γ-Aminobutyrate-A Receptor Modulation by 3-Aryl-1-(arylsulfonyl)-1,4,5,6-tetrahydropyridazines

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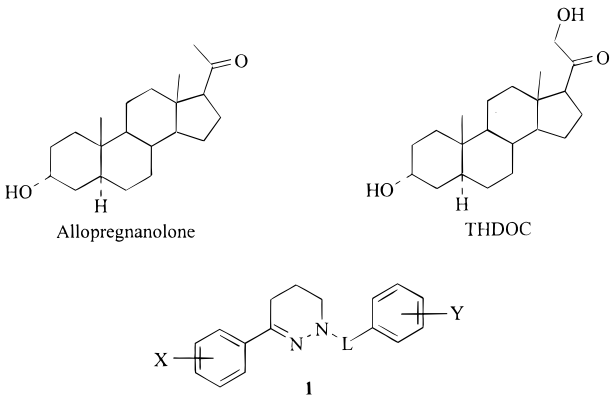
A series of 3-aryl-1-(arylsulfonyl)-1,4,5,6-tetrahydropyridazine allosteric modulators of the $GABA_A$ receptor was synthesized, and biological activity was examined in vitro and in vivo. Beginning with **1a,** stepwise modification of the substituents and conservation of the scaffold yielded a chemical series in which the modulatory activity was enhanced by the presence of GABA. The SAR suggests, but does not establish, that the compounds bind to the steroid binding site on the $GABA_A$ receptor. The GABA shift for each compound indicates that all compounds in this series are either agonists or partial agonists.

Introduction

The amino acid γ-aminobutyrate (GABA) is the major inhibitory neurotransmitter in cerebral tissues. It is estimated that GABA is the neurotransmitter at approximately 30% of the synapses in the brain of mammals. The inhibitory effect of GABA on neuronal excitability is mediated primarily by the activation of specific membrane receptors, termed $GABA_A$ receptors. These receptors are heteropentameric protein complexes, and when activated by GABA they serve as channels through which Cl^- flows into the postsynaptic neuron, thereby hyperpolarizing the membrane and reducing neuronal excitability.

In addition to being activated by GABA, $GABA_A$ receptors are allosterically modulated by several types of compounds; these include ethanol, benzodiazepines,[1] steroids,[1a,2] barbiturates, and the novel anticonvulsant loreclazole.[1a,3] Some of these allosteric modulators have established therapeutic value as anxiolytic and hypnotic agents, anticonvulsants, or anesthetics. Because of our general interest in steroids and nonsteroids that mimic some of the actions of steroids, we are particularly interested in compounds that modulate the activity of $GABA_A$ receptors by binding to the steroid site. Notably, the effect of different endogenous steroids such as allopregnanolone and THDOC varies with gender,[4] brain region,[5] and stress levels.[6] The pharmacological effects of steroids that modulate $GABA_A$ receptors are frequently similar to those of the barbiturates and benzodiazepines but are often more complex.[4] To date, no steroids have proven to be acceptable for use as therapeutic agents. Our intent is to discover nonsteroids that modulate $GABA_A$ receptors at the steroid binding site without causing unwanted effects associated with the steroids.

Experimentally, the modulatory effect of steroids on $GABA_A$ receptors is observed through the modified binding of [^{35}S]-*tert*-butylbicyclophosphorothionate ([^{35}S]-TBPS) to its site near the chloride channel.[4] Typically, steroids exert a biphasic effect on the binding of [^{35}S]-TBPS, increasing binding at low concentrations but decreasing binding at high concentrations. Furthermore, the presence of GABA can affect the affinity of a steroid. If GABA increases the affinity (potency) of a steroid, this is interpreted as an indication that the steroid has a positive modulatory effect on the activity of GABA. If GABA decreases the affinity of a steroid, this is a negative modulation. These define agonist and inverse agonist effects, respectively. A steroid antagonist has equal affinity in the presence or absence of GABA.



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While work has been published on the effect of the endogenous[3a−g] and synthetic[3h−p] steroids, we have examined a series of tetrahydropyridazines (**1**)[7] that modulate the binding of [^{35}S]TPBS to $GABA_A$ receptors with the biphasic concentration−response profile expected for compounds that bind to the steroid site. Tetrahydropyridazines have been shown to bind to the progestin receptor and act as nonsteroidal progestins in functional assays.[7b,c] At the same time some endogenous ligands of the $GABA_A$ receptor steroid site are derived from progesterone. With this in mind the possible use of these compounds as $GABA_A$ receptor modulators was initiated. The SAR of this nonsteroidal series was explored with regard to substituents X and Y and the linker L. Generally, the best X substituents were dichloro or small alkyl. Substituent Y on the linked aromatic was, again, dichloro or small alkyl, while the linker L was varied between sulfonyl and mixed phosphate/phosphonamide. The primary goal of this program was to find steroid mimics that acted as full agonists and could potentially be used as anxiolytics.

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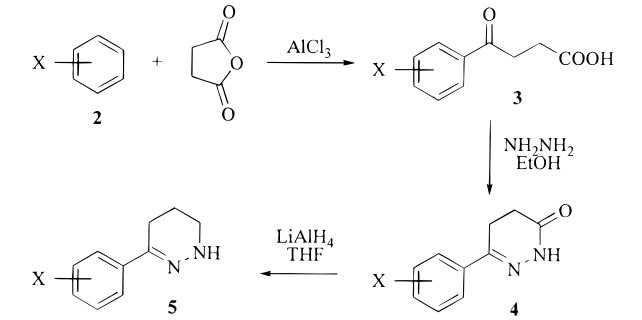
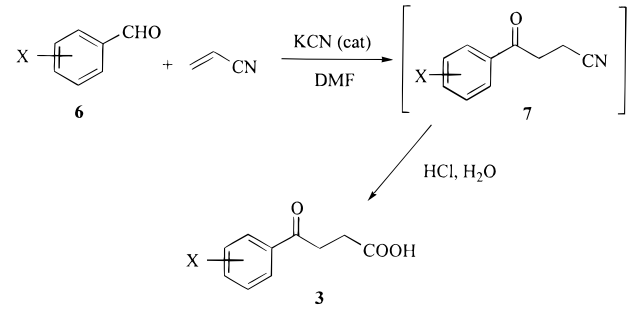
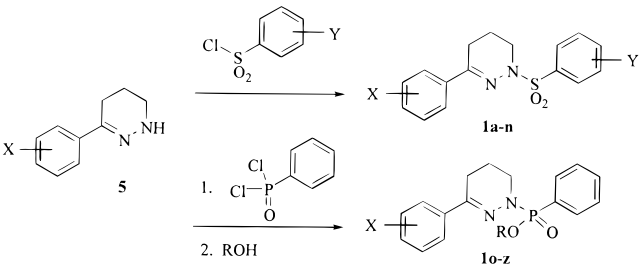
Scheme 1



Scheme 2



Scheme 3



Chemistry

The synthesis of tetrahydropyridazines[7] **1** is outlined in Schemes 1−3. In Scheme 1 an alkylarene **2a**−**e**,**n** and succinic anhydride are treated with aluminum chloride at 0 °C and then heated to 50 °C, neat. The keto ester **3** is isolated by crystallization or extraction in yields of 50−80%. Treatment of **3** with hydrazine in ethanol at reflux gives the tetrahydropyridazinone **4** quantitatively, and the tetrahydropyridazine **5** is obtained by reduction with lithium aluminum hydride.

Alternatively a substituted benzaldehyde **6v**,**x** is reacted with acrylonitrile and potassium cyanide in DMF at 60 °C to yield a keto nitrile **7** (Scheme 2). Exposure of the crude reaction mixture to aqueous HCl gives **3**, which is converted to **5** as shown in Scheme 1. Finally, **5** is treated with a sulfonyl chloride to yield **1a**−**n**, or **5** is treated with phenylphosphonic dichloride and an alcohol to yield **1o**−**z** (Scheme 3).

Biology

Compounds are screened in vitro[8] at 10 μM using membranes from the three brain areas (cerebellum, cerebral cortex, and brain stem). If a compound was active at this concentration in any area, it was then tested at four concentrations in order to establish concentration−response relationships. Compounds of particular interest were further studied using nine different concentrations.

Activity in vivo is determined by inhibition of pentylenetetrazole-induced (PTZ) convulsions.[9] PTZ (85 mg/kg sc) is administered 1 h after oral or intraperitoneal administration of test compounds or vehicle (10 mL/kg). Mice were housed individually for 30 min for observation of clonic convulsions (present or absent).

Motor impairment was determined in the horizontal screen test.[10] Immediately before PTZ is administered (to the mice, as described above) the mice were tested for their ability to climb to the top side of the inverted screen within 1 min (pass or fail).

Results and Discussion

The in vitro data (Table 1) was examined with regard to affinity of the compounds for the $GABA_A$ receptor (IC_{50}), in the presence or absence of GABA, and the intrinsic activity of the compounds from the GABA shift (GS, ratio of IC_{50} without GABA/IC_{50} with GABA). The data in Table 1 is from testing with cerebellum tissue. This area of the brain is principally responsible for fine motor skills coordination. For comparison purposes the in vitro data for allopregnanolone and THDOC in cerebellum tissue is included in Table 1. Both compounds display nanomolar affinity in the presence of GABA (IC_{50} values of 80 and 90 nM, respectively).

Interest in the series arose from broad screening of compounds and obtaining the results for **1a**.[11] The submicromolar IC_{50} with GABA and the GS of 13.7 led to the synthesis of a group of compounds where the link was held as sulfonyl and the substituent Y was 4-iodo. The longer, straight chain 4-hexyl of **1b** eliminated all in vitro affinity, and the same was true of **1c**, where X was the shorter, branched isobutyl. When the X group was shortened by one methylene to isopropyl (**1d**), one-tenth of the affinity returned and made **1d** a partial agonist. Finally, replacement of 4-butyl with 4-ethyl (**1e**) made a compound nearly equipotent with **1a**.

While none of these compounds exceeded **1a** in binding affinity, this small series provided insight into the nature of the binding pocket. The compounds substituted with butyl and ethyl, **1a** and **1e**, acted as allosteric modulators of the receptor, while the hexyl-substituted **1b** did not. Also, the branching in the isobutyl and isopropyl of **1c** and **1d** greatly reduced the potency, indicating a short, narrow binding pocket for that portion of the ligand.

Next, the impact of the Y substituent was examined as it relates to electronics and sterics. Replacement of the iodine in **1a** with the smaller, harder chlorine eliminated binding affinity (**1f**). Some of that affinity was regained when the halogen was removed (**1g**) or replaced with methyl (**1h**), but the best results were not observed until the introduction of the larger, more lipophilic butyl (**1i**). This small change in structure yielded a compound with a GS of 52.4, larger than the GS displayed by endogenous steroids that bind to this site (allopregnanolone and THDOC, GS = 32.6 and 33.9, respectively). This indicated that the size and lipophilicity of the Y substituent were key components in the binding nature of the compound series.

The relationship between this change in Y (from iodine to butyl) and the substituent X was readily

Table 1. In Vitro Binding of THPs to the GABA$_A$ Receptor Complex in the Absence and Presence of GABA

analogue	X	L	Y	IC$_{50}$ (μM) no GABA	IC$_{50}$ (μM) GABA	GS[a]	runs
1a	4-Bu	SO_2	4-I	10.0	0.77	13.7	3
1b	4-Hex	SO_2	4-I	>11	>11		1
1c	4-iBu	SO_2	4-I	>11	>11		5
1d	4-iPr	SO_2	4-I	>11	6.31	1.7	1
1e	4-Et	SO_2	4-I	10	0.9	11.1	1
1f	4-Bu	SO_2	4-Cl	>11	>11		3
1g	4-Bu	SO_2	H	>11	1.1	10.0	3
1h	4-Bu	SO_2	4-Me	>11	2.2	5	4
1i	4-Bu	SO_2	4-Bu	>11	0.21	52.4	3
1j	4-iBu	SO_2	4-Bu	>11	>11		5
1k	4-iPr	SO_2	4-Bu		10		5
1l	4-Et	SO_2	4-Bu	3.77	1.8	2.1	1
1m	4-Bu	SO_2	2-Naph	>11	>11		4
1n	2-Naph	SO_2	H	>11	>11		3
1o	4-Bu	P(O)OMe	H	2.0	0.5	4.0	2
1p	4-Bu	P(O)OEt	H	1.12	0.73	1.5	1
1q	4-OMe	P(O)OMe	H	>11	6.4	1.7	2
1r	H	P(O)OMe	H		>11		2
1s	4-F	P(O)OMe	H	>11	10	1.1	2
1t	4-F	P(O)OEt	H	>11	10	1.1	2
1u	4-Br	P(O)OMe	H	>11	>11		2
1v	3-CF_3,4-Cl	P(O)OMe	H	8.3	6.6	1.3	2
1w	3-CF_3,4-Cl	P(O)OEt	H	5.4	1.1	4.9	2
1x	3,4-Cl_2	P(O)OEt	H	1.39	1.05	1.3	1
1y	3,4-Cl_2	P(O)OiPr	H	10.0	1.4	7.1	2
1z	3,4-Cl_2	P(O)OcPent	H	8.0	6.0	1.3	2
allopregnanolone				2.61	0.08	32.6	1
THDOC				3.05	0.09	33.9	1

[a] The intrinsic activity relates to GABA shift as follows: GS > 2 for a full agonist; GS = 1−2 for a partial agonist; GS = 1 for an antagonist; GS < 1 for an inverse agonist.

probed using the pattern set above. Excluding the larger hexyl and beginning with the shorter chains, it was again observed that the branching in an isobutyl (**1j**) or isopropyl (**1k**) substituent destroyed affinity. The 4-ethyl (**1l**) restored the affinity to a measurable level, but with only a fraction of that for **1f** and a GS 25 times smaller. The iodine was more acceptable to its pocket of the receptor, allowing the ethyl of **1e** to adopt a favorable binding conformation. By comparison the butyl that enhanced binding of **1i** inhibited the binding of ethyl-substituted **1l**.

Returning to the series where X was butyl, the 2-naphthyl of **1m** took the molecule beyond the limits of the binding site. Reversing the roles, X-Ph as naphthyl (**1n**) and Y as H, was also larger than the receptor could accept (compare to **1g**). The overall trend from **1a** through **1m** was that the GABA$_A$ receptor steroid binding site was highly specific for short, unbranched aliphatics in the X position and more tolerant in the Y position of alkyl or iodine groups but that this site must also stay within limits. Additional analogues brought more perspective to this with relation to halogens at X and different linkers.

The next portion of the study examined whether the sulfonyl was necessary or perhaps isosteric with the phosphonic acid mixed ester amide. For this series the commercially available phenylphosphonic dichloride was used, since **1g** could be used as a comparator without a lengthy synthesis of reagents. The closest analogues were **1o** and **1p** where the ester portion was methyl and ethyl, respectively. The methyl analogue **1o** was a full agonist with a better IC$_{50}$ than **1g** but an inferior GS. The ethyl **1p** was only a partial agonist but again had a better IC$_{50}$ than **1g**. It was notable that **1o** and **1p** have measurable binding to the receptor in the absence of GABA, a property virtually unseen in this series to this point (the exception is **1l**).

Since both of these mixed phosphonic acid derivatives were more potent than **1g**, we utilized this combination of linker and Y to examine more changes in X. Introduction of the methoxy at the 4 position in **1q** reduced affinity 10-fold vs **1o**, and the GS indicates that it was a partial agonist. Removal of the substituent (**1r**, X = H) had the effect of eliminating affinity. The halogenated compounds **1s**, **1t**, and **1u** suffered the same fate, with IC$_{50}$'s that barely registered under test conditions. This was in line with the findings described above where the X group must be a straight chain alkyl. The lower lipophilicity and the polar nature of the methoxy and halogens made them poor substituents in this chemical series.

The last five compounds in the table (**1v**−**1z**) brought a return of binding affinity. None of these compounds were remarkable when compared to **1o** and **1p**, but their in vitro behavior was difficult to reconcile in light of the results to this point. Analogue **1v** replaced the butyl group of **1o** with 3-trifluoromethyl-4-chloro substitution and provided a *partial* agonist with a micromolar IC$_{50}$. The 3-trifluoromethyl-4-chloro analogue of **1p** was **1w**, with the ethyl ester in place. It was a *full* agonist with a smaller IC$_{50}$ than **1v**. By comparison **1o** was the full agonist, **1p** the partial; **1o** had a smaller IC$_{50}$ than **1p**. The reason for this reversal of relative position was not clear. In addition both compounds **1v** and **1w** had measurable IC$_{50}$'s in the absence of GABA. The aberrant behavior continued when chlorine replaced the 3-trifluoromethyl. Analogue **1x** had a good IC$_{50}$, but now the ethyl ester became a partial agonist. Replacement of the ethyl with the isopropyl ester (**1y**) took the compound back to a full agonist, with a reasonably good GS of 7.1.

Table 2. In Vivo Horizontal Screen Test for Motor Impairment and Suppression of Pentylenetetrazole-Induced Convulsions by THPs

analogue	dose (mg/kg), route	horizontal screen (no. passed/ no. tested)	induced convulsion (no. convulsed/ no. tested)
1a	30, ip	3/6	6/6
1g	100, ip	4/6	5/6
1i	30, po	12/12	12/12
1i	1, ip	11/12	9/12
1i	10, ip	12/12	8/12
1i	30, ip	10/11	10/11
1p	10, ip	5/6	5/6
1x	1, ip	5/6	6/6
1x	10, ip	5/6	6/6
1y	100, ip	0/6	4/6

Finally, formation of the cyclopentyl ester (**1z**) reduced the IC_{50} and made the compound a partial agonist. In this final group (**1v**−**1z**) of compounds the ethyl ester was the best for binding to the receptor, and **1x** was part of the group evaluated in vivo. Overall the mixed phosphonic acid amide was isosteric with the sulfonyl linker, and that portion of the binding site accommodated a number of ester shapes and sizes.

In vivo data was obtained for compounds **1a**, **1g**, **1i**, **1p**, **1x**, and **1y** in the horizontal screen test (for motor impairment) and the pentylenetetrazole-induced convulsion test (Table 2). Compound **1i** was dosed by the oral (30 mg/kg) and intraperitoneal (1, 10, and 30 mg/kg) routes. This compound was thought to represent the best chance for in vivo activity given the IC_{50} with GABA of 0.21 mM and the GS of 52.4. Compound administration did not result in motor impairment but provided little protection against induced seizures (1 and 10 mg/kg ip, compare to 30 mg/kg ip). Other compounds in the 4-butyl series (**1a**, **1g**, and **1p**) were tested in vivo, ip administration. Again, little protection against induced seizures was afforded. Compounds **1x** and **1y** fared poorly in the in vivo evaluation as well. **1x** had no activity, but while **1y** protected one-sixth against seizures, no animals passed the horizontal screen test.

The poor in vivo performance by these compounds may be related to an overall lack of potency in the series, or a poor pharmacokinetic profile. The steroid standards in Table 1 had EC_{50}'s below 100 nM, a level of affinity never achieved with these compounds. The difference may also be accounted for by the inability of the compounds to pass the blood−brain barrier. No specific testing of this parameter was conducted.

Conclusions

Tetrahydropyridazines are a class of nonsteroidal allosteric modulators at the $GABA_A$ receptor, possibly acting at the steroid binding site. The compounds show moderate to high-affinity binding in the presence and absence of GABA, compared with steroid standards. In vivo activity of the compounds however was unfavorable. It is clear from these data that even at high doses, ip administration, these compounds were poor inhibitors of pentylenetetrazole-induced convulsions. Despite this shortcoming the compounds should be useful biochemical tools for the investigation of GABA receptors.

Experimental Section

Chemical Synthesis. Melting points (°C) were determined on a Hoover melting point apparatus and are uncorrected. Proton NMR spectra were performed on a GE QE-300 NMR spectrometer. *J* values are given in hertz (Hz). Microanalyses were performed on a Perkin-Elmer model 240c elemental analyzer.

Starting keto acids **2a**−**e**,**n** were prepared by the acylation of the corresponding alkylarene with succinic anhydride and aluminum chloride.[7c] Compounds **2q**−**s** were purchased from Aldrich Chemical Co.; **2u** was purchased from Lancaster Synthesis, Inc. Compounds **2v** and **2x** were prepared by reaction of 4-chloro-3-(trifluoromethyl)benzaldehyde (Oakwood Products, Inc.) or 3,4-dichlorobenzaldehyde (Aldrich Chemical Co.) with acrylonitrile and potassium cyanide.[7d] Treatment of **2a**−**e**,**n**,**q**−**s**,**u**,**v**,**x** with hydrazine in ethanol gave 3-aryl-6-oxo-1,4,5,6-tetrahydropyridazines **3a**−**e**,**n**,**q**−**s**,**u**,**v**,**x**.[7c] These were reduced to afford 3-aryl-1,4,5,6-tetrahydropyridazines **4a**−**e**,**n**,**q**−**s**,**u**,**v**,**x**.[7c] Compounds **4a**−**n** were acylated as previously reported.[7b] All biologically tested compounds had satisfactory elemental analyses (C, H, N) and spectral data for the assigned structure.

3-(4-Butylphenyl)-1-(4-iodophenylsulfonyl)-1,4,5,6-tetrahydropyridazine (1a): from **4a**, 32%; mp 121−122 (ethyl acetate); ^{1}H NMR ($CDCl_3$) δ 7.85 (d, J = 8.5, 2H), 7.62 (m, 4H), 7.16 (d, J = 8.2, 2H), 3.39 (t, J = 5.5, 2H), 2.61 (t, J = 7.6, 2H), 2.52 (t, J = 6.8, 2H), 2.14 (m, 2H), 1.59 (m, 2H), 1.35 (m, 2H), 0.93 (t, J = 7.3 3H). Anal. ($C_{20}H_{23}IN_2O_2S$) C, H, N.

3-(4-Hexylphenyl)-1-(4-iodophenylsulfonyl)-1,4,5,6-tetrahydropyridazine (1b): from **4b**, 39%; mp 102−103 (hexanes); ^{1}H NMR ($CDCl_3$) δ 7.85 (d, J = 8.5, 2H), 7.62 (m, 4H), 7.16 (d, J = 8.2, 2H), 3.39 (t, J = 5.5, 2H), 2.61 (t, J = 7.5, 2H), 2.52 (t, J = 6.9, 2H), 2.16 (m, 2H), 1.60 (m, 2H), 1.29 (m, 6H), 0.88 (m, 3H). Anal. ($C_{22}H_{27}IN_2O_2S$) C, H, N.

3-(4-Isobutylphenyl)-1-(4-iodophenylsulfonyl)-1,4,5,6-tetrahydropyridazine (1c): from **4c**, 34%; mp 157−158 (hexanes); ^{1}H NMR ($CDCl_3$) δ 7.85 (d, J = 8.6, 2H), 7.65 (d, J = 8.6, 2H), 7.58 (d, J = 8.3, 2H), 7.13 (d, J = 8.3, 2H), 3.39 (t, J = 5.6, 2H), 2.49 (m, 4H), 2.16 (m, 2H), 1.85 (sep, J = 6.7, 1H) 0.90 (d, J = 6.6, 6H). Anal. ($C_{20}H_{23}IN_2O_2S$) C, H, N.

3-(4-Isopropylphenyl)-1-(4-iodophenylsulfonyl)-1,4,5,6-tetrahydropyridazine (1d): from **4d**, 26%; mp 202−204 (acetone/hexanes); ^{1}H NMR ($CDCl_3$) δ 7.85 (d, J = 8.5, 2H), 7.64 (d, J = 8.5, 2H), 7.61 (d, J = 8.6, 2H), 7.21 (d, J = 8.6, 2H), 3.39 (t, J = 6.1, 2H), 2.92 (sep, J = 6.9, 1H), 2.52 (t, J = 6.8, 2H), 2.16 (m, 2H), 1.25 (d, J = 6.9, 6H). Anal. ($C_{19}H_{21}IN_2O_2S$) C, H, N.

3-(4-Ethylphenyl)-1-(4-iodophenylsulfonyl)-1,4,5,6-tetrahydropyridazine (1e): from **4e**, 33%; mp 189−190 (acetone/hexanes); ^{1}H NMR ($CDCl_3$) δ 7.85 (d, J = 8.6, 2H), 7.62 (m, 4H), 7.18 (d, J = 8.4, 2H), 3.39 (t, J = 5.5, 2H), 2.65 (q, J = 7.6, 2H), 2.52 (t, J = 6.8, 2H), 2.17 (m, 2H), 1.24 (t, J = 7.6, 3H). Anal. ($C_{18}H_{19}IN_2O_2S$) C, H, N.

3-(4-Butylphenyl)-1-(4-chlorophenylsulfonyl)-1,4,5,6-tetrahydropyridazine (1f): from **4a**, 25%; mp 108−109 (ethyl acetate); ^{1}H NMR ($CDCl_3$) δ 7.88 (d, J = 8.6, 2H), 7.59 (d, J = 8.3, 2H), 7.47 (d, J = 8.6, 2H), 7.16 (d, J = 8.3, 2H), 3.39 (t, J = 5.5, 2H), 2.61 (t, J = 7.5, 2H), 2.52 (t, J = 6.8, 2H), 2.14 (m, 2H), 1.59 (m, 2H), 1.35 (h, J = 7.6, 2H), 0.93 (t, J = 7.2, 3H). Anal. ($C_{20}H_{23}ClN_2O_2S$) C, H, N.

1-(Phenylsulfonyl)-3-(4-butylphenyl)-1,4,5,6-tetrahydropyridazine (1g): from **4a**, 30%; mp 109−110 (ethyl acetate); ^{1}H NMR ($CDCl_3$) δ 7.95 (d, J = 6.9, 2H), 7.55 (m, 5H), 7.15 (d, J = 8.2, 2H), 3.40 (t, J = 5.6, 2H), 2.61 (t, J = 7.8, 2H), 2.50 (t, J = 6.8, 2H), 2.13 (m, 2H), 1.59 (m, 2H), 1.34 (h, J = 7.6, 2H), 0.92 (t, J = 7.4, 3H). Anal. ($C_{20}H_{24}N_2O_2S$) C, H, N.

3-(4-Butylphenyl)-1-(4-methylphenylsulfonyl)-1,4,5,6-tetrahydropyridazine (1h): from **4a**, 17%; mp 106−107 (ethyl acetate); ^{1}H NMR ($CDCl_3$) δ 7.82 (d, J = 8.2, 2H), 7.60 (d, J = 8.2, 2H), 7.28 (d, J = 8.2, 2H), 7.15 (d, J = 8.2, 2H), 3.38 (t, J = 5.6, 2H), 2.61 (t, J = 7.8, 2H), 2.50 (t, J = 6.8, 2H), 2.39 (s, 3H), 2.13 (m, 2H), 1.59 (m, 2H), 1.34 (h, J = 7.6, 2H), 0.92 (t, J = 7.4, 3H). Anal. ($C_{21}H_{26}N_2O_2S$) C, H, N.

3-(4-Butylphenyl)-1-(4-butylphenylsulfonyl)-1,4,5,6-tetrahydropyridazine (1i): from **4a**, 15%; mp 102−103 (ethyl acetate); ^{1}H NMR ($CDCl_3$) δ 7.84 (d, J = 8.2, 2H), 7.60 (d, J = 8.2, 2H), 7.29 (d, J = 8.2, 2H), 7.15 (d, J = 8.2, 2H), 3.39 (t, J = 5.6, 2H), 2.62 (m, 4H), 2.50 (t, J = 6.8, 2H), 2.13 (m, 2H), 1.59 (m, 4H), 1.34 (m, 4H), 0.91 (m, 6H). Anal. ($C_{24}H_{32}N_2O_2S$) C, H, N.

3-(4-Isobutylphenyl)-1-(4-butylphenylsulfonyl)-1,4,5,6-tetrahydropyridazine (1j): from **4c**, 40%; mp 148−150 (hexanes); ^{1}H NMR ($CDCl_3$) δ 7.84 (d, J = 8.3, 2H), 7.60 (d, J = 8.4, 2H), 7.29 (d, J = 8.4, 2H), 7.12 (d, J = 8.3, 2H), 3.39 (t, J = 5.7, 2H), 2.64 (t, J = 7.7, 2H), 2.49 (m, 4H), 2.14 (m, 2H), 1.86 (sep, J = 6.7, 1H), 1.59 (m, 2H), 1.33 (h, J = 7.5, 2H), 0.88 (m, 9H). Anal. ($C_{24}H_{32}N_2O_2S$) C, H, N.

3-(4-Isopropylphenyl)-1-(4-butylphenylsulfonyl)-1,4,5,6-tetrahydropyridazine (1k): from **4d**, 14%; mp 131−133 (hexanes); ^{1}H NMR ($CDCl_3$) δ 7.84 (d, J = 8.2, 2H), 7.62 (d, J = 8.2, 2H), 7.29 (d, J = 8.2, 2H), 7.21 (d, J = 8.2, 2H), 3.39 (t, J = 5.6, 2H), 2.91 (sep, J = 6.8, 1H), 2.64 (t, J = 7.6, 2H), 2.50 (t, J = 6.8, 2H), 2.13 (m, 2H), 1.57 (m, 2H), 1.33 (m, 2H), 1.25 (d, J = 6.8, 6H), 0.91 (t, J = 7.2, 3H). Anal. ($C_{23}H_{30}N_2O_2S$) C, H, N.

3-(4-Ethylphenyl)-1-(4-butylphenylsulfonyl)-1,4,5,6-tetrahydropyridazine (1l): from **4e**, 21%; mp 132−133 (hexanes); ^{1}H NMR ($CDCl_3$) δ 7.83 (d, J = 8.3, 2H), 7.62 (d, J = 8.3, 2H), 7.28 (d, J = 8.3, 2H), 7.18 (d, J = 8.3, 2H), 3.40 (t, J = 5.6, 2H), 2.65 (q, J = 7.5, 4H), 2.50 (t, J = 7.3, 2H), 2.17 (m, 2H), 1.55 (m, 2H), 1.37 (m, 2H), 1.23 (t, J = 7.5, 3H), 0.91 (t, J = 7.2, 3H). Anal. ($C_{22}H_{28}N_2O_2S$) C, H, N.

3-(4-Butylphenyl)-1-(2-naphthalenylsulfonyl)-1,4,5,6-tetrahydropyridazine (1m): from **4a**, 30%; mp 140−141 (ethyl acetate); ^{1}H NMR ($CDCl_3$) δ 8.51 (s, 1H), 7.94 (m, 4H), 7.60 (m, 4H), 7.14 (d, J = 8.1, 2H), 3.45 (t, J = 5.5, 2H), 2.60 (t, J = 7.6, 2H), 2.48 (t, J = 6.8, 2H), 2.14 (m, 2H), 1.58 (m, 2H), 1.36 (h, J = 7.6, 2H), 0.92 (t, J = 7.6, 3H). Anal. ($C_{24}H_{26}N_2O_2S$) C, H, N.

1-(Phenylsulfonyl)-3-(2-naphthyl)-1,4,5,6-tetrahydropyridazine (1m): from **4n**, 31%; mp 198−200 (ethyl acetate); ^{1}H NMR ($CDCl_3$) δ 7.98 (m, 5H), 7.81 (d, J = 8.1, 2H), 7.50 (m, 5H), 3.47 (t, J = 5.7, 2H), 2.66 (t, J = 6.7, 2H), 2.20 (m, 2H). Anal. ($C_{20}H_{18}N_2O_2S$) C, H, N.

Ethyl [3-(3,4-Dichlorophenyl)-1,4,5,6-tetrahydropyridazin-1-yl]phenylphosphate (1x). 3-(3,4-Dichlorophenyl)-1,4,5,6-tetrahydropyridazine (**4x**; 2.0 g, 8.7 mmol) was dissolved in pyridine and cooled to 0 °C, and phenylphosphonic dichloride (1.2 mL, 8.7 mmol) was added. The mixture was stirred at room temperature for 1 h, ethanol (1.5 mL, 26 mmol) was added, and stirring continued overnight at room temperature. The mixture was diluted with 2 N HCl and extracted with dichloromethane. The extracts were washed with 2 N HCl, dried ($MgSO_4$), and filtered. The solvent was evaporated, and the product was isolated by column chromatography with 20% ether in dichloromethane. Recrystallization afforded **1x** (0.28 g, 8%) as a yellow solid: mp 117−119 (ether); ^{1}H NMR ($CDCl_3$) δ 7.92 (m, 3H), 7.68 (d, J = 1.9, 1H), 7.45 (m, 4H), 4.21 (m, 2H), 3.78 (m, 1H), 3.47 (m, 1H), 2.50 (m, 2H), 2.00 (m, 2H), 1.40 (t, J = 7.1, 3H). Anal. ($C_{18}H_{19}Cl_2N_2O_2P$) C, H, N.

In the same manner **4a**,**q**−**s**,**u**,**v**,**x** were treated with phenylphosphonic dichloride and either methanol, ethanol, 2-propanol, or cyclopentanol to yield **1o**−**w**,**y**,**z**.

Methyl [3-(4-butylphenyl)-1,4,5,6-tetrahydropyridazin-1-yl]phenylphosphate (1o): from **4a**, 12%; mp 74−76 (CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.93 (m, 2H), 7.57 (d, J = 8.3, 2H), 7.44 (m, 3H), 7.15 (d, J = 8.3, 2H), 3.83 (d, J = 11.5, 3H), 3.80 (m, 1H), 3.45 (m, 1H), 2.63 (m, 4H), 2.00 (m, 2H), 1.59 (m, 2H), 1.35 (h, J = 7.7, 2H), 0.92 (t, J = 7.3, 3H). Anal. ($C_{21}H_{27}N_2O_2P$) C, H, N.

Ethyl [3-(4-butylphenyl)-1,4,5,6-tetrahydropyridazin-1-yl]phenylphosphate (1p): from **4a**, 19%; oil; ^{1}H NMR ($CDCl_3$) δ 7.95 (m, 2H), 7.58 (d, J = 8.4, 2H), 7.44 (m, 3H), 7.15 (d, J = 8.4, 2H), 4.22 (m, 2H), 3.78 (m, 1H), 3.46 (m, 1H), 2.50 (m, 4H), 2.00 (m, 2H), 1.59 (m, 2H), 1.39 (m, 5H), 0.92 (t, J = 7.3, 3H). Anal. ($C_{22}H_{29}N_2O_2P$) C, H, N.

Methyl [3-(4-methoxyphenyl)-1,4,5,6-tetrahydropyridazin-1-yl]phenylphosphate (1q): from **4q**, 7%; mp 155−156 (ethyl acetate/ether); ^{1}H NMR ($CDCl_3$) δ 7.93 (m, 2H), 7.60 (d, J = 9.0, 2H), 7.44 (m, 3H), 6.86 (d, J = 9.0, 2H), 3.85 (s, 3H), 3.81 (d, J = 2.8, 3H), 3.79 (m, 1H), 3.44 (m, 1H), 2.55 (m, 2H), 2.00 (m, 2H). Anal. ($C_{18}H_{21}N_2O_3P$) C, H, N.

Methyl (3-phenyl-1,4,5,6-tetrahydropyridazin-1-yl)-phenylphosphoramidate (1r): from **4r**, 15%; mp 89−91 (ether); ^{1}H NMR ($CDCl_3$) δ 7.91 (m, 2H), 7.63 (d, J = 8.1, 2H), 7.40 (m, 6H), 3.84 (d, J = 11.4, 3H), 3.79 (m, 1H), 3.47 (m, 1H), 2.58 (m, 2H), 2.01 (m, 2H). Anal. ($C_{17}H_{19}N_2O_2P$) C, H, N.

Methyl [3-(4-fluorophenyl)-1,4,5,6-tetrahydropyridazin-1-yl]phenylphosphate (1s): from **4s**, 12%; mp 129−131 (ethyl acetate/hexanes); ^{1}H NMR ($CDCl_3$) δ 7.91 (m, 2H), 7.63 (m, 2H), 7.42 (m, 3H), 7.02 (t, J = 8.7, 2H), 3.83 (d, J = 11.4, 3H), 3.80 (m, 1H), 3.48 (m, 1H), 2.55 (m, 2H), 2.03 (m, 2H). Anal. ($C_{17}H_{18}FN_2O_2P$) C, H, N.

Ethyl [3-(4-fluorophenyl)-1,4,5,6-tetrahydropyridazin-1-yl]phenylphosphate (1t): from **4s**, 13%; mp 111−114 (ethyl acetate/hexanes); ^{1}H NMR ($CDCl_3$) δ 7.92 (m, 2H), 7.64 (m, 2H), 7.44 (m, 3H), 7.02 (t, J = 8.6, 2H), 4.22 (m, 2H), 3.79 (m, 1H), 3.45 (m, 1H), 2.54 (m, 2H), 2.00 (m, 2H), 1.40 (t, J = 7.1, 3H). Anal. ($C_{18}H_{20}FN_2O_2P$) C, H, N.

Methyl [3-(4-bromophenyl)-1,4,5,6-tetrahydropyridazin-1-yl]phenylphosphate (1u): from **4u**, 6%; mp 171−172 (ethyl acetate); ^{1}H NMR ($CDCl_3$) δ 7.92 (m, 2H), 7.48 (m, 7H), 3.83 (d, J = 11.4, 3H), 3.80 (m, 1H), 3.48 (m, 1H), 2.53 (m, 2H), 2.01 (m, 2H). Anal. ($C_{17}H_{18}BrN_2O_2P$) C, H, N.

Methyl [3-(4-chloro-3-(trifluoromethyl)phenyl)-1,4,5,6-tetrahydropyridazin-1-yl]phenylphosphate (1v): from **4v**, 13%; mp 92−93 (ethyl acetate); ^{1}H NMR ($CDCl_3$) δ 7.91 (m, 2H), 7.67 (d, J = 8.5, 1H) 7.47 (m, 5H), 3.83 (d, J = 11.4, 3H), 3.80 (m, 1H), 3.49 (m, 1H), 2.58 (m, 1H), 2.50 (m, 1H), 2.04 (m, 2H). Anal. ($C_{18}H_{17}ClF_3N_2O_2P$) C, H, N.

Ethyl [3-(4-chloro-3-(trifluoromethyl)phenyl)-1,4,5,6-tetrahydropyridazin-1-yl]phenylphosphate (1w): from **4v**, 9%; mp 89−90 (hexanes); ^{1}H NMR ($CDCl_3$) δ 7.92 (m, 3H), 7.66 (d, J = 8.4, 1H), 7.47 (m, 4H), 4.21 (m, 2H), 3.78 (m, 1H), 3.45 (m, 1H), 2.53 (m, 2H), 2.03 (m, 2H), 1.40 (t, J = 7.1, 3H). Anal. ($C_{19}H_{19}ClF_3N_2O_2P$) C, H, N.

1-Methylethyl [3-(3,4-dichlorophenyl)-1,4,5,6-tetrahydropyridazin-1-yl]phenylphosphate (1y): from **4x**, 16%; mp 103−104 (CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.89 (m, 3H), 7.68 (d, J = 2.1, 1H), 7.45 (m, 4H), 4.80 (m, 1H), 3.78 (m, 1H), 3.47 (m, 1H), 2.49 (m, 2H), 2.00 (m, 2H), 1.43 (d, J = 6.2, 3H), 1.38 (d, J = 6.2, 3H). Anal. ($C_{19}H_{21}Cl_2N_2O_2P$) C, H, N.

Cyclopentyl [3-(3,4-dichlorophenyl)-1,4,5,6-tetrahydropyridazin-1-yl]phenylphosphate (1z): from **4x**, 5%; mp 115−116 (ether); ^{1}H NMR ($CDCl_3$) δ 7.87 (m, 3H), 7.68 (d, J = 2.0, 1H), 7.40 (m, 4H) 5.03 (m, 1H), 3.79 (m, 1H), 3.45 (m, 1H), 2.49 (m, 2H), 1.95 (m, 10H). Anal. ($C_{21}H_{23}Cl_2N_2O_2P$) C, H, N.

Biological Material. Male Wistar rats weighing 200−300 g (7−10 weeks old) were sacrificed by cervical dislocation. The whole brain was excised and placed on an ice-cold Petri dish. A specified region, usually the cerebral cortex, was isolated, weighed, and homogenized in a 0.3 M aqueous sucrose solution (∼50 mL/g of tissue) buffered to pH 7.6 with 10 mM Na-HEPES, using a motor-driven Teflon pestle and polished glass tube. The homogenate was centrifuged at 1000*g* for 10 min at 4 °C, and the resulting supernatant was centrifuged at 42000*g* for 10 min. The resulting pellet (P_2 fraction) was resuspended in ∼50 volumes of 4 mM K_2HPO_4−KH_2PO_4 (pH 7.5 at 23 °C). This suspension was stored for 10−15 min at 23 °C and then centrifuged at 42000*g*. This washing step was repeated once. The sediment was resuspended in ∼30 volumes of the phosphate-buffered solution, which served as the membrane suspension in the binding reactions. The concentration of GABA was <10 nM in membrane suspensions obtained by this procedure (unpublished observations).

[^{35}S]TBPS Binding Reaction. Each sample included 1.25 mL of the phosphate-buffered solution, 0.1 mL of ligand ([^{35}S]-TBPS, 0.02 μCi; NEN Products, s.a. 50−120 Ci/mmol), 0.2 mL of 4 M NaCl, 0.1 mL of 20 μM GABA, 0.25 mL of the membrane

suspension (0.2−0.3 mg of protein), and sufficient water to adjust the final volume to 2.0 mL. To determine nonspecific binding for [^{35}S]TBPS binding, 0.1 mL of water was replaced by an aqueous solution of either 20 mM GABA or 0.2 mM TBPS, which under normal incubation conditions yielded similar values. The final concentration of phosphate in all samples was ∼3 mM. Samples were incubated in groups of 24 at 23 °C for 90 min. The reaction was terminated using vacuum filtration to collect the synaptosomal material on GF/B filter sheets (LKB filter mats, Brandel M-R cell harvester). The samples were washed twice with 2 mL of ice-cold HEPES-buffered solution. The radioactivity collected on the filter sheets was quantified by liquid scintillation spectrometry using a Wallac BetaPlate scintillation counter.

Test Compounds and Other Chemicals. Test compounds were dissolved in either dimethylformamide (DMF) or dimethyl sulfoxide (DMSO) at 1 mM. These solutions were diluted serially into water. GABA and reference steroids were purchased from Sigma Chemical Co. (St. Louis, MO). Some reference steroids were a gift from Dr. Robert A. Purdy.

Analysis of Concentration−Response Curves for TBPS Binding. Test compounds were screened at 10 μM with and without GABA present in the medium at 1 μM. For active compounds concentration−response curves were obtained using five to eight concentrations, usually ranging between 1 nM and 10 μM. In general, the data were analyzed using only data on the portion of the concentration−response curve associated with an inhibition of [^{35}S]TBPS binding. IC_{50} values were calculated from the percent inhibition of [^{35}S]TBPS binding after the data were transformed to a log−logit format. A GABA shift was calculated from the ratio of the IC_{50} obtained in the absence of GABA to that obtained in the presence of GABA.

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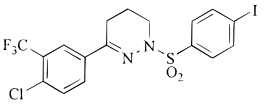

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