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GABAergic radioligands labelled with tritium

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The synthesis and applications of GABAergic radioligands labelled with tritium are reviewed.

Keywords: GABA; tritium; radioligand

Introduction

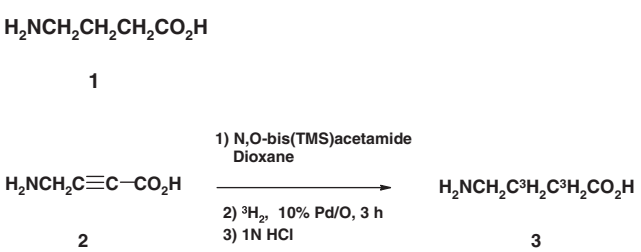
It has been nearly 60 years since the discovery of gamma-aminobutyric acid (GABA, **1**) in the mammalian central nervous system[1] and since then it has been recognized as the main inhibitory neurotransmitter. Furthermore, study of the GABA receptor system has revealed it to be a complex family of three pharmacologically distinct binding sites designated as the $GABA_A$, $GABA_B$ and $GABA_C$ receptors. $GABA_A$ is the most abundant of the subclasses. It is ligand gated and, when activated, selectively admits chloride ions through its ion channel, resulting in neuron hyperpolarization and neurotransmission inhibition. $GABA_B$ is a metabotropic transmembrane receptor, among a family of G protein-linked binding sites that couple to potassium channels. Its inhibitory action is mediated by an increase in potassium ion conductivity as well as a decrease in cellular calcium flux. $GABA_C$ receptors, or more appropriately termed $GABA_A$-rho, structurally resemble $GABA_A$, but are largely restricted to the retina. These three receptors are differentiated on the basis of what specific GABA agonists and antagonists interact or fail to interact with them.

Among the most useful tools that have been employed to study GABA receptors are radioligands, and in particular, tritiated compounds. Tritium confers the high specific activity needed for receptor binding assay without any structural alteration of the substance. The subject of this paper will therefore be a review of the intriguing chemistry and applications of tritiated radioligands for the complex GABA receptor system. The numerous papers devoted to this important topic make an exhaustive coverage impossible, but the examples cited here will be both informative and representative. What is absolutely fascinating from the standpoint of medicinal chemistry and molecular topology is the incredibly diverse structures of compounds that bind to some component of the complicated GABA receptor system. Examples will be included of both small synthetic molecules as well as elaborate polyfunctional natural products that tightly dock at various venues on the GABA receptor surface. The arrangement of this discussion will be a sequential consideration of tritiated radioligands that act as agonists, positive allosteric site modulators, antagonists, negative allosteric site modulators and various other biological roles related to the GABA receptor system.

GABA receptor agonists

Any discussion of this topic would clearly have to start with the issue of tritium labelling the simple and tiny agonist GABA itself. The availability of [^{3}H] GABA has spawned literally hundreds of published studies of the $GABA_A$ and $GABA_B$ receptors and a few recent ones are highlighted to illustrate the diversity of its applications.[2–6] In an earlier approach to the tritiation of GABA, we and others had originally employed an olefin precursor with catalytic tritiation. However, to achieve even higher specific activity for receptor binding assay and other biological applications, we considered the possible construction of a suitable alkyne precursor. We were well aware that French investigators had reported the use of such a phthalimide-protected alkyne intermediate in tritiating GABA, but they faced the challenge of protecting group removal with rather harsh conditions.[7] We reasoned that there could possibly be a more efficient way to tritium label GABA at high specific activity, by employing not only an alkyne precursor but utilizing alternative protecting groups that are more easily removed. For that purpose we turned our attention to 4-aminotetrolic acid (**2**). Besides attracting interest itself in GABA research[8] and even quantum mechanical calculations,[9] a preparation of **2** had been reported in low yield from commercially available 2-butyne-1,4-diol.[10] However, our difficulty in repeating the last step of this synthesis prompted an investigation and our report of an improved method for the preparation of **2**.[11] With substantial amounts of **2** in hand, we protected it as the *bis* TMS derivative, utilizing that as a key precursor to routinely prepare [^{3}H] GABA at 100 Ci/mmol (**3**, Scheme 1) by catalytic tritiation.[12]

Muscimol (**4**), a natural product first isolated from the fungus *Amanita muscaria*,[13] is a potent agonist at the $GABA_A$ receptor.



Scheme 1. Synthesis of [^{3}H] GABA **3**.

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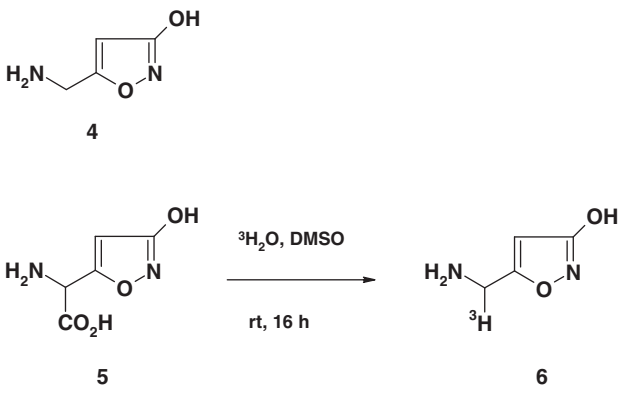
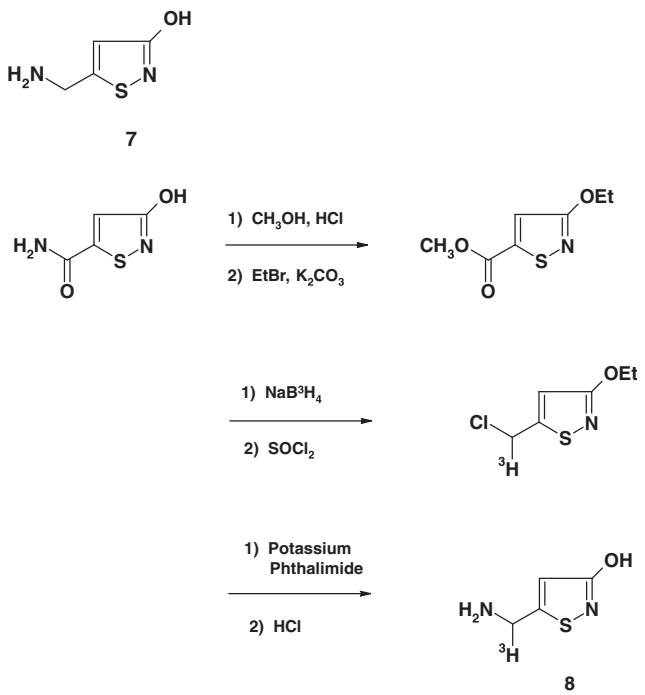
Given its structure, the options for tritiation of **4** were rather limited, but colleagues in our laboratory cleverly surmounted that obstacle by the knowledge that a related companion natural product, ibotenic acid (**5**), could be decarboxylated to **4**.[14] In fact, both **4** and **5** are often found naturally co-mingled in some fungal species. Also, at least one of these investigators was likely technically influenced by his personal experience and training with the Krapcho reaction[15] and the special role that DMSO plays in such decarboxylations. Our co-workers reasoned that the decarboxylation of **5** when conducted in DMSO along with high specific activity tritiated water could afford [^{3}H] muscimol (**6**, Scheme 2) at high specific activity and reported their successful results at an American Chemical Society regional meeting.[16] A proton-decoupled tritium NMR (D_2O) of **6** further revealed by a sharp resonance at 4.13 ppm that tritium had indeed been regiospecifically installed exclusively on the methylene group, the very site of decarboxylation. Later, we ourselves reinvestigated the process of both the deuteration and tritiation of **4** by this intriguing reaction, drawing conclusions as to the rate accelerating role of DMSO.[17] Radioligand **6** has been valuably employed in many hundreds of receptor binding studies[18–20] including photoaffinity labelling of the $GABA_A$ receptor.[21–23] This latter application is really rather remarkable. Most photoaffinity agents require an auxiliary group like azide, diazo or diazirine for photoactivation. Lacking these, there is apparently something intrinsically photolabile about the structure of **4** itself to support its photoactivated irreversible insertion into the nearby receptor protein.

The tritiation of other useful agonists for the $GABA_A$ receptor also resulted from our productive joint effort with noted GABA investigator, Povl Krogsgaard-Larsen and his colleagues at the Royal Danish School of Pharmacy. They had earlier discovered that a structurally related sulfur analogue of **4**, thiomuscimol **7**, was also an effective intrinsically activated photoaffinity label for the $GABA_A$ receptor.[24] However, with regard to isotopic labelling of **7**, there was unfortunately no convenient and corresponding thioibotenic acid analogue to exploit as in the case of **4**. The Danish chemists had earlier conducted some initial deuteration studies of **7**, involving a catalytic deuterium dehalogenation process.[25] However, when later collaborating with us on the tritiation of **7**, they had already optimized another approach using the sodium borotritide reduction of an ester precursor. The resulting tritiated alcohol intermediate was then converted to a chloride and finally to [^{3}H] thiomuscimol **8** *via* phthalimide displacement as seen in Scheme 3. The outcome was the efficient insertion of tritium in precisely the same corresponding methylene position as that of **6**.[26] Further technical partnership with the Krogsgaard-Larsen group also resulted in the synthesis of [^{3}H] THIP (or gaboxadol, **9**) at high specific activity.[27] It is a conformationally restricted cyclic analogue of **4** and has been widely employed to study the $GABA_A$ receptor as well.[28–30] Our collaboration further accomplished the radiolabelling of agonist piperidine-4-sulfonic acid[31] whose catalytic tritiation method was directly analogous to that described for the synthesis of the unlabelled substance.[32]

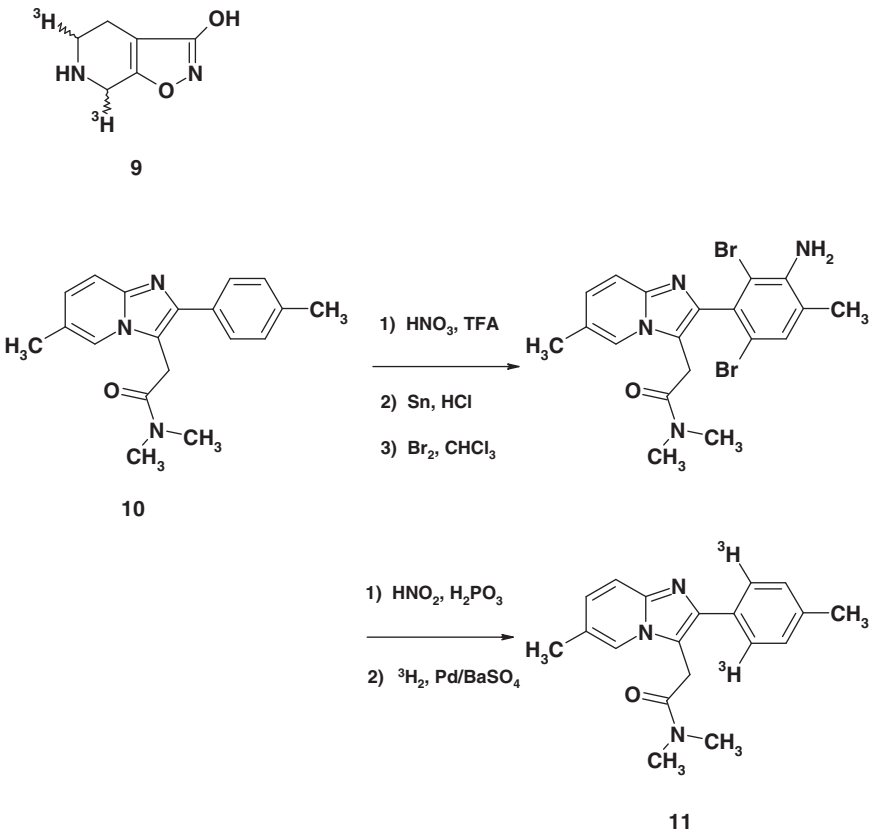
Besides the direct binding pocket that accommodates GABA and all the agonists described above for the $GABA_A$ receptor, there are other docking sites termed allosteric which indirectly promote the receptor's inhibitory activity. For this reason they are referred to as positive allosteric modulators. Clearly, the most prominent of these modulators are the benzodiazepine ligands and because of this, the location of their attachment has also been termed the benzodiazepine site. Compounds that bind at this location firmly lock the $GABA_A$ receptor into a restrained conformation that presents a much higher affinity state for GABA itself, thereby prompting an inhibitory and anxiolytic effect. Obviously, most of the agents that interact at this benzodiazepine site possess the signature diazepam heterocyclic core structure. Over the years we have tritiated many of these substances, with N-methyl-^{3}H derivatives often being a convenient radiolabelling option. However, there have been examples of compounds that bind to the benzodiazepine site which are not structurally related to diazepam and one of these is the widely used hypnotic zolpidem (**10**). Zolpidem was first tritiated at nearly theoretical specific activity by Allen and co-workers of then Synthelabo (L. E. R. S.), applying a bromination — catalytic tritium dehalogenation strategy[33] affording radioligand **11** (Scheme 4) which has been useful to elucidate the pharmacology of the benzodiazepine site.[34–38] Perhaps the most fascinating of the $GABA_A$ positive allosteric modulators are anesthetic agents and, in particular, the potent



Scheme 2. Synthesis of [^{3}H] muscimol **6**.



Scheme 3. Synthesis of [^{3}H] thiomuscimol **8**.

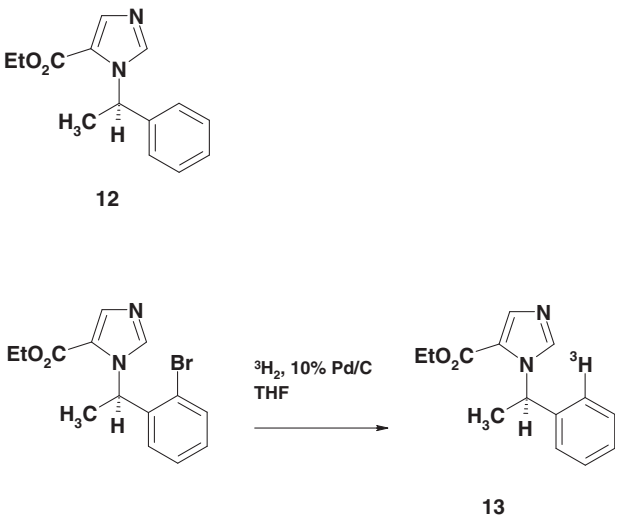


Scheme 4. Synthesis of [^{3}H] zolpidem **11**.

drug (*R*)-etomidate (**12**). Emerging from the very successful Janssen Pharmaceutica discovery pipeline of compounds over 40 years ago, **12** was also first tritiated on the phenyl ring (**13**, Scheme 5) by Janssen radiochemists.[39,40] Later, we also radiolabelled **12** with tritium on the imidazole ring, providing it to investigators at Massachusetts General Hospital and Harvard Medical School, who then modified it with a diazirine functionalized butyl ester chain, creating the useful irreversible analogue [^{3}H] (*R*)-azietomidate.[41] This photoaffinity reagent continues to be valuable in probing the location and function of anesthetic action at the $GABA_A$ receptor.[42,43]

While the major interest and effort in tritium labelling of GABA agonists has focused on the dominant $GABA_A$ receptor, tritiated reagents have also been created for the other two subclasses as well. Baclofen is essentially GABA with an appended *p*-chlorophenyl group and it is a potent agonist for the $GABA_B$ receptor subclass. Our laboratories were initially able to tritiate racemic baclofen (**14**), placing the radiolabel on the amino methylene. However, the added *p*-chlorophenyl group also confers chirality upon the GABA backbone, with the *R* (−) free base of baclofen being the more potent at the $GABA_B$ receptor. We were later able to tritium label this enantiomer exclusively and still provide radioligand **15** to global neuroscientists studying the $GABA_B$ receptor.[44–46]

The $GABA_C$ agonists [^{3}H] (E)-4-amino-2-butenoic acid (**16**) and [^{3}H] (Z)-4-amino-2-butenoic acid (**17**) are in essence dehydro GABA analogues, with the former being the more trenchant at this receptor subclass. It appears that there has only been one report of their synthesis by Australian radiochemists.[47] Using the same phthalimido alkyne precursor as the earlier French workers,[7] they cleverly exploited Wilkinson's homogeneous



Scheme 5. Synthesis of [^{3}H] (R)-etomidate **13**.

catalyst[48] to accomplish its slow reduction with tritium over the course of several weeks time. Based on some earlier literature[49] the authors speculated that this catalyst's ability to hydrogenate alkynes faster than olefins might possibly allow for the isolation of the desired pair of tritiated $GABA_C$ agonists along with the expected complete precursor reduction, yielding [^{3}H] GABA. Furthermore, they anticipated that the significant degree of structural difference in the radiolabelled products would facilitate their reasonably efficient HPLC separation. After performing the tritiation, preliminary HPLC analysis revealed as

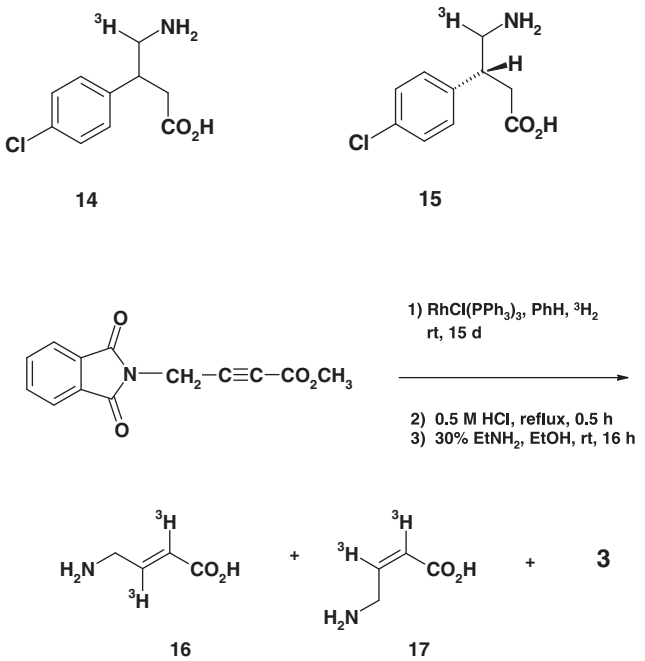
expected that the majority of product was [^{3}H] GABA (**3**) itself. However, the crude product also contained small but useful amounts (5–7%) of **16** and **17** as seen in Scheme 6. After extensive purification, the two tritium labelled olefin products were isolated in modest radiopurity but high specific activity.

GABA receptor antagonists

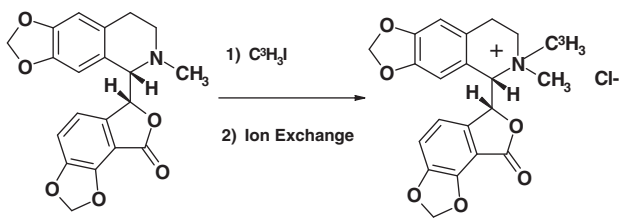
The tritiation of GABA antagonists presents an equally compelling story and we start with the quintessential $GABA_A$ competitive antagonist, bicuculline (**18**), a naturally occurring substance. Initially discovered as the (+) form in the flowering plant *Dicentra cucullaria* by Manske[50] and first synthesized in racemic form by Sir Robert Robinson,[51] phthalideisoquinoline alkaloid **18** has a complex and intriguing dimeric structure. However, for decades any significant interest in this substance waned until the discovery by Curtis and co-workers that it was a potent and specific $GABA_A$ antagonist.[52,53] It is important to emphasize that natural product **18** is a competitive antagonist of GABA in that it exerts its preferential binding at the same receptor target site as GABA itself. It was also providently discovered that the (−) quaternary methochloride salt of **18** was also active as a competitive $GABA_A$ antagonist.[54] This beneficial finding not only enhanced the water solubility of **18**, but also immediately suggested an easy and robust method to prepare a tritiated analogue; namely, to simply react **18** with an appropriate tritium labelled methylating reagent giving quaternary methochloride salt **19** (Scheme 7). This exact approach has been described by Swiss radiochemists at Hoffmann-La Roche.[55] At about this time our laboratory also prepared **19**, providing it to early GABA investigators.[56] For many years it was a useful radioligand, advancing knowledge in the $GABA_A$ receptor field.[57–61]

Although **18** and its various other methylated salts had emerged as the most selective competitive $GABA_A$ antagonists at that time, criticism was growing about their potency as well as reliability.[62] A possible reason for this may have been due to their relative instability in aqueous solutions, especially when tritium labelled.[63] For that reason, colleagues in our laboratory collaborated with neurochemists at then Sanofi to synthesize [^{3}H] SR 95531 (gabazine, **20**).[64] This selective and competitive $GABA_A$ antagonist was also very water soluble but much more chemically stable and several hundred times more potent than **18** at displacing GABA from the $GABA_A$ receptor. Their tritiation strategy was closely patterned after the synthesis of the unlabelled substance,[65] deviating only at the penultimate step with the installation of a butenyl side chain component, affording a useful olefin precursor for catalytic tritiation (Scheme 8). Use of radioligand **20** has surpassed that of **19** as well as its methylated salts and **20** has proven to be a valuable tritiated reagent in this important area.[34,66–69]

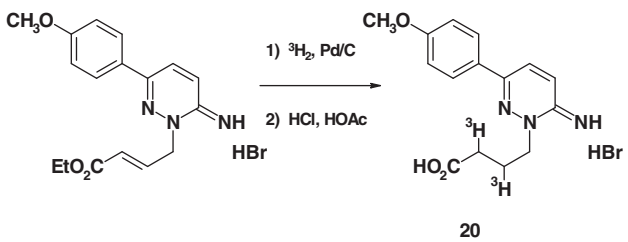
The two preceding $GABA_A$ antagonists dock very tightly at the exact same location as that occupied by GABA itself. However, there exists a diverse and intriguing family of $GABA_A$ antagonists that exert their negative noncompetitive blocking action at an alternative allosteric site on the $GABA_A$ receptor, likely in or around the location of the chloride ion channel. These substances are therefore collectively referred to as negative allosteric modulators and the first one of this class to be discovered was the natural product picrotoxinin (**21**). Isolated at the early part of the 19th century from the moonseed plant family *Menispermaceae* along with a structurally related tertiary alcohol analogue picrotin, **21** is remarkably unique. Unlike almost all of the other compounds considered in this review, **21** contains no nitrogen. Its functionally complex and tightly crowded polycyclic structure defied elucidation for over a century until the painstaking and ingenious work of Conroy, who in a series of six classic and extraordinary papers correctly predicted its molecular topology.[70–75] It must be appreciated that this incredible single investigator structure elucidation was accomplished just before the advent of NMR and mass spectrometry, employing mostly infrared spectra, melting points and elemental analyses to guide sound chemical reasoning. The proposed molecular architecture of **21** was conclusively confirmed a few years later by X-ray crystal determination[76]



Scheme 6. Synthesis of **16** and **17**.



Scheme 7. Synthesis of **19**.

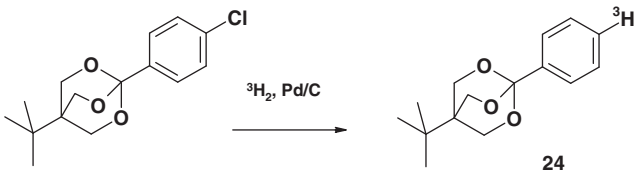


Scheme 8. Synthesis of **20**.

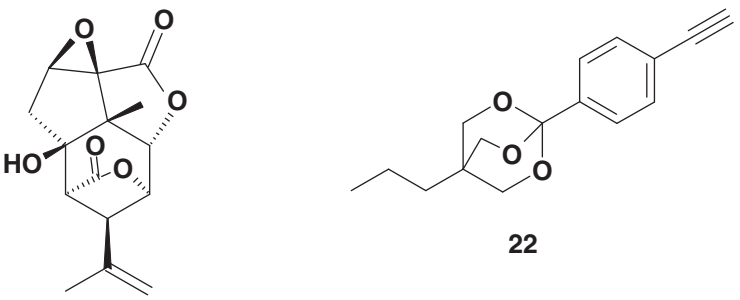
and its total synthesis was elegantly accomplished nearly two decades later with the work of Corey and Pearce.[77] It appears, unsurprisingly, that **21** itself has not been radiolabelled with tritium. However, we were able to catalytically tritiate the isopropenyl group of **21**, obtaining the corresponding [^{3}H] dihydropicrotoxinin[78] and this radioligand has also been widely employed to explore crucial details of the allosteric $GABA_A$ binding site.[79–85]

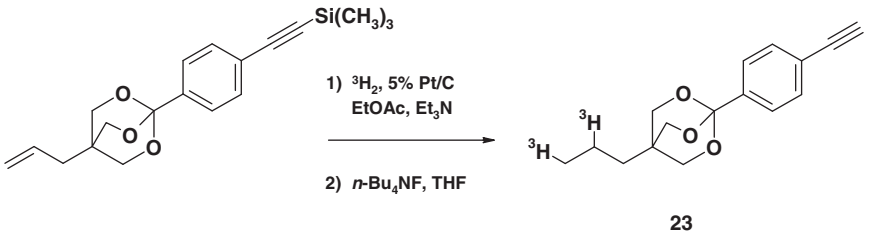
The next series of compounds that are extremely active as negative allosteric modulators for $GABA_A$ provide one of the most fascinating stories of this review with a large contribution toward their discovery and applications due to the prolific work of noted Berkeley entomologist-medicinal chemist-radiochemist, John E. Casida. In a recent seminal paper[86] Casida cogently summarized the astounding structural diversity of these agents that act as $GABA_A$ antagonists at the chloride ionophore. One of the earliest members of this structurally disparate group was apparently discovered by a degree of serendipity.[87] Casida and co-workers had originally designed the insecticide cage compound 1-(4-ethynylphenyl)-4-*n*-propyl-2,6,7-trioxabicyclo[2.2.2]octane (EBOB, **22**) as an antagonist of the enzyme acetylcholinesterase. However, it was later discovered that **22** was indeed a powerful insecticide, but acting instead as another noncompetitive $GABA_A$ antagonist at the chloride ion channel. The tritiation of **22** at high specific activity was clearly challenging because of the almost certain concomitant reduction of the terminal alkyne moiety in any conceivable catalytic tritiation method. This taxing problem was creatively solved by the Berkeley radiochemists with the attachment of a bulky TMS protecting group on the terminal acetylene,[88] blocking catalyst access to the alkyne and allowing the selective catalytic tritiation of an olefin precursor affording radioligand **23** (Scheme 9).[89] This clever steric protection strategy is reminiscent of the later related use of the bulky TBDMS group appended to a morphinan allylic alcohol, hindering olefin reduction and facilitating selective aromatic ring catalytic tritium dehalogenation by Seltzman and co-workers.[90] Radioligand **23** continues to be used by researchers all over the world in studies of the $GABA_A$ receptor.[91–95] Casida also developed a companion ligand to **22**; namely, [^{3}H] *t*-butylbicycloorthobenzoate (TBOB, **24**). Lacking the radiolabelling complications of the alkyne group in **22**, the preparation of **24** was more straightforward and accomplished by a catalytic tritium aromatic dechlorination (Scheme 10).[96] Radioligand **24** has also been employed by neuroscientists in this area with great success.[97–101].

Two more compounds to be considered in this section were also $GABA_A$ noncompetitive antagonist targets of the Casida laboratory. Fipronil (**25**) is a significant insecticide acting as a noncompetitive antagonist at the $GABA_A$ chloride ion channel.[102] Casida designed a tritiated photoaffinity diazirine analogue (**26**) of the parent substance,[103] and employed a diiodo precursor to efficiently prepare **26** using the chemoselective catalytic tritium deiodination strategy (Scheme 11)[104] reported by Rousseau.[105–107] The final example of the work in this area by the Casida group is perhaps the most intriguing story from an artistic, cultural and historical perspective. It involves the monoterpene natural product alpha-thujone (**27**), isolated from the wormwood bush *Artemisia absinthium*. Its indirect tritiation by biochemical means had been reported,[108] but the interesting contribution of the Berkeley investigators exclusively involved the unlabelled compound studied with tritiated radioligands. Their interest in **27** was prompted both by the fact that wormwood apparently possessed insecticidal

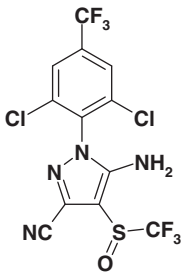


Scheme 10. Synthesis of **24**.





Scheme 9. Synthesis of **23**.



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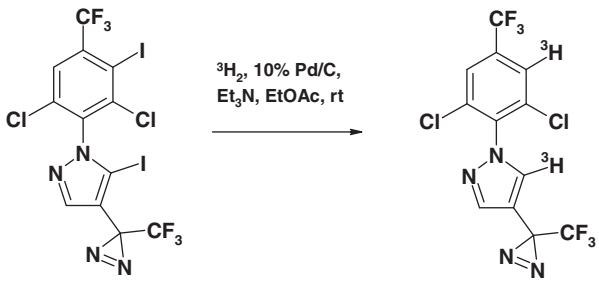

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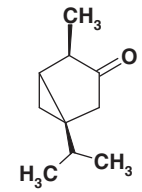
Scheme 11. Synthesis of **26**.



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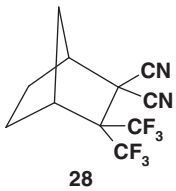

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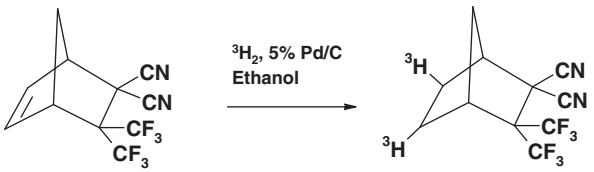


29 30

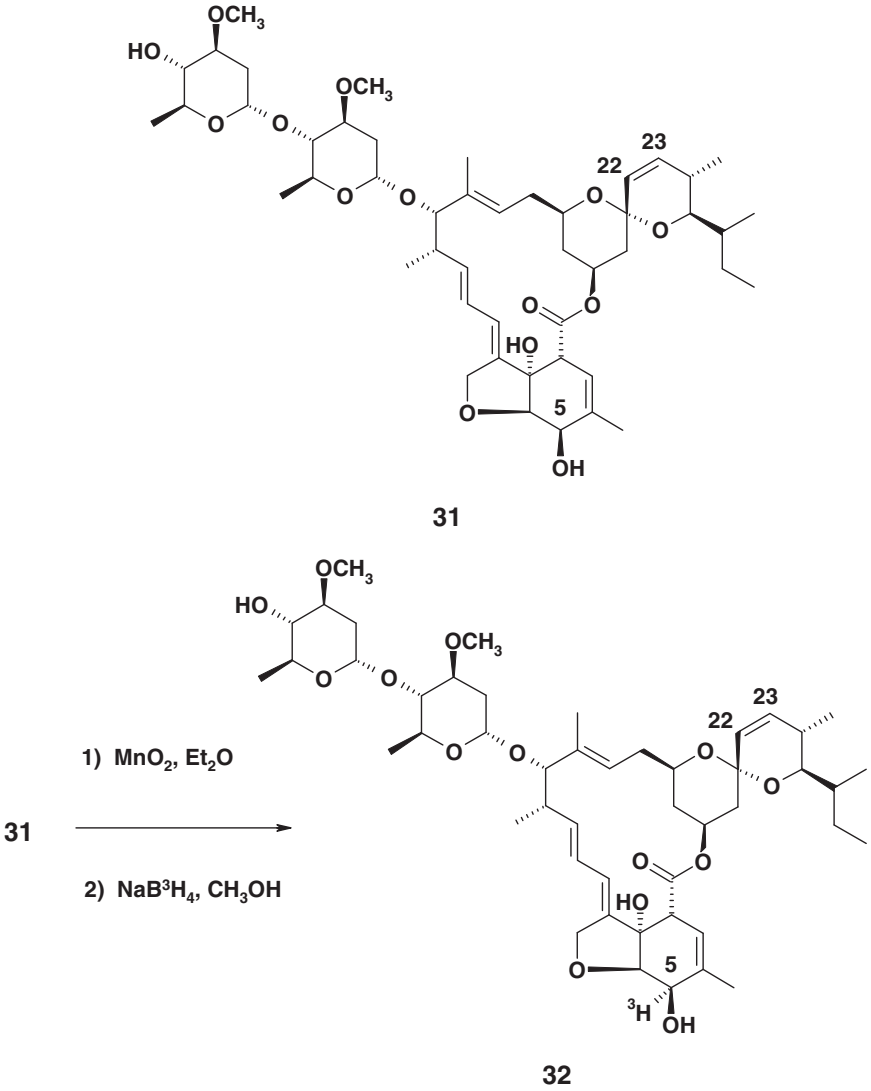
Scheme 12. Synthesis of **30**.

properties along with the knowledge that this substance was a significant constituent of the emerald green liqueur absinthe, a very popular drink of artist Vincent van Gogh and other culturally elite contemporaries in 19th century France. Absinthe consumption was then estimated to be in the hundreds of millions of liters per year in Paris alone and was frequently accompanied by special glassware and great ritual. Indeed, some art historians have attributed the unique ailments, hallucinations and psychoses suffered by van Gogh in the last few years of his life directly to ingestion of **27**.[109] Using radioligand **23** in binding studies with **27**, Casida conclusively demonstrated that **27** was indeed acting as a noncompetitive antagonist at the $GABA_A$ chloride ion channel.[110]

The final example of a useful negative $GABA_A$ allosteric modulator at the chloride ionophore is the rather small molecule BIDN (**28**) whose tritiation was accomplished by our collaboration with DuPont biologists and chemists. The story first started with the synthesis of the norbornene flucybene (**29**) decades ago at the DuPont Experimental Station[111] and the discovery that it itself possessed insecticidal activity. As occasionally and fortunately happens in radioligand reagent development (see, for instance, the now classic case of [^{3}H] dihydroalprenolol from our laboratory[112]) the hydrogenation of the olefin group in **29** did not significantly diminish the insecticidal activity of **28**. Using this identical approach, we were therefore able to catalytically tritiate **29**, preparing **30** (Scheme 12), radiolabelled on the norbornane ring, at very high specific activity for the DuPont Stine-Haskell laboratory investigators.[113] It has proven to be a useful tool for the investigation of the $GABA_A$ receptor chloride ion channel site.[114–116]

Other GABA agents

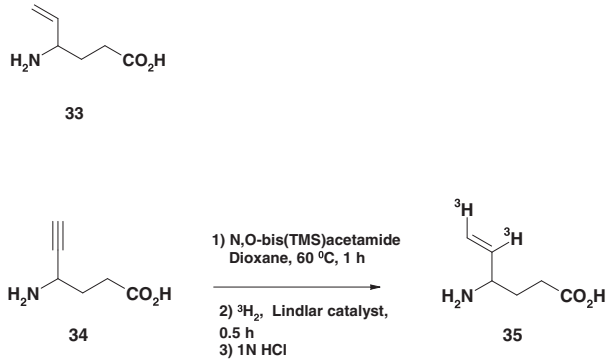
The final section of this review has been reserved for those substances that do not as easily fit into the GABA agonist or antagonist category and begins with the family of largest molecules yet considered in our discussion. The avermectins are a group of structurally complex natural product macrocyclic (16 member ring) lactones isolated from soil actinomycete *Streptomyces avermitilis* whose discovery[117] and structure determination[118,119] were first reported by Merck scientists. As a remarkable compound class they have demonstrated potent activity against various parasitic helminths, arachnids and insects. Avermectin B_{1a} (**31**) is among the most studied of this compound collection. Early on, it was proposed that the avermectins mechanism of action was largely derived from $GABA_A$ receptor interaction but a puzzling and contradictory enigma arose regarding their effects. For instance, with regard to **31**, some studies showed $GABA_A$ activation[120] while others indicated its inhibition of $GABA_A$.[121] This apparent contradiction was elegantly resolved by Casida using with the demonstration that these seemingly opposite effects of **31** on the $GABA_A$ system were due to its binding at two different sites in the $GABA_A$-gated chloride ionophore, eliciting dissimilar responses.[122] He discovered that the binding of **31** to the high affinity site activated the $GABA_A$ chloride ion channel, while its docking at the low affinity site blocked it. Compound **31** was first tritiated by Chabala and Merck co-workers at the 5 position by manganese dioxide oxidation to produce a 5-keto precursor, which was then stereoselectively reduced with sodium borotritide to afford **32** (Scheme 13).[123] Radioligand **32** has been useful to advance understanding of the $GABA_A$ receptor system.[122,124–127] An analogue of **31**, 22, 23-dihydroavermectin B_{1a}, also known as ivermectin, was introduced in 1981 as a successful broad spectrum agent against various parasites. Toth and co-workers were the first to efficiently prepare [22, 23-^{3}H] ivermectin by the selective Wilkinson catalyst tritiation of the 22, 23 double bond of **31**, observing essentially no reduction of the other three olefins.[128] This tritiated reagent has also been used in numerous published $GABA_A$ receptor studies as well.[129–135]



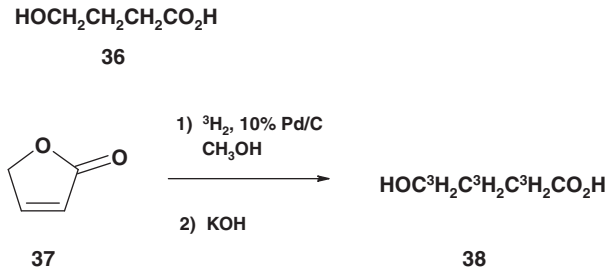
Scheme 13. Synthesis of **32**.

A second topic in this section has absolutely nothing to do with receptor binding at the $GABA_A$ site complex but focuses on GABA catabolism, degradation and, in particular, the important CNS enzyme GABA aminotransferase (E. C. 2.6.1.19)[136] This topic has drawn significant attention because of the conclusions of some neuroscientists that GABA brain deficiencies might be linked to neurological disorders such as epilepsy, Parkinson's disease and Huntington's chorea. Because GABA cannot itself cross the blood brain barrier (BBB), one proposed way to raise therapeutically useful levels of its concentration would be to interfere with this enzyme. Suicide enzyme substrates have often been used for this purpose, and we have been very interested in the tritiation of these agents.[137,138] Regarding GABA, one of the most potent and selective of GABA transaminase inhibitors was found to be 4-amino-5-hexenoic acid (**33**), initially discovered by Merrell International chemists in France.[139,140] Using [6-^{14}C] **33** as a probe, it was later revealed that there were two separate modes of GABA aminotransferase inactivation by **33**.[141] We desired to tritiate **33** in the hope that its radiolabelling would afford a substance which could provide further critical information about this enzyme inactivation. It seemed reasonable to us that a valuable intermediate for this task would be the alkyne analogue **34** also described earlier by the same Merrell International workers.[142] Lindlar catalyst tritiation of this alkyne afforded racemic radioligand **35** (Scheme 14)[143], which was then successfully evaluated.[144]

The final compound considered here is also a GABA metabolite, gamma-hydroxybutyric acid (GHB, **36**). It is a natural product manufactured in the mammalian brain[145,146] from GABA, which is first transformed by GABA transaminase to succinic semialdehyde. This intermediate is then further reduced by NADPH as mediated by succinic semialdehyde reductase to GHB. High affinity binding sites have been identified for this substance, thus promoting the concept of distinct GHB receptors.[147,148] Interestingly, GHB itself, unlike GABA, easily crosses the BBB and for that reason it has been suggested as a treatment for various ailments. Recently however, GHB has also emerged with a darker side as both a recreational drug of abuse[149] and as one associated with criminal activity.[150] Because of continued interest in this important area, we decided to radiolabel GHB at high specific activity and accomplished this quite easily by the catalytic tritiation of 2(5H) furanone (**37**),



Scheme 14. Synthesis of **35**.



Scheme 15. Synthesis of **38**.

obtaining **38** (Scheme 15) and characterizing the product by tritium NMR as well.[151] Radioligand **38** continues to be useful for elucidating details of the purported GHB receptor.[152,153]

Conclusion

As can be easily seen from the various substances considered here, the GABA receptor area includes an eclectic assembly of diverse compound structures. To radiolabel these challenging agents with tritium at high specific required numerous inventive methods and creative approaches. Given the many aspects of human health that research in GABA receptors impacts, it is certain that tritiated radioligands for this field will be critical reagents for years to come.

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