**  
Compounds interacting with the General Anesthetics site of GABA<sub>A</sub> receptors (Bold text denotes compound available from BIOTREND with catalogue number).



**Ethanol** also interacts with extrasynaptic GABA<sub>A</sub> receptors depending on its concentration in the brain.  $\alpha_4$  and  $\delta$  subunits are abundant in the thalamus, striatum and the outer layers of the cortex, whereas  $\alpha_6$  and  $\delta$  subunits are colocalized in cerebellar granule cells<sup>64</sup>. It interacts at concentrations of > 3 mM (half a glass of wine) with high sensitivity sites of  $\alpha_4(\alpha_6)\beta_3\delta$  GABA<sub>A</sub> receptor subtypes, at concentrations of > 30 mM (five glasses of wine) with medium sensitivity sites of  $\alpha_4(\alpha_6)\beta_2\delta$  GABA<sub>A</sub> receptor subtypes and at concentrations of > 100 mM (16 glasses of wine) with low sensitivity sites of  $\alpha_4(\alpha_6)\beta_3\gamma_2$  GABA<sub>A</sub> receptor subtypes<sup>65,66</sup>. Ro-15-4513 (Figure 7) acts on these receptor subtypes.

One of the most valuable pharmacological tools for studying interactions of drugs with GABA<sub>A</sub> receptors is [<sup>35</sup>S]TBPS ([<sup>35</sup>S]t-butylbicyclophosphorothioate<sup>67</sup>, Figure 14). Benzodiazepine receptor agonists enhance, and inverse benzodiazepine receptor agonists reduce [<sup>35</sup>S]TBPS binding. Both picrotoxin and muscimol inhibited [<sup>35</sup>S]TBPS binding with IC<sub>50</sub>'s of 250 nM and 200 nM, respectively<sup>68</sup>. The reagent of choice to block GABA<sub>A</sub> receptors is picrotoxin<sup>69</sup>, which consists of two substances, picrotoxinin and picrotin (Figure 14).

**Figure 14.**  
Compounds interacting with the Picrotoxinin site of GABA<sub>A</sub> receptors (Bold text denotes compound available from BIOTREND with catalogue number).

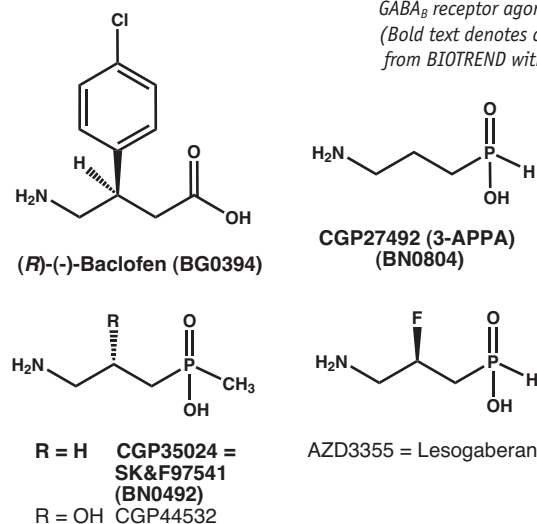


For many years GABA<sub>A</sub> receptors were considered to be located exclusively postsynaptically. Very recently presynaptic GABA<sub>A</sub> receptors were found at hippocampal mossy fiber synapses, which facilitate information flow to the hippocampus both directly and by enhancing LTP<sup>70</sup>.

### GABA<sub>B</sub> Receptors

GABA<sub>B</sub> receptors belong to the family 3 of G-protein coupled receptors as the metabotropic glutamate receptors, the calcium sensing receptor, taste receptors and a family of orphan receptors<sup>71</sup>. The GABA<sub>B</sub> receptor was discovered by Norman G. Bowery and coworkers in 1980, who found that GABA decreased the release of [<sup>3</sup>H]-noradrenaline from rat atria and of [<sup>3</sup>H]-acetylcholine from preganglionic terminals in the rat superior cervical ganglion *in vitro*<sup>72</sup>. These effects could not be antagonized by the GABA antagonist bicuculline. Bowery showed, that the GABA analogue **baclofen** was as active as GABA in reducing evoked transmitter output and that the effect was stereoselective with the (*R*)-(-)-enantiomer (Figure 15), being >100 fold more active than the (*S*)-(+)-enantiomer<sup>72</sup>. The term GABA<sub>B</sub> receptor was designated in March 1981<sup>73</sup>. Baclofen was synthesized in September 1962 by Heinrich Keberle of CIBA Pharmaceuticals in Basel and was introduced to the market as Lioresal in 1972. It is widely used as a muscle relaxant for the treatment of spasticity in hemi- and tetraplegic and in multiple sclerosis patients, for the treatment of trigeminal neuralgia and of tetanus. Baclofen effectively reduces craving for drugs of abuse, such as alcohol, nicotine and cocaine<sup>74</sup>.

**Figure 15.**  
GABA<sub>B</sub> receptor agonists (Bold text denotes compound available from BIOTREND with catalogue number).



In fall of 1984 it was discovered, that the phosphonous acid analogue of GABA, i.e. **CGP27492** (3-APPA) (Figure 15), showed an extraordinary high affinity towards GABA<sub>B</sub> receptors ( $IC_{50} = 2$  nM; inhibition of binding of [<sup>3</sup>H]baclofen to GABA<sub>B</sub> receptors of cat cerebellum)<sup>75</sup>. Due to its 15 times higher potency, its high specific binding and the possibility to carry out filtration assays, [<sup>3</sup>H]**CGP27492** has replaced [<sup>3</sup>H]baclofen as a radioligand for GABA<sub>B</sub> receptor binding assays<sup>76</sup>.

The methyl-phosphinic acid derivative **CGP35024** (identical with **SK&F97541**; Figure 15) was seven times more potent against neuropathic hyperalgesia than (*R*)-(-)baclofen. It induced nociceptive responses at doses well below those that cause sedation<sup>77</sup>.

CGP27492 and CGP35024 (SK&F97541) act as antagonists to GABA<sub>C</sub> receptors ( $IC_{50} = 2.47$  μM for CGP27492 at human ρ1 GABA<sub>C</sub> receptors;  $IC_{50} = 0.75$  μM at human ρ1 GABA<sub>C</sub> receptors and  $IC_{50} = 3.5$  μM at human ρ2 GABA<sub>C</sub> receptors for CGP35024 (SK&F97541), respectively<sup>78,79</sup>.

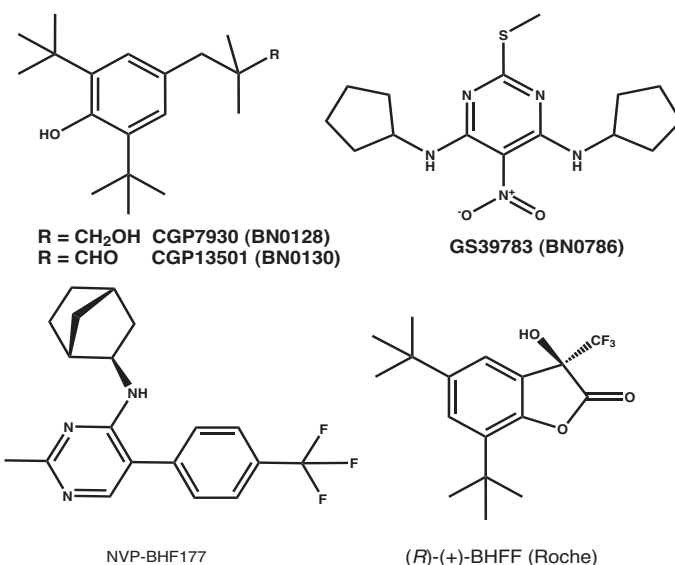
**CGP44532** (Figure 15) showed muscle relaxant activity in the rotarod test in rats with  $ED_{50}$ 's of 0.4 mg/kg s.c. and 6.5 mg/kg p.o. and had a duration of action 3 times longer than that of baclofen. It showed a gastro-intestinal and CNS side effect profile significantly superior to baclofen in *Rhesus* monkeys. Repeated administration of CGP44532 at doses of 0.3 mg/kg s.c. for five days and of 3 mg/kg p.o. for ten days produced significant anti-hyperalgesic effects in neuropathic rats with no evidence for tolerance<sup>80</sup>. CGP44532 was also tested in several animal models of suppression of craving for drugs of abuse, such as **alcohol**<sup>81</sup>, **cocaine** in rats<sup>82,83</sup> and baboons<sup>84</sup> and **nicotine**<sup>85</sup>. Also (*S*)-(-)-CGP44532 and its (*R*)-(+)-enantiomer CGP44533 act as antagonists to GABA<sub>C</sub> receptors ( $IC_{50} = 17$  μM for CGP44532 and  $IC_{50} = 5$  μM for CGP44533 at human ρ1 GABA<sub>C</sub> receptors<sup>86</sup>.

The phosphonous acid derivative **AZD3355** (**Lesogaberan**; Figure 15) inhibits transient lower esophageal sphincter relaxation<sup>87,88</sup>. It is currently in Phase 2 clinical evaluation for the treatment of gastro-intestinal esophageal reflux disease (GERD).

In 2000 the first positive allosteric modulators (PAMs) of GABA<sub>B</sub> receptors were discovered at Novartis Basel, first **CGP7930** and its oxidation product, the aldehyde **CGP13501**<sup>89</sup> followed by **GS39783**<sup>90</sup> and **NVP-BHF177**<sup>91</sup> and the Roche compound **(+)-BHFF**<sup>92</sup> (Figure 16). Novartis molecular biologists located the binding site of GS39783 in the 6<sup>th</sup> transmembrane domain of the GABA<sub>B2</sub> receptor<sup>93</sup>. As the positive modulators of GABA<sub>A</sub> receptors, the benzodiazepines, all four PAMs of GABA<sub>B</sub> receptors showed pronounced anxiolytic properties<sup>74</sup>. In addition, these drugs are effective to suppress the craving for drugs of abuse, such as alcohol<sup>94-96</sup>, nicotine<sup>97</sup> and cocaine<sup>98</sup>.

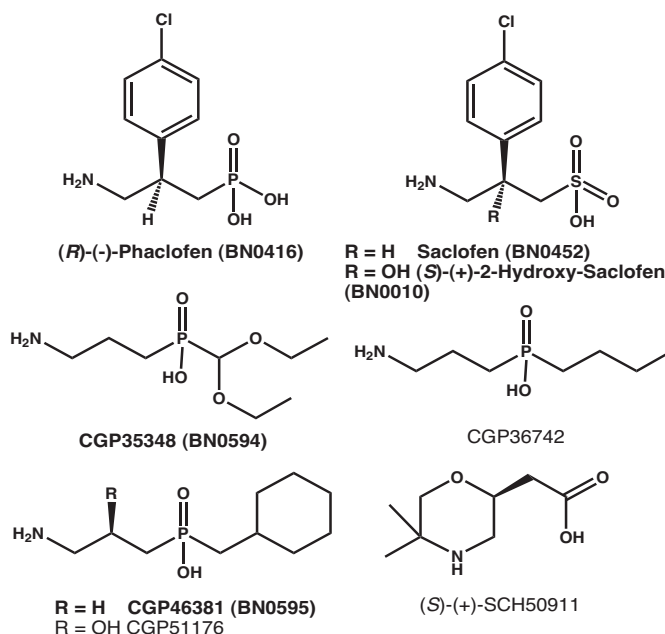
**Figure 16.**

Positive allosteric modulators (PAMs) of GABA<sub>B</sub> receptors  
(**Bold text** denotes compound available from BIOTREND with catalogue number).



Addex is testing ADX-71943 (structure not disclosed) in clinical trials for the treatment of osteoarthritic pain and chronic nociceptive pain. AstraZeneca scientists published ten patents between 2006 and 2009 in the search for novel drugs to treat gastro-esophageal reflux disease. A review on the patent literature was published in 2010<sup>99</sup>.

In 1987 the discovery of the first GABA<sub>B</sub> receptor antagonist, the phosphonic acid analogue of baclofen, **phaclofen**, was reported by Kerr et al.<sup>100</sup> in Australia followed by the sulfonic acid derivatives **2-hydroxy-saclofen**<sup>101</sup> and the at least twice as potent **saclofen**<sup>102</sup> (Figure 17). The active enantiomers are (*R*)-(-)-phaclofen and (*S*)-(+)-2-hydroxy-saclofen. At the same time, Ciba-Geigy scientists in Switzerland discovered that 3-aminopropyl phosphinic acids with substituents larger than methyl are GABA<sub>B</sub> receptor antagonists, such as **CGP35348**, **CGP36742**, **CGP46381** and **CGP51176** (Figure 17)<sup>103,104</sup>. Schering scientists reported on the GABA<sub>B</sub> antagonistic properties of SCH50911, a pure (*S*)-(+)-enantiomer (Figure 17)<sup>105</sup>.



**Figure 17.**

Low affinity GABA<sub>B</sub> receptor antagonists

(**Bold text** denotes compound available from BIOTREND with catalogue number).

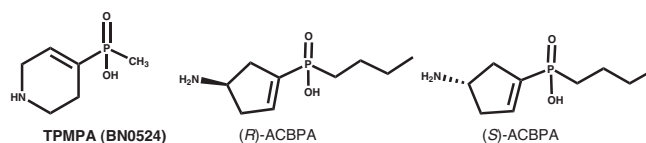


## GABA<sub>C</sub> Receptors

G. A. R. Johnston and his group provided the first GABA<sub>C</sub> receptor agonists already in 1975, cis and trans amino-crotonic acid (CACA: IC<sub>50</sub> for GABA<sub>A</sub> receptors, i.e. inhibition of binding of [<sup>3</sup>H]GABA: 25 mM; EC<sub>50</sub> at GABA<sub>C</sub> receptors: 37 mM; TACA: IC<sub>50</sub> for GABA<sub>A</sub> receptors, i.e. inhibition of binding of [<sup>3</sup>H]GABA: 0.14 mM and EC<sub>50</sub> at GABA<sub>C</sub> receptors: 0.44 mM)<sup>125,78</sup>. They claimed in 1984 that the GABA<sub>C</sub> receptor is a bicuculline-insensitive and baclofen-insensitive GABA receptor<sup>126</sup>. GABA<sub>C</sub> receptors are (as GABA<sub>A</sub> receptors) chloride ion channel receptors built up by five subunits to form homo-pentameric receptors from ρ1 (473 amino acids), ρ2 (465 amino acids) or ρ3 subunit (464 amino acids) or form pseudo-heteromeric receptors from ρ1 + ρ2 or ρ2 + ρ3 subunits. The ρ1 subunit of GABA<sub>C</sub> receptors was cloned in 1991<sup>127,128</sup>, the ρ2 subunit in 1992<sup>129</sup> and the ρ3 subunit in 1996<sup>130</sup>.

The first selective, but not brain penetrating GABA<sub>C</sub> antagonist TPMPA was prepared by L. E. Overman and colleagues at Irvine<sup>131</sup> ( $K_b = 2.1 \mu\text{M}$ <sup>78</sup>; Figure 20). The reduced piperidine derivative<sup>132</sup> is also available as radioligand [<sup>3</sup>H]P4MPA.

In a joint collaboration between the groups of Wolfgang Froestl at Ciba-Geigy (Novartis) in Basel and of Graham A. R. Johnston in Sydney several GABA<sub>B</sub> receptor agonists and antagonists were measured for their interactions with ρ1 and ρ2 GABA<sub>C</sub> receptors<sup>78</sup>. The GABA<sub>B</sub> receptor agonists CGP's 27492, 35024 (= SK&F97541), 38593, 44530, 70522 and 70533 turned out to be GABA<sub>C</sub> receptor antagonists, the GABA<sub>B</sub> receptor antagonist CGP36742 showed an IC<sub>50</sub> of 38 μM for GABA<sub>B</sub> receptors and an IC<sub>50</sub> of 62 μM for GABA<sub>C</sub> receptors. All other GABA<sub>B</sub> receptor antagonists tested (CGP's 35348, 46381, 51176 and 55845A) did not interact with GABA<sub>C</sub> receptors. The binding of CGP36742 to the ρ1 GABA<sub>C</sub> receptor was analyzed in a homology model of the GABA<sub>C</sub> receptor<sup>133</sup>. By conformational restriction of the γ-aminopropyl phosphinic acid side chain of CGP36742 in a five membered ring to obtain cis-(3-amino-cyclopentanyl)-n-butyl-phosphinic acid (cis-3-ACBPA) the affinity to GABA<sub>B</sub> receptors was destroyed, but the interaction with GABA<sub>C</sub> receptors was significantly enhanced (IC<sub>50</sub> = 5 μM). Intravitreal administration of cis-3-ACBPA to the eyes of chicken prevented experimental myopia development<sup>134</sup>. The corresponding cis-cyclopentenyl derivative was resolved into the two enantiomers (Figure 20) to show that the (S)-enantiomer had a higher affinity to ρ1 receptors ( $K_b = 5 \mu\text{M}$  for ρ1 and 11 μM for ρ2), whereas the (R)-enantiomer had a higher affinity for ρ2 receptors ( $K_b = 60 \mu\text{M}$  for ρ1 and 6 μM for ρ2)<sup>135,136</sup>. Both enantiomers enhanced learning and memory functions in mice at 10 mg/kg administered intraperitoneally (i.p.) comparable to 150 mg/kg i.p. of CGP36742.



**Figure 20.**

GABA<sub>C</sub> receptor antagonists

(**Bold text denotes compound available from BIOTREND with catalogue number.**)

It is not unusual that the same scaffold is used for the search of different G-protein coupled receptors. But here we have a unique example, that the same scaffold can be used to discover potent antagonists for a G-protein coupled receptor (GABA<sub>B</sub>) and for an ion channel receptor (GABA<sub>C</sub>).

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## GABA<sub>A</sub> receptor compounds

<i>GABA<sub>A</sub> receptor</i>		
<b>Cat. No.</b>	<b>Product</b>	<b>Category</b>
BG0030	γ-Aminobutyric acid (GABA)	Endogenous GABA agonist
BN0277	Isoguvacine hydrochloride	Selective GABA <sub>A</sub> agonist
BN0352	Muscimol	Potent GABA <sub>A</sub> agonist, GABA <sub>C</sub> partial agonist
BN0512	TACA	GABA <sub>A</sub> agonist, GABA-T substrate and uptake inhibitor
BN0520	THIP hydrochloride	GABA <sub>A</sub> agonist, GABA <sub>C</sub> antagonist
BN0106	(+)-Bicuculline	Potent GABA <sub>A</sub> antagonist
BN0110	(-)-Bicuculline methobromide	Water-soluble GABA <sub>A</sub> antagonist
BN0108	(-)-Bicuculline methochloride	Water-soluble GABA <sub>A</sub> antagonist
BN0107	(-)-Bicuculline methiodide	Water-soluble GABA <sub>A</sub> antagonist
BN0419	Picrotoxin	GABA <sub>A</sub> antagonist
BN0507	SR 95531 hydrobromide	Selective, competitive GABA <sub>A</sub> antagonist
BG0522	Thiocolchicoside	Potent GABA <sub>A</sub> receptor antagonist
BG0497	Carbamazepine	GABA <sub>A</sub> ligand, Na <sup>+</sup> channel blocker, anticonvulsant
BN0145	Chlormethiazole hydrochloride	GABA <sub>A</sub> potentiator
BS0076	Etazolate hydrochloride	GABA <sub>A</sub> positive allosteric modulator, selective PDE4 inhibitor
BG0367	Etomidate	GABA <sub>A</sub> modulator
BG0536	Indiplon	Potent GABA <sub>A</sub> positive allosteric modulator
BN0309	Loreclezole hydrochloride	GABA <sub>A</sub> modulator
BG0404	Primidone	GABA <sub>A</sub> agonist
BN0457	SB 205384	GABA <sub>A</sub> modulator
BN0477	SCS	GABA <sub>A</sub> antagonist, β1 selective
BG0434	Desmethylzopiclone	GABA <sub>A</sub> (BZ site) agonist, metabolite of Zopiclone
BG0435	(S)-Desmethylzopiclone hydrochloride	GABA <sub>A</sub> (BZ site) agonist, active metabolite of (S)-Zopiclone
BG0424	Diazepam	GABA <sub>A</sub> (BZ site) agonist
BN0818	6,2'-Dihydroxyflavone	GABA <sub>A</sub> (BZ site) partial inverse agonist, α3 selective
BG0423	Flunitrazepam	GABA <sub>A</sub> (BZ site) agonist
BN0218	GBLD 345	GABA <sub>A</sub> (BZ site) agonist
BN0287	L-655,708	GABA <sub>A</sub> ligand, α5 selective
BG0425	Triazolam	GABA <sub>A</sub> (BZ site) agonist
BG0417	Zolpidem	GABA <sub>A</sub> (BZ site) agonist
BG0418	Zopiclone	GABA <sub>A</sub> (BZ site) agonist, cyclopyrrolone derivative
BG0430	(S)-Zopiclone	GABA <sub>A</sub> (BZ site) agonist, active enantiomer
BN0637	FG 7142	GABA <sub>A</sub> (BZ site) inverse agonist
BN0442	Ro 15-4513	GABA <sub>A</sub> (BZ site) partial inverse agonist
BN0443	Ro 19-4603	GABA <sub>A</sub> (BZ site) partial inverse agonist
BG0396	Flumazenil	GABA <sub>A</sub> (BZ site) antagonist

**Peripheral benzodiazepine receptor compounds**

<i>Cat. No.</i>	<i>Product</i>	<i>Category</i>
BP0091	Diazepam binding inhibitory fragment	Peripheral benzodiazepine receptor agonist
BN0210	FGIN-1-27	Potent, specific mitochondrial BDI receptor ligand
BN0212	FGIN-1-43	Potent, specific mitochondrial BDI receptor ligand
BN0423	PK 11195	Peripheral benzodiazepine receptor antagonist

**Related Radioligands**

<i>Cat. No.</i>	<i>Product</i>	<i>Category</i>
ART-0207	[ <sup>3</sup> H]-γ-Aminobutyric acid (GABA)	Endogenous GABA agonist
ART-1474	[ <sup>3</sup> H]-7-Aminoflunitrazepam	GABA <sub>A</sub> (BZ site) agonist
ART-0576	[ <sup>3</sup> H]-(-)-Bicuculline methylchloride	Water-soluble GABA <sub>A</sub> antagonist
ART-0746	[ <sup>3</sup> H]-4'-Chlorodiazepam (RO5-4864)	GABA <sub>A</sub> (BZ site) agonist
ART-1335	[ <sup>3</sup> H]-Fludiazepam	GABA <sub>A</sub> (BZ site) agonist

**GABA<sub>C</sub> receptor**

<i>Cat. No.</i>	<i>Product</i>	<i>Category</i>
BN0352	Muscimol	GABA <sub>C</sub> partial agonist, potent GABA <sub>A</sub> agonist
BN0492	SKF 97541 hydrochloride	GABA <sub>C</sub> antagonist, very potent GABA <sub>B</sub> agonist
BN0520	THIP hydrochloride	GABA <sub>C</sub> antagonist, GABA <sub>A</sub> agonist
BN0524	TPMPA	Selective GABA <sub>C</sub> antagonist

**Related Radioligand**

<i>Cat. No.</i>	<i>Product</i>	<i>Category</i>
ART-1210	[ <sup>3</sup> H]-P4MPA	GABA <sub>C</sub> antagonist

## GABA receptor compounds

<b>GABA<sub>B</sub> receptor</b>		
<b>Cat. No.</b>	<b>Product</b>	<b>Category</b>
BG0030	γ-Aminobutyric acid (GABA)	Endogenous GABA agonist
BN0804	3-APPA (CGP 27492)	Potent, selective GABA <sub>B</sub> agonist
BG0101	( <i>RS</i> )-Baclofen	Selective GABA <sub>B</sub> agonist
BG0394	( <i>R</i> )-(-)-Baclofen	Selective GABA <sub>B</sub> agonist, active enantiomer
BG0444	( <i>R</i> )-(+)-Baclofen hydrochloride	Selective GABA <sub>B</sub> agonist, active enantiomer
BN0492	SKF 97541 hydrochloride	Very potent GABA <sub>B</sub> agonist, GABA <sub>C</sub> antagonist
BN0594	CGP 35348	Brain penetrant, selective GABA <sub>B</sub> antagonist
BN0595	CGP 46381	Brain penetrant, selective GABA <sub>B</sub> antagonist
BN0596	CGP 52432	Potent, selective GABA <sub>B</sub> antagonist
BN0597	CGP 54626 hydrochloride	Potent, selective GABA <sub>B</sub> antagonist
BN0598	CGP 55845	Potent, selective GABA <sub>B</sub> antagonist
BN0010	2-Hydroxysaclofen	Selective GABA <sub>B</sub> , more potent than saclofen
BN0416	Phaclofen	Weak, selective GABA <sub>B</sub> antagonist
BN0452	Saclofen	Selective GABA <sub>B</sub> antagonist
BN0128	CGP 7930	GABA <sub>B</sub> positive modulator
BN0130	CGP 13501	GABA <sub>B</sub> positive modulator
BN0242	GS 39783	GABA <sub>B</sub> positive modulator
BN0786	rac BHFF	Potent GABA <sub>B</sub> positive allosteric modulator

### Related Radioligand

<b>Cat. No.</b>	<b>Product</b>	<b>Category</b>
ART-0207	[ <sup>3</sup> H]-γ-Aminobutyric acid (GABA)	Endogenous GABA agonist

### Miscellaneous GABA receptor compounds

<b>Cat. No.</b>	<b>Product</b>	<b>Category</b>
BN0215	Gabapentin	Anticonvulsant, increases brain GABA, binds to Ca <sup>2+</sup> channels
BN0278	Ivermectin	Glutamate/GABA-activated Cl <sup>-</sup> channel modulator
BN0747	NCS-382	Anticonvulsant, γ-Hydroxybutyrate (GHB) antagonist
BG0301	Propofol	GABA <sub>A</sub> positive modulator
BG0351	Valproic acid sodium	GABA transaminase (GABA-T) inhibitor
BN0538	Vigabatrin	GABA transaminase (GABA-T) inhibitor
BN0802	( <i>S</i> )-Vigabatrin	GABA transaminase (GABA-T) inhibitor, active enantiomer

### Related Radioligand

<b>Cat. No.</b>	<b>Product</b>	<b>Category</b>
ART-0356	[ <sup>3</sup> H]-Valproic acid	GABA transaminase (GABA-T) inhibitor

**Table GABA Transporter inhibitors**

<b>GABA Transporter</b>	<b>GAT-1</b>	<b>GAT-2</b>	<b>GAT-3</b>	<b>BGT-1</b>
Tissue Localisation	Mainly neuronal cells in CNS	Epithelial, glial and neuronal cells (mainly CNS)	Mainly glial cells in CNS and kidney	Mainly glial cells in CNS and retina
<b>Inhibitors</b>	<b>IC<sub>50</sub> (µM)</b>	<b>IC<sub>50</sub> (µM)</b>	<b>IC<sub>50</sub> (µM)</b>	<b>IC<sub>50</sub> (µM)</b>
<sup>1</sup> β-Alanine <b>BG0081</b>	5690	19	58	1320
<sup>1</sup> Cl 966 <b>BN0149</b>	0.26	297	333	300
<sup>1</sup> Guvacine <b>BN0243</b>	14	58	119	1870
<sup>1</sup> (±)-Nipecotic acid <b>BN0382</b>	8	38	106	2370
<sup>1</sup> NNC 711 <b>BN0388</b>	0.04	171	1700	622
<sup>1</sup> SKF 89976A <b>BN0612</b>	0.13	550	944	7210
<sup>2</sup> (S)-SNAP 5114 <b>BN0494</b>	388	21	5	140

IC<sub>50</sub> values for [<sup>3</sup>H]-GABA uptake inhibition of cloned human GAT-1, rat GAT-2, human GAT-3 and human BGT-1.

<sup>1</sup>Borden et al. (1994) Eur J Pharmacol 269:219, <sup>2</sup>Borden et al. (1994) Receptor Channels 2:207

**Products**

<b>Cat. No.</b>	<b>Product</b>	<b>Category</b>
BG0081	β-Alanine	GABA uptake inhibitor, endogenous glycine receptor agonist
BN0149	Cl 966 hydrochloride	Selective GABA transporter GAT-1 inhibitor
BN0744	FrPbAII	Selective GABA and glycine uptake inhibitor
BN0243	Guvacine hydrochloride	Specific GABA uptake inhibitor
BN0382	(±)-Nipecotic acid	GABA uptake inhibitor
BN0388	NNC 711	Selective GABA transporter GAT-1 inhibitor
BN0439	Riluzole	GABA uptake inhibitor, glutamate release inhibitor
BN0612	SKF 89976A hydrochloride	Potent, selective GABA transporter GAT-1 inhibitor
BN0494	(S)-SNAP 5114	GABA uptake inhibitor (GAT-2 and -3)
BN0512	TACA	GABA-T substrate and uptake inhibitor, GABA <sub>A</sub> agonist

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