Design, Synthesis, and Evaluation of Analogues of 3,3,3-Trifluoro-2-Hydroxy-2-Phenyl-Propionamide as Orally Available General Anesthetics

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Received December 4, 2002

We have recently discovered a novel class of compounds that have oral general anesthetic activity, potent anticonvulsant activity, and minimal hemodynamic effects. The 3,3,3-trifluoro-2-hydroxy-2-phenyl-propionamide (**1**) demonstrated potent ability to reduce the minimum alveolar concentration (MAC) of isoflurane, with no effects on heart rate or blood pressure at therapeutic concentrations. Analogue **1** also had potent oral anticonvulsant activity against maximal electroshock (MES) and subcutaneous metrazol (scMET) models with a therapeutic index of 10 for MES activity. In this study, we further synthesized nine new racemic analogues and evaluated these compounds for effects on isoflurane MAC reduction and blood pressure. Preliminary data demonstrate potent reduction in the isoflurane MAC for two new compounds. Current mechanistic studies were unrevealing for effects on voltage-gated ion channels as a putative mechanism. Liposomal partitioning studies using ^{19}F NMR reveal that the aromatic region partitions into the core of the lipid. This partitioning correlated with general anesthetic activity of this class of compounds. Further, compound **1** was used at a concentration of 1 mM and slightly enhanced $GABA_A$ current in hippocampal neurons at 10 μM. Altogether, 3,3,3-trifluoro-2-hydroxy-2-phenyl-propionamide exhibited excellent oral general anesthetic activity and appears devoid of significant side effects (i.e., alterations in blood pressure or heart rate).

Introduction

General anesthesia is defined by reversible unconsciousness, lack of response to noxious stimuli, and amnesia induced by chemical agents. Successive improvements in these agents produced today's inhaled anesthetics, compounds that allow precise control over the anesthetic state. Such control extends to induction, maintenance of, and recovery from anesthesia.[1] Present mechanism(s) and physiological site(s) of action of general anesthetics remain controversial and multimodal. On the basis of the correlation between oil solubility and anesthetic potency, Meyer and Overton originally proposed that anesthetic drugs acted on the cell's lipid membranes.[2] However, an observation in 1984 by Franks and Lieb[3] indicated that anesthetic inhibition of purified (i.e., lipid-free) firefly protein, luciferase, closely related to potency. This observation challenged Meyer and Overton's theory and introduced the concept of a protein-binding site. Along with the lack of stereoselective differences in lipid solubility,[4] these results strongly argue against a simple lipid site as a primary mechanism of action. More recently, it has been demonstrated that anesthetic agents act on or within specific proteins of the cellular membrane of neurons, or both. Anesthetic compounds have demonstrated specific structure−activity relationships (SAR),[5] stereoselectivity,[6−8] and saturability at several receptor targets, including γ-aminobutyric acid ($GABA_A$ and $GABA_B$),[9,10] nicotinic,[11] and voltage-gated ion channels such as calcium,[12,13] potassium,[14] and sodium.[15−20] Because of the increasing studies on the direct effects of inhalational anesthetics on ion channels and receptors, many researchers now believe these targets are the site(s) of action of volatile anesthetics.[21] However, debate continues as to whether the anesthetic "receptor" is a membrane lipid or protein complex.

Currently available general anesthetics are either not optimal or not without side effects.[21] Common post-anesthetic side effects include somnolence, nausea, emesis, transient disorders of mentation (emergence excitement), post-anesthetic tremor (shivering), and dysrhythmias (particularly sinus tachycardia). Thus, there is a need for improved anesthetic agents having decreased post-anesthetic side effects along with increased anesthetic control.

Propofol, a simple formulation of 2,6-diisopropylphenol, is an effective intravenous anesthetic and is used for induction and maintenance of general anesthesia (Figure 1). This compound, when administered by continuous infusion or by intermittent bolus doses, has found increased use for its quick anesthetic onset and titratability. Unfortunately, propofol has significant limitations due to poor aqueous solubility and must be formulated as an oil−water emulsion. Good sterile technique must also be observed upon administration of this preparation since bacterial contamination has been associated with sepsis and death. Further, propofol

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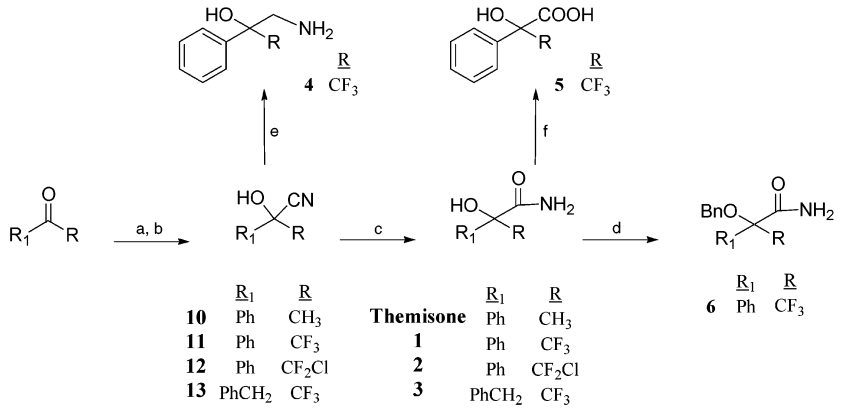
10.1021/jm020546r CCC: $25.00
Published on Web 05/14/2003

Scheme 1[a]



[a] Reaction Conditions: (a) TMSCN, KCN, 18-crown-6; (b): 15% HCl; (c) 1,4-dioxane, concd. HCl, HCl gas; (d) BnBr, Bu_4NBr, 5% NaOH, CH_2Cl_2; (e): $LiAlH_4$, Et_2O; (f) 1,4-dioxane, concd. HCl, 100 °C.

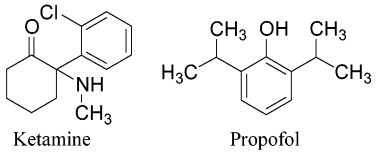


Figure 1. Common general anesthetics.

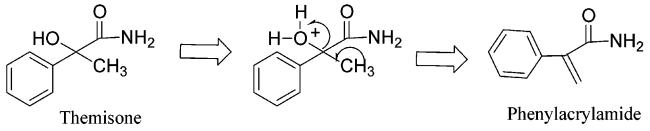


Figure 2. Potential themisone metabolism.

administration can lower blood pressure as a result of a decrease in systemic vascular resistance, cardiac contractility,[22] and preload.

Over the years, we have been involved with the National Institutes of Health's Neurological Diseases and Strokes Anticonvulsant Drug Development Program (NINDS ADD program). Recent evaluation in the NINDS ADD program revealed 3,3,3-trifluoro-2-hydroxy-2-phenyl-propionamide (**1**) to have potent anticonvulsant activity and potential oral anesthetic ability. Compound **1**'s fluorination was originally designed by us in an effort to avoid the potential formation of the toxin phenylacylamide (Figure 2).[23,24]

Using traditional medicinal chemistry transformations, we designed a series of compounds to explore the SAR of stepwise changes in electronic, conformational, and lipophilic properties of **1** on general anesthesia (Figure 3). With this in mind, compound **2** was used to evaluate the effects of different halogens on the methyl group on anesthetic activity. Analogues **3** and **9** are methylene-inserted derivatives of **1** and explore the steric tolerance of the aromatic and aliphatic-binding regions. Compounds **4** and **5** represent homologous transformations introducing charge into the amide region. Analogue **6** has increased the steric bulk in the hydroxyl-binding region as compared to compound **1**. Compounds **7** and **8** are ring-closed analogues of the lead **1** and will allow us to evaluate the effects of phenyl ring conformation on general anesthetic activity.

Results

Compound **1** was synthesized (Scheme 1) and 300 mg sent to the NINDS ADD program. Anticonvulsant

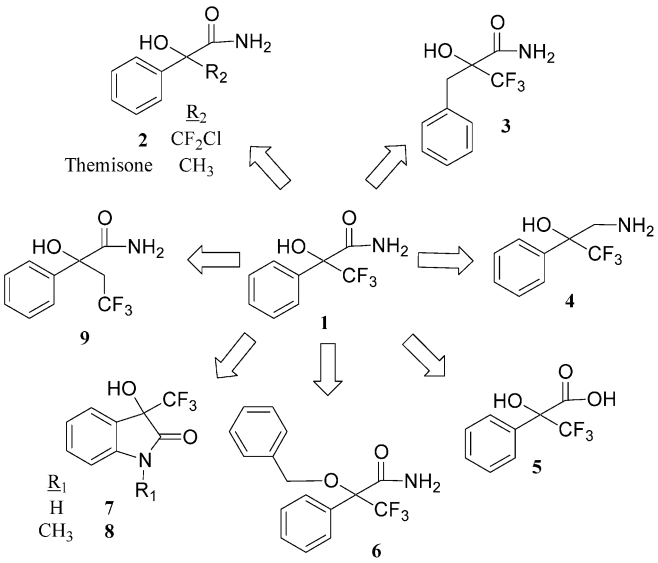


Figure 3. Medicinal chemistry transformations of analogue **1** in the study.

Table 1. Subcutaneous Administration in Mice for Compound **1**

Phase I			
		time (h)	
	dose (mg/kg)	0.5	4.0
MES	30	0/1	0/1
	100	3/3	3/3
	300	1/1	1/1
scMet	30	0/1	0/1
	100	5/5	0/1
	300	1/1	1/1
rotorod	30	0/4	0/2
	100	4/8	2/4[c]
	300	4/4[b]	2/2[a]

[a] Anesthesia. [b] Loss of righting reflex. [c] Unable to grasp rotorod.

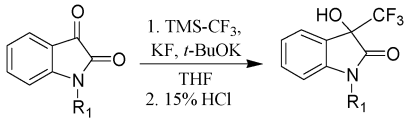
evaluation of compound **1** administered intraperitoneally (ip) in mice (Table 1) demonstrated complete (4/4 mice) protection at a dose of 100 mg/kg up to 4 h when challenged with MES. Compound **1** also demonstrated effectiveness against scMet (5/5 mice protected) for 0.5 h at the same dose. At a 100 mg/kg dose, 50% of the mice were unable to grasp the rotating rod and exhibited the loss of the righting reflex upon falling off the rod. Interestingly enough, anesthesia was observed and

Table 2. Oral Anticonvulsant Data in Rats for Analogue **1**

	Phase II, mg/kg[a]			
compd	MES ED_{50}	scMET ED_{50}	rotorod ED_{50}	T. I.[b]
1	9.9 (6.9−13)	39 (25−52)	100	MES 10 ScMET 2.6
phenytoin	9.5	>300 (53−72)	66	MES 6.9

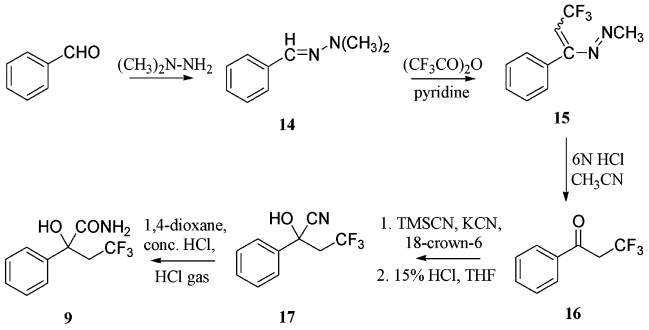
[a] ( ) 95% confidence level. [b] T.I. = therapeutic index.

Scheme 2



	R_1
7	H
8	CH_3

Scheme 3



reported at a dose of 300 mg/kg in 2/2 animals with effects up to 4 h. Our laboratory provided another 1000 mg of compound **1** to the NINDS ADD program, which revealed a MES ED_{50} of 9.9 mg/kg, scMet ED_{50} of 39 mg/kg, and TD_{50} of 100 mg/kg upon oral administration (Table 2).

With the emergent anesthetic activity of **1**, compounds **2**−**9** were synthesized and evaluated for general anesthetic activity. The general synthetic methods are shown in Schemes 1−3. Final products **1**, **2**, **3**, **9**, and themisone were synthesized by converting the corresponding ketones to the trimethylsilyl ether with trimethyl silyl cyanide (TMSCN). Subsequent hydrolysis with 15% HCl generated the cyanohydrin. Conversion of the corresponding cyanohydrin to the hydroxyamide was accomplished under acidic conditions by saturating with HCl gas and allowing the mixtures to stand at room temperature for 16 h (Scheme 1). Analogue **1** was heated at 100 °C for 24 h in concentrated HCl to obtain **5**, the acid of the lead compound. Analogues **7** and **8** were obtained by treating isatin and methyl−isatin with TMS−CF_3 to generate the TMS ether (Scheme 2), and the TMS ethers were hydrolyzed with acid to obtain the final products. Analogue **4** was synthesized from the reduction of compound **11** with $LiAlH_4$.

Compound **9** was synthesized by reacting dimethylhydrazine with benzaldehyde to give the *N*′-benzylidene-*N*,*N*-dimethyl-hydrazine **14**. Addition of the anhydride generated the methyl-(3,3,3-trifluoro-1-phenyl-propenyl)-diazene **15**. Intermediate **15** was converted to the 3,3,3-trifluoro-1-phenyl-propan-1-one **16** under acidic conditions (Scheme 3).[25] TMSCN was added to the ketone **16** to produce the cyanohydrin, and then the hydroxyamide was made using the method discussed above.

Table 3. Effects on MAC Reduction and Blood Pressure in Rats for Analogues in This Study

compound	mean BP[a] (mmHg) ± SEM	MAC (vol %) reduction[a] ± SEM	log p[b]
Themisone	127 ± 7	0.0 ± 0	0.62
1	119 ± 12	−34 ± 3	1.3
2	81 ± 10	−43 ± 3	1.5
3	111 ± 5	0.0 ± 0	1.5
4	116 ± 3	−6.5 ± 2	1.4
5	116 ± 5	−9.1 ± 4	1.9
6	121 ± 9	−4.4 ± 3	3.4
7	113 ± 4	−4.3 ± 3	1.1
8	112 ± 7	−4.4 ± 3	1.4
9	107 ± 2	−11 ± 3	1.5

[a] All compounds tested at 60 mg/kg administered by intraperitoneal injection. [b] Log p calculation using the Crippen's method in Chemdraw.

The anesthetic observation reported in Table 1 by the NINDS ADD program led us to evaluate compound **1** independently for anesthetic activity. Testing was performed on rats to determine the percent reduction in the concentration of isoflurane required to prevent the response to a standardized stimulus. The rats were first induced with isoflurane, intubated, and ventilated, and then femoral arterial and venous lines were inserted. After the rat had been stable for 15 min, the initial minimum alveolar concentration (MAC) value was determined. Then 60 mg/kg of drug was sonicated in 3 mL of peanut oil and injected ip. After an additional 30 min, the second MAC value was determined. Finally, after 1 h the third MAC value was determined. At each MAC determination, a sample of blood was taken to determine pH, pCO_2, and pO_2.

SARs between mean BP and isoflurane MAC reduction (Table 3) were revealing. Analogue **1** exhibited a 34% reduction in isoflurane MAC with no effects on blood pressure at 60 mg/kg. An increase in halogen size (fluorine to chlorine) resulted in improved MAC reduction (43%) with a large drop in blood pressure at the same dose for compound **2**. This demonstrates that haliform content is important to anesthetic activity and blood pressure. A methylene insertion between the quaternary carbon and the phenyl ring (**3** vs **1**) did not improve MAC reduction. Likewise, compound **9**, which possesses a methylene insertion between the quaternary carbon and the trifluoromethyl group, also did not demonstrate ability to greatly reduce the MAC. Taken together, these data suggest that the CF_3 and phenyl ring regions do not tolerate a probe depth of greater than a methylene group in this region.

Compound **4** places a protonated amine in the region of the amide (**1** vs **4**). This essentially places a positive charge in this region. The SAR reveals a decreased MAC reduction without effects on blood pressure. Compound **5**, which contains a negative group (COO−) in the amide region, also did not demonstrate any statistical increase in MAC reduction in comparison to analogue **4**. These data suggest that charged groups in this area do not contribute significantly to activity in comparison to that of the neutral amide in **1**.

Compound **6** places steric bulk in the hydroxyl region and lacks the ability to hydrogen bond in comparison

to compound **1**. Both of these properties appear to decrease the ability to reduce the MAC and do not modulate blood pressure.

Compounds **7** and **8** were designed to evaluate phenyl ring conformation. Both compounds have restricted phenyl ring rotation. In both cases, the *N*-methylated and the NH-restricted analogues do not possess the ability to reduce the MAC. These compounds hold the phenyl ring outside of the range of lowest-energy conformers for lead **1** and have poor anesthetic activity. This suggests that phenyl ring orientation is important.

A poor correlation ($R^2 = 0.4$) of mean BP and percent MAC reduction in Table 3 was also obtained. This is encouraging and suggests the possibility of developing compounds that have effects on MAC reduction but are devoid of effects on BP.

Recent data support that ketamine interacts with sodium channels in a local anesthetic-like fashion, including sharing a binding site with commonly used clinical local anesthetics. Ketamine (Figure 1) blocked sodium channels in a local anesthetic-like fashion, exhibiting tonic blockade (concentration for half-maximal inhibition, $IC_{50} = 0.8$ mM), phasic blockade ($IC_{50} = 2.3$ mM), and leftward shift of the steady-state inactivation.[26] Our previous demonstration that phenylhydroxyamides bind to the hydantoin-anesthetic binding site in the novel voltage-gated sodium channel[27] led us to evaluate this mechanism for these similar compounds. We evaluated the effects of 10 μM and 100 μM of analogue **1** on rNa_V 1.3 and rNa_V 1.3 coexpressed with β 3 in xenopus oocytes and in HEK293. The results of this study demonstrate that analogue **1** does not block voltage-gated Na^+ channels.

Other mechanisms of action thus far include K^+ channels and protein kinase C. Compound **1** did not activate or inhibit rat TASK-1- and TASK-3-leak K^+ channels expressed in HEK293 cells at 100 μM. Compound **1** also did not activate protein kinase C at 100 μM.

Preliminary experiments to investigate addictive potentials were also unrevealing. We found no effects when the μ-opioid receptor antagonist naloxone was administered in an attempt to reverse the hemodynamic depression and MAC reduction following treatment with analogue **1**.

As a method of exploring the mechanism of action, we pursued a liposome partitioning methodology. It has been found that xenon, when equilibrated with a membrane anesthetic model, interacts preferentially with the amphiphilic regions of the lipid. This is unlike nonanesthetics which partition deep into the core of the membrane.[28] 1-Palmitoyl-2-oleoyl-*sn*-glycero-3-phosphocholine (POPC) was chosen as the lipid membrane environment to evaluate our compounds for lipid partitioning. The buffer (pH = 7.0) was 10 mM $K_2HPO_4 \cdot 3H_2O$ in 20% D_2O. The trifluoromethyl functionality allowed us to utilize ^{19}F NMR for measurements because the functional group resulted in a sharp singlet in the spectrum and compounds **1** and **3** were evaluated for lipid membrane partitioning. Compound **3** was chosen because it was not found to lower the MAC of isoflurane at 60 mg/kg in a rat model for general anesthesia, thus labeled as a nonanesthetic for this study, whereas **1**, which lowered the MAC by 33%, represents a potent anesthetic. The observed chemical shifts were referenced to the compounds in a lipid-free environment in buffer. Using a simplified two-site exchange model (eq 1) and a plot of the reciprocal of frequency changes as a function of the reciprocal of lipid concentration, we can calculate the partitioning coefficient.

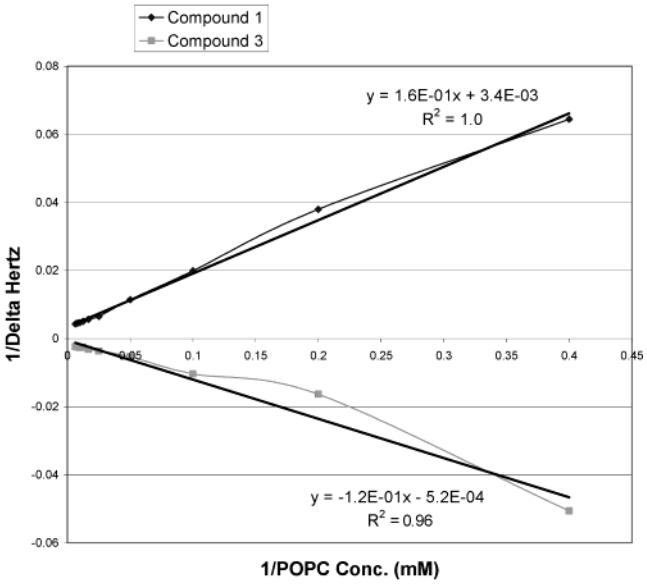


Figure 4. Determination of partition coefficients using ^{19}F NMR.

$$\frac{1}{\Delta\nu} = \frac{1}{\nu_M - \nu_W}\left[1 + \frac{54.4 \times 10^3}{D_M/D_W} \times \frac{1}{m}\right] \qquad (1)$$

In the above model, m_w (molarity of water) was used as 54.4×10^3 mM because a 1:4 (v/v) mixture of D_2O:H_2O was used in the buffer and m is the molarity of the lipid. The symbols ν_M and ν_W represent the frequencies in pure lipid and water. With a fast exchange between the lipid and water layers, the reciprocal graph yields a straight line (Figure 4) and the partition coefficient (D_M/D_W) is the intercept/slope times m_w. The coefficient was found to be 240 for compound **1** and 1180 for compound **3**. Therefore, when equal amount of **1** and **3** are added to a membrane system, the concentration of **1** bound to the membrane will be 4.9 times greater than the membrane-bound concentration of **3**. These data are consistent with nonanesthetics having higher partition coefficients and partitioning into the core of the membrane. Once more compounds have been used in the study, we hope to make decisive correlates between MAC reduction and partitioning in regards to the mechanism of action.

Several anesthetic agents including propofol enhance $GABA_A$ receptor currents. It was therefore important to evaluate effects of compound **1** on $GABA_A$ receptors in rat hippocampal neurons. Hippocampal neurons in culture for 10−14 days were studied with whole-cell patch-clamp recording technique. Application of 1 mM of compound **1** evoked $GABA_A$ currents at 10 μM (Figure 5).

Discussion

Volatile anesthetics are routinely utilized to produce surgical anesthesia. Although it is rapidly titratable,

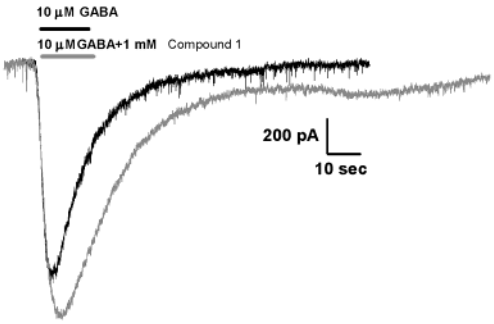


Figure 5. Compound **1** (1 mM) enhances 10 μM $GABA_A$ currents in rat hippocampal neurons.

volatile anesthetic administration is limited because of depression of myocardial contractility and peripheral vasodilation resulting in decreased blood pressure. In clinical practice, a balanced anesthetic is frequently obtained by the concurrent administration of a combination of drugs.

General anesthetics have demonstrated both anticonvulsant and proconvulsant activity.[29] One possible factor is an inherent pharmacodynamic variability in the responsiveness of inhibitory and excitatory target tissues in the central nervous system. This variability in neuronal responsiveness could also explain the conflicting findings for low versus high doses of fentanyl and etomidate. Furthermore, biological variation in the individual patient's responsiveness to certain anesthetic drugs could be an additional contributory factor. Different SARs might also explain why some anesthetic agents possess both proconvulsant and anticonvulsant properties. Therefore, identification of mechanism(s) will be useful in further development of compound **1**. Along with the anesthetic effect, compound **1** also demonstrated potent anticonvulsant activity. Independently, 30 mg/kg of compound **1** provided complete (4/4 animals) antiseizure protection in rats subjected to MES. As an anticonvulsant, compound **1**'s antiseizure profile (MES ED_{50} of 9.9 mg/kg, scMet ED_{50} of 39 mg/kg, and TD_{50} of 100 mg/kg) was equally efficacious to phenytoin (a currently clinically prescribed sodium channel active anticonvulsant) and exhibited consistently lower neurotoxicity.

Conclusion

We have demonstrated the MAC-reducing effect of a novel class of phenylamide derivatives and are encouraged that compound **1** was hemodynamically well tolerated at therapeutically relevant doses separate from toxicity. This study confirms that compound **1** does indeed possess potent general anesthetic activity and appears devoid of significant side effects (i.e., altering blood pressure or heart rate or causing respiratory depression).

Experimental Section

Chemistry. All reactions requiring anhydrous conditions were performed in flame-dried glassware under an argon or nitrogen atmospherere. Melting points were determined with an Electrothermal Mel-Temp melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were measured on a General Electric 300 MHz instrument, unless specified otherwise. Chemical shifts are reported in ppm relative to resonances of the solvent, $CDCl_3$ (unless specified otherwise): 7.24 ppm (s) in the ^{1}H spectra and 77.0 ppm (t) in the ^{13}C spectra. IR spectra were recorded on either a Perkin-Elmer 1310 or FT-IR Impact 400D. High-resolution mass spectrometry was performed at the UIUC School of Chemical Science. Elemental analyses were performed by Atlantic Microlabs. Concentration in vacuo refers to high vacuum (0.35 mmHg). Concentration refers to a rotary evaporator with a water aspirator. Anhydrous THF, diethyl ether, and dichloromethane were purified by pressure filtration through activated alumina. Flash chromatography was performed on silica gel (Merck grade 9385, 230−400 mesh, 60 Å).

General Preparation of Cyanohydrins from Ketones. The ketone (1.0 equiv) was dissolved in dry CH_2Cl_2. Trimethylsilyl cyanide (2.2 equiv) and ZnI_2 (1.0 equiv) (or KCN and 18-crown-6, 10 mg each for every 1.0 mmol of ketone) were added. The mixture was stirred at room temperature for 4 h. The reaction progress was monitered by TLC, by the disappearance of the carbonyl stretching peak (1770 cm^{-1}), and by the appearance of the nitrile stretching peak (2200 cm^{-1}) in the IR spectrum. The CH_2Cl_2 layer was concentrated in vacuo, and a minimal amount of dry THF was added. The mixture was cooled to 0 °C, and 15% HCl (5 mL) was added and then stirred at room temperature for 2 h. The solution was diluted with H_2O and extracted with Et_2O (3 × 25 mL), dried over $MgSO_4$, filtered, and concentrated to yield the product.

2-Hydroxy-2-phenyl-propionitrile (10) was obtained as a colorless oil (6.2 g, 100%). IR: (neat) 2220, 3400 cm^{-1}.

3,3,3-Trifluoro-2-hydroxy-2-phenyl-propionitrile (11) was obtained as a white solid (8.0 g, 99%). IR: (neat) 2240, 3360 cm^{-1}.

3-Chloro-3,3-difluoro-2-hydroxy-2-phenyl-propionitrile (12) was obtained as a yellow oil (3.3 g, 96%). IR: (neat) 2246, 3383 cm^{-1}.

2-Benzyl-3,3,3-Trifluoro-2-hydroxy-propionitrile (13) was obtained as a light yellow solid (1.3 g, 94%). IR: (neat) 2244, 3384 cm^{-1}.

4,4,4-Trifluoro-2-hydroxy-2-phenyl-butyronitrile (17) was obtained as a brown oil (1.8 g, 97%). IR: (neat) 2248, 3403 cm^{-1}.

General Preparation of α-Hydroxyamides from Cyanohydrins. The cyanohydrin was dissolved in 1,4-dioxane (2 mL) and cooled to 0 °C. Previously cooled concentrated HCl (0.2 mL for every 1 mmol of cyanohydrin) was added. HCl gas was then passed through the reaction mixture for 45 min at 0 °C. The mixture was then allowed to stand, without stirring, at room temperature for 16 h. The mixture was extracted with EtOAc (3 × 25 mL), dried over $MgSO_4$, filtered, and concentrated to yield the crude α-hydroxyamide. Purification was performed on a flash column (1:1 hexanes:EtOAc), collecting all fractions with a component of $R_f = 0.28$ to yield the pure α-hydroxyamide.

2-Hydroxy-2-phenyl-propionamide (Themisone) was obtained as a white solid (288 mg, 30%): mp 97−99 °C. ^{1}H NMR: δ 2.15 (s, 3H), 6.61 (d, $J = 7.7$ Hz, 2H), 7.10−7.71 (m, 5H). ^{13}C NMR: δ 29.8, 72.0, 129.9, 128.4, 128.5, 141.3, 173.7. IR (KBr): 1733, 3193, 3371 cm^{-1}. APCI MS *m*/*z*: 148.1, loss of H_2O, ($M + H^+$).

3,3,3-Trifluoro-2-hydroxy-2-phenyl-propionamide (1)[30] was obtained as a white solid (8.6 g, 99%): mp 83−85 °C. ^{1}H NMR: δ 4.84 (s, 1H), 6.25 (d, $J = 26.4$ Hz, 2H), 7.67−7.42 (m, 5H). ^{13}C NMR: δ 121.7, 125.5, 126.2, 128.9, 129.6, 129.8, 134.0, 169.5 134.0. IR (KBr): 1697, 3360 cm^{-1}. APCI MS *m*/*z*: 220.0 ($M + H^+$). HRMS (EI): calcd for $C_9H_8F_3NO_2$, 219.0507; found, 219.0507. Anal. Calcd for $C_9H_8F_3NO_2$: C, 49.32; H, 3.68; N, 6.39. Found: C, 49.62; H, 3.63; N, 6.45.

3-Chloro-3,3-difluoro-2-hydroxy-2-phenyl-propionamide (2) was obtained as a white solid (1.8 g, 50%): mp 79−81 °C. ^{1}H NMR: (CD_3OD) δ 7.76−7.31 (m, 5H). ^{13}C NMR: (CD_3OD) δ 126.7, 127.8, 129.0, 130.0, 130.7, 134.7, 136.4, 173.0. IR (KBr): 1700, 3224, 3340, 3510 cm^{-1}. APCI MS *m*/*z*: 236.0 ($M + H^+$). HRMS (EI) calcd for $C_9H_8ClF_2NO_2$, 235.0212; found, 235.0214. Anal. Calcd for $C_9H_8ClF_2NO_2$: C, 45.88; H, 3.42; N, 5.94. Found: C, 45.88; H, 3.44; N, 6.01.

2-Benzyl-3,3,3-trifluoro-2-hydroxy-propionamide (3) was obtained as a white solid (1.1 g, 78%): mp 114−116 °C. ^{1}H NMR: (CD_3OD) δ 2.94 (d, J = 13.5 Hz, 1H), 3.36 (d, J = 13.8 Hz, 1H), 7.22−7.16 (m, 5H). ^{13}C NMR: (CD_3OD) δ 38.4, 78.8, 110.2, 123.5, 127.3, 127.6, 128.5, 131.2, 134.5, 171.4. IR (KBr): 1700, 3210, 3385, 3503 cm^{-1}. ESI MS m/z: 232.2 (M − H$^-$). HRMS (EI): calcd for $C_{10}H_{10}F_3NO_2$, 233.0664; found, 233.0668. Anal. Calcd for $C_{10}H_{10}F_3NO_2$: C, 51.51; H, 4.32; N, 6.01. Found: C, 51.27; H, 4.36; N, 5.99.

4,4,4-Trifluoro-2-hydroxy-2-phenyl-butyramide (9) was obtained as white solid (1.6 g, 82%): mp 75−76 °C. ^{1}H NMR: δ 2.70 (m, 1H), 3.30 (m, 1H), 4.02 (bs, 1H), 5.62 (s, 1H), 6.77 (s, 1H), 7.48−7.33 (m, 5H). ^{13}C NMR: δ 41.8, 109.3, 123.6, 124.7, 127.2, 128.4, 128.6, 140.8, 174.9. IR (KBr): 1675, 3426 cm^{-1}. ESI MS m/z: 232.3 (M − H$^-$). HRMS (EI): calcd for $C_{10}H_{10}F_3NO_2$, 233.0664; found, 233.0665. Anal. Calcd for $C_{10}H_{10}F_3NO_2$: C, 51.51; H, 4.32; N, 6.01. Found: C, 51.62; H, 4.27; N, 6.03.

Preparation of 3-Amino-1,1,1-trifluoro-2-phenyl-propan-2-ol (4).[31] 3,3,3-Trifluoro-2-hydroxy-2-phenyl-propionitrile (**11**) (1.0 g, 5.0 mmol) was dissolved in dry Et_2O (2 mL) and added to cold (0 °C) $LiAlH_4$ (0.2 g, 5.3 mmol) dissolved in dry Et_2O (4 mL). The reaction mixture was stirred at room temperature for 2 h, then cooled to 0 °C. After allowing the reaction mixture to warm to room temperature, H_2O (0.8 mL) and 15% NaOH (0.2 mL) were added dropwise. The precipitate was filtered, washed with Et_2O, and concentrated. Purification was performed on a flash column (3:2 hexanes:EtOAc), collecting all fractions with a component of R_f = 0.14. The product was recrystallized from 1:1 hexanes:EtOAc to yield a white solid (600 mg, 58%): mp 57−59 °C. ^{1}H NMR: δ 3.04 (d, J = 13.5 Hz, 1H), 3.52 (d, J = 13.2 Hz, 1H), 7.60−7.38 (m, 5H). ^{13}C NMR: δ 46.0, 125.0, 126.7, 128.2, 128.8, 129.0, 137.9. IR (KBr): 2973, 3349 cm^{-1}. APCI MS m/z: 206.1 (M + H$^+$). HRMS (EI): calcd for $C_9H_{10}F_3NO$, 206.0793; found, 206.0789. Anal. Calcd for $C_9H_{10}F_3NO$: C, 52.68; H, 4.91; N, 6.83. Found: C, 52.87; H, 5.02; N, 6.78.

Preparation of 3,3,3-Trifluoro-2-hydroxy-2-phenyl-propionic Acid (5). A solution of **1** (1.0 g, 4.6 mmol) was dissolved in 1,4-dioxane (1.5 mL). Concentrated HCl (2.5 mL) was added to the reaction mixture dropwise at 0 °C. The mixture was heated at 100 °C for 24 h. After cooling, the solution was washed with H_2O (4 × 20 mL) and concentrated. Purification was performed on a flash column (1:1 hexanes: EtOAc), collecting all fractions with a component of R_f = 0.20 to yield a white solid (700 mg, 70%): mp 96−97 °C. ^{1}H NMR: δ 7.69−7.32 (m, 5H). ^{13}C NMR: δ 170.2, 134.9, 129.7, 129.3, 128.3, 126.8, 126.0, 122.3, 109.9. IR (KBr): 1735, 3403 cm^{-1}. EI MS m/z: 220.0. HRMS (EI): calcd for $C_9H_7F_3O_3$, 220.0344; found, 220.0343. Anal. Calcd for $C_9H_7F_3O_3$: C, 49.10; H, 3.20. Found: C, 48.99; H, 3.21.

Preparation of 2-Benzyloxy-3,3,3-trifluoro-2-phenyl-propionamide (6).[32] Compound **1** (0.63 g, 2.9 mmol) was dissolved in dry CH_2Cl_2 (14 mL), and 5% NaOH (7 mL) was added. Benzyl bromide (0.5 g, 2.9 mmol) was added, and the mixture was allowed to stir for 10 min. Bu_4NBr (0.1 g, 0.3 mmol) was added to the reaction mixture and stirred for 16 h at room temperature. The organic layer was washed with H_2O (3 × 10 mL), dried over Na_2SO_4, filtered, and concentrated. Purification was performed on a flash column (3:1 hexanes: EtOAc), collecting all fractions with a component of R_f = 0.35. The product was recrystallized from hot toluene to yield a white solid (605 mg, 68%): mp 70−72 °C. ^{1}H NMR: δ 4.61 (m, 2H), 6.68 (d, 2H), 7.64−7.34 (m, 10H). ^{13}C NMR: δ 69.4, 109.3, 125.7, 127.7, 128.5, 128.7, 128.9, 129.0, 129.7, 132.4, 136.7, 169.4. IR (KBr): 3227, 1700 cm^{-1}. ESI MS m/z: 308.5 (M − H$^-$). HRMS (EI): calcd for $C_{16}H_{14}F_3NO_2$, 309.0977; found, 309.0979. Anal. Calcd for $C_{16}H_{14}F_3NO_2$: C, 62.13; H, 4.56; N, 4.53. Found: C, 62.20; H, 4.63; N, 4.59.

General Procedure for the Preparation of Trifluorinated Isatin Derivatives. Anhydrous KF (510 mg, 5.4 mmol) and a solution of isatin or methylisatin (27.2 mmol) in dry THF (100 mL) were added dropwise via syringe, followed by trimethyl(trifuoromethyl)silyl (5.8 g, 40.8 mmol). A saturated solution of *t*-BuOK in dry THF (30 mL) was added until the reaction began to reflux. The mixture was then brought to ambient temperature and allowed to stir for 2 h. The mixture was extracted with hexanes (3 × 40 mL), dried over $MgSO_4$, filtered, and concentrated. The crude product was dissolved in dry THF (5 mL), cooled to 0 °C, and 15% HCl (6 mL) was added and allowed to stir for 15 min. The mixture was extracted with hexanes (3 × 40 mL), dried over $MgSO_4$, filtered, and concentrated to yield the crude product. Purification was performed on a flash column (10:1 CH_2Cl_2:acetone), collecting all fractions containing a component of R_f = 0.81 to yield the pure product.

3-Hydroxy-3-trifluoromethyl-1,3-dihydro-indol-2-one (7) was obtained as a white solid (4.4 g, 75%): mp 194−196 °C. ^{1}H NMR: δ 4.81 (s, 1H), 6.7−7.5 (m, 4H). ^{13}C NMR: δ 110.6, 122.0, 123.0, 125.1, 125.8, 126.0, 131.5, 143.1, 173.7. IR (KBr): 1717, 3421 cm^{-1}. APCI MS m/z: 218.0 (M + H$^+$). HRMS (EI): calcd for $C_9H_6F_3NO_2$, 217.0351; found, 217.0352.

3-Hydroxy-1-methyl-3-trifluoromethyl-1,3-dihydro-indol-2-one (8) was obtained as a yellow solid (2.2 g, 35%): mp 168−170 °C. ^{1}H NMR: δ 3.18 (s, 3H), 4.75 (s, 1H), 7.0−7.5 (m, 5H). ^{13}C NMR: δ 25.8, 109.4, 123.5, 123.6, 124.5, 125.7, 125.8, 131.8, 144.8, 171.8. IR (KBr): 1717, 3302 cm^{-1}. APCI MS m/z: 232.0 (M + H$^+$). HRMS (EI): calcd for $C_{10}H_8F_3NO_2$, 231.0507; found, 231.0509. Anal. Calcd for $C_{10}H_8F_3NO_2$: C, 51.96; H, 3.49; N, 6.06. Found: C, 52.22; H, 3.45; N, 6.01.

Preparation of *N*′-Benzylidene-*N*,*N*-dimethyl-hydrazine (14). Benzaldehyde (0.5 g, 4.7 mmol) and ethanol (24 mL) were cooled to 10 °C, and a solution containing *N*,*N*-dimethylhydrazine (0.54 mL, 7.1 mmol) and ethanol (5 mL) was added dropwise. The resulting mixture was allowed to warm to ambient temperature, followed by stirring for 30 min, and then heated to reflux for 24 h. After cooling, the reaction mixture was concentrated in vacuo and the resulting mixture diluted with H_2O and extracted with Et_2O (3 × 20 mL). The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated to yield a colorless oil (636 mg, 91%). ^{1}H NMR: δ 3.02 (s, 6H), 7.31−7.45 (m, 5H), 7.70 (s, 1H). ^{13}C NMR: δ 43.4, 126.2, 127.9, 129.1, 133.2, 137.6. The product was used without further purification.

Preparation of Methyl-(3,3,3-trifluoro-1-phenyl-propenyl)-diazene (15). To a solution of **16** (2.0 g, 13.5 mmol) in pyridine (40 mL) at 0 °C was added trifluoroacetic anhydride (18 mL, 130 mmol) dropwise with stirring. After stirring for 5 h at room temperature, the solution was concentrated in vacuo, and CH_2Cl_2 was added to the residue. The mixture was washed with 0.1 N HCl (100 mL), H_2O (100 mL), and saturated Na_2CO_3 (100 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated to give an oil (2.1 g, 76%). The product was used without further purification. All spectral data matched the one from the literature.[25]

Preparation of 3,3,3-Trifluoro-1-phenyl-propan-1-one (16). A solution of **15** (2.1 g, 9.8 mmol) in CH_3CN (20 mL) and 6 N HCl (20 mL) was allowed to stir for 24 h at room temperature. The mixture was concentrated in vacuo, extracted with CH_2Cl_2 (4 × 20 mL), dried over Na_2SO_4, filtered, and concentrated to yield an oil (450 mg, 13%). ^{1}H NMR: δ 3.79 (q, J = 9.9 Hz, 2H), 8.05−7.20 (m, 5H). ^{13}C NMR: δ 42.6 (q, $^2J_{CF}$ = 28.2 Hz), 109.9, 128.8, 129.4, 134.7, 136.3, 190.2. IR (neat): 1700, 3200 cm^{-1}.

Biology

Vertebrate Animals. The Department of Comparative Anatomy operates a vivarium that is fully accredited by the American Association for Accreditation of Laboratory Animal Care. Standard experimental protocols were used to determine anesthetic activity and were approved by the Animal Care and Use Committee at the University of Virginia.

Methods for Determining MAC. This model was used as a screening test using animals receiving a 60 mg/kg dose administered ip. In addition, this method allows for a more detailed examination of the anesthetic-sparing properties of selected compounds over a greater dose range. Male Sprague−Dawley rats were placed in a clear plastic cone and anesthe-

tized with 5% isoflurane (Ohmeda; Liberty Corner, NJ) and oxygen for 3−5 min. The inspired isoflurane concentration was reduced to 2%, and the animal was allowed to breathe spontaneously until cannulation of a femoral artery and vein with a 24-gauge polyethylene catheter (Johnson and Johnson Medical Inc., Arlington, TX) had been accomplished. The trachea was then intubated with a 16-gauge polyethylene catheter (Johnson and Johnson Medical Inc., Arlington, TX). The isoflurane concentration was decreased further to 1.5% and ventilation controlled with a Harvard animal respirator using measurement of arterial blood gases (IRMA series 2000 Blood Analysis System, Diametric Medical Inc., St. Paul, MN) to maintain normal pO_2, pCO_2, and pH. Alveolar isoflurane concentrations and end-tidal CO_2 measurements were obtained using a Datex Engstrom Capnomac gas monitor (Helsinki, Finland). Additional confirmation of volatile anesthetic concentrations was obtained using gas chromatography. Heart rate and systolic and diastolic blood pressures were monitored and recorded using an ADInstruments MacLab (Mountain View, CA) data recording system. Temperature was measured using a FHC temperature controller (FHC, Bowdoinham, ME) and maintained at normothermia using a heating blanket and warming lights. Under control conditions, the MAC was established according to the methods described by Eger and colleagues using a long hemostat (8-in. Rochester Dean hemostatic forceps) clamped to the first ratchet lock on the tail for 1 min.[33] The tail was stimulated proximal to a previous test site. Gross movement of the head, extremities, body, or all three were taken as a positive test, whereas grimacing, swallowing, chewing, or tail flick were considered negative. The isoflurane concentration was reduced in decrements of 0.1% until the negative response became positive, allowing 12−15 min equilibration after changes in concentration. The MAC was considered to be the concentration midway between the highest concentration that permitted movement in response to the stimulus and the lowest concentration that prevented movement.

Compounds with limited aqueous solubility were administered by intraperitoneal injection after being sonicated in peanut oil (3 mL). We have previously shown the lack of effect of the vehicle (peanut oil) on MAC determinations.[34] After determination of the baseline MAC, the compounds were administered by intraperitoneal injection. The order of administration of the various doses was performed in an unblinded, random manner. A single investigator performed all the MAC determinations to reduce inter-observer variability. Four animals were typically studied at each dose. An isoflurane concentration was chosen at the movement that did not occur in the last negative response before the positive test. At this isoflurane concentration, 30 min after the administration of the test compound, the MAC was again determined with the concentration of isoflurane reduced and the response to the tail clamp was checked every 12−15 min thereafter until a positive response was achieved. After recording the experimental MAC, an additional hour was allowed to elapse before the MAC was again determined. Assessment of differences in anesthetic activity and effects on heart rate and blood pressure was performed by multifactor analysis of variance (ANOVA) models fit using restricted maximum likelihood techniques. All models included an adjustment for any effects associated with the experiment. A natural logarithmic transformation of anesthetic activity and effects on heart rate and blood pressure was employed. This allowed for the use of the anti-logarithm of differences to compare the ratio of two quantities (interpreted as fold change) and aided in meeting the assumptions of the linear model (constant variance across categories and normally distributed error terms).

$GABA_A$ Enhancement. GABA and various concentrations of the test drug dissolved in extracellular solution were applied to hippocampal neurons using a modified U-tube "multipuffer" rapid application system with the tip of the application pipet placed 100−200 μm from the cell. The rate of solution exchange was rapid with a mean 10−90 rise time of 54.4 ms ± 4.96 ms (n = 5). Drugs were co-applied with 10 μM of GABA. This concentration of GABA was selected for several reasons. First, it is on the rising phase of the GABA concentration−response curve, allowing accurate assessment of enhancement without saturating maximum current. Second, with 10 μM, GABA desensitization was minimal and the GABAR current rundown was slow, thus reducing trial-to-trial variability of responses.

The magnitude of the enhancement or inhibition of the $GABA_A$ receptor current by compound **1** was measured by dividing the peak amplitude of the $GABA_A$ receptor current elicited in the presence of a given concentration of the drug and GABA by the peak amplitude of control current elicited by GABA alone and multiplying the fraction by 100 to express it as percent control (eq 2).

$$I = \frac{I_{max}}{1 + 10^{(\log_{EC50} - \log_{drug})(\text{Hill}\cdot\text{slope})}} \quad (2)$$

Thus the control response was 100%. Peak $GABA_A$ receptor currents at various concentrations of compound **1** were fitted to a sigmoidal function using a four-parameter logistic equation with a variable slope. Equation 2 was used to fit the concentration−response relationship, where I is the GABAR current at a given GABA concentration and $I_{(max)}$ was the maximal GABAR current. Maximal current and concentration−response curves were obtained after pooling data from all neurons tested for GABA. Convergence was reached when two consecutive iterations changed the sum of squares by less than 0.01%. The curve fit was performed on an IBM PC compatible personal computer using a prism program (Graph Pad Software inc., San Diego, CA). All data were presented as mean ± standard error of the mean.

Acknowledgment. M.L.B. would like to thank J. Randall Moorman, M.D., Paul Lenkowski, Manoj Patel, Ph.D., Julianne Sando, Ph.D., Carl Lynch, M.D., Ph.D., Doug Bayliss, Ph.D., and James Stables for contributions to this study and the Jeffress Trust Fund and the UVA department of chemistry for financial support.

References

(1) Eger, E. I., II. Current and Future Perspectives on Inhaled Anesthetics. *Pharmacotherapy* **1998**, *18*, 895−910.
(2) Katz, Y. Anesthesia and the Meyer-Overton Rule II. A Solution Theory View of Anesthesia and Perturbations. *J. Theor. Biol.* **1994**, *167*, 99−105.
(3) Franks, N. P.; Lieb, W. R. Do General Anesthetics Act by Competitive Binding to Specific Receptors? *Nature* **1984**, *310*, 599−601.
(4) Franks, N. P.; Lieb, W. R. Stereospecific Effects of Inhalational General Anesthetic Optical Isomers on Nerve Ion Channels. *Science* **1991**, *25*, 427−430.
(5) Sanna, E.; Motzo, C.; Usala, M.; Serra, M.; Dazzi, L.; Maciocco, E.; Trapani, G.; Latrofa A.; Liso, G.; Biggio, G. Characterization of the Electrophysiological and Pharmacological Effects of 4-iodo-2,6-diisopropylphenol, a Propofol Analogue Devoid of Sedative-Anaesthetic Properties. *Br. J. Pharmacol.* **1999**, *126*, 1444−1454.
(6) Dickinson, R.; White, I.; Lieb, W. R.; Franks, N. P. Stereoselective Loss of Righting Reflex in Rats by Isoflurane. *Anesthesiology* **2000**, *93*, 837−843.
(7) Aboul-Enein, H. Y.; Bojarski, J.; Szymura-Oleksiak, J. The Impact of Chirality of the Fluorinated Volatile Inhalation Anaesthetics on Their Clinical Applications. *Biomed. Chromatogr.* **2000**, *14*, 213−218.
(8) Sidebotham, D. A.; Schug, S. A. Stereochemistry in Anaesthesia. *Clin. Exp. Pharmacol. Physiol.* **1997**, *24*, 126−130.
(9) Hirota, K.; Roth, S. H. Sevoflurane Modulates Both GABAA and GABAB Receptors in Area CA1 of Rat Hippocampus. *Br. J. Anaesth.* **1997**, *78*, 60−65.
(10) Hirota, K.; Roth, S. H.; Fujimura, J.; Masuda, A.; Ito, Y. GABAergic Mechanisms in the Action of General Anesthetics. *Toxicol. Lett.* **1998**, *100−101*, 203−207.
(11) Violet, J. M.; Downie, D. L.; Nakisa, R. C.; Lieb, W. R.; Franks, N. P. Differential Sensitivities of Mammalian Neuronal and Muscle Nicotinic Acetylcholine Receptors to General Anesthetics. *Anesthesiology* **1997**, *86*, 866−874.
(12) Study, R. E. Isoflurane Inhibits Multiple Voltage-Gated Calcium Currents in Hippocampal Pyramidal Neurons. *Anesthesiology* **1994**, *81*, 104−116.

(13) Drenger, B.; Heitmiller, E. S.; Quigg, M.; Blanck, T. J. Depression of Calcium Channel Blocker Binding to Rat Brain Membranes by Halothane. *Anesth. Analg.* **1992**, *74*, 758−761.
(14) Kohro, S.; Hogan, Q. H.; Nakae, Y.; Yamakage, M.; Bosnjak, Z. Anesthetic Effects on Mitochondrial ATP-Sensitive K Channel. *J. Anesthesiology* **2001**, *95*, 1435−1440.
(15) Ratnakumari, L.; Hemmings, H. C., Jr. Effects of Propofol on Sodium Channel-Dependent Sodium Influx and Glutamate Release in Rat Cerebroccortical Synaptosomes. *Anesthesiology* **1997**, *86*, 428−439.
(16) Rehberg, B.; Duch, D. S. Suppression of Central Nervous System Sodium Channels by Propofol. *Anesthesiology* **1999**, *91*, 512−520.
(17) Ratnakumari, L.; Hemmings, H. C. Effects of Propofol on Sodium Channel-Dependent Sodium Influx and Glutamate Release in Rat Cerebroccortical Synaptosomes. *Anesthesiology* **1997**, *86*, 428−439.
(18) Frenkel, C.; Urban, B. W. Interactions of Intravenous Anesthetics with Human CNS Ion Channels. Electrophysiologic Studies with a New Type of Voltage Clamp Technique. *Anaesthesist* **1994**, *43*, 229−234.
(19) Frenkel, C.; Urban, B. W. Molecular Actions of Racemic Ketamine on Human CNS Sodium Channels. *Br. J. Anaesth.* **1992**, *69*, 292−297.
(20) Frenkel, C.; Urban, B. W. The Molecular Action Profile of Intravenous Anesthetics. *Anasthesiologie, Intensivmedizin, Notfallmedizin, Schmerztherapie* **1992**, *27*, 101−108.
(21) Berthoud, M. C.; Reilly, C. S. Adverse Effects of General Anaesthetics. *Drug Safety* **1992**, *7*, 434−459.
(22) Hirota, K.; Masuda, A.; Ito, Y. Volatile Anesthetics Reduce Calcium Current in Parasympathetic Neurons from Bullfrog Hearts. *Anesth. Analg.* **1999**, *89*, 225−229.
(23) Tanaka, G.; Okeda, R. *N*-[4-(3-ethoxy-2-hydropropoxy)phenyl] Acrylamide Selectively Induces Apoptosis of Cerebellar Granule Cells in Vivo and in Vitro in Rats. *Acta Neuropathol.* **2000**, *99*, 337−344.
(24) Calleman, C. J. The Metabolism and Pharmacokinetics of Acrylamide: Implications for Mechanisms of Toxicity and Human Risk Estimation. *Drug Metab. Rev.* **1996**, *28*, 527−590.
(25) Kamitori, Y.; Hojo, M.; Masuda, R.; Ohara, S.; Kawamura, Y.; Ebisu, T. Convenient Synthesis of 1,1,1-Trifluoro-4,5-diaza-2,4-alkadienes and 1-Aryl-3,3,3-trifluoro-1-propanones. *Synthesis* **1989**, 43−45.
(26) Wagner, L. E., II; Gingrich, K. J.; Kulli, J. C.; Yang, J. Ketamine Blockade of Voltage-Gated Sodium Channels: Evidence for a Shared Receptor Site with Local Anesthetics. *J. Anesthesiology* **2001**, *95*, 1406−1413.
(27) Brown, M. L.; Van Dyke, C. C.; Brown, G. B.; Brouillette, W. J. Comparative Molecular Field Analysis of Hydantoin Binding to the Neuronal Voltage-Dependent Sodium Channel. *J. Med. Chem.* **1999**, *42*, 1537−1545.
(28) Tang, P.; Yan, B.; Xu, Y. Different Distribution of Fluorinated Anesthetics and Nonanesthetics in Model Membrane: A ^{19}F NMR Study. *Biophys. J.* **1997**, *72*, 1676−1682.
(29) Modica, P. A.; Tempelhoff, R.; White, P. F. Pro- and Anticonvulsant Effects of Anesthetics (Part II). *Anesth. Analg.* **1990**, *70*, 433−444.
(30) Soloshonok, V. A.; Gerus, I. I.; Yagupol'skii, Y. L.; Kukhar, V. P. a-Trifluoromethyl-a-hydroxy Carboxylic Acids. *J. Org. Chem. USSR (Engl. Trans)* **1987**, *23*, 1298−1303.
(31) Mioskowski, C.; Solladie, G. Purete Enantiomerique Et Configuration Absolue De L′acide β-Hydroxy β-Trifluoromethyl β-Phenyl Propionique Obtenu Par Synthese Asymmetrique. *Tetrahedron* **1973**, *29*, 3669−3672.
(32) Bhattacharjee, A.; Chattopadhyay, P.; Kundu, A. P.; Mukhopadhyay, R.; Bhattacharjya, A. A Simple Procedure For O-Allylation of Carbohydrate Derivatives Using Phase-Transfer Catalyst. *Indian J. Chem., Sect. B* **1996**, *35*, 69−70.
(33) Eger, E. I.; Saidman, L. J. Minimum Alveolar Anesthetic Concentration: A Standard of Anesthetic Potency. *Anesthesiology* **1965**, *26*, 756−763.
(34) Pajewski, T. N.; DiFazio, C. A. Nitrict Oxide Synthase Inhibitors, 7-Nitro Indazole and Nitro sup G-L-Arginine Methyl Ester, Dose Dependently Reduce the Threshold for Isoflurane Anesthesia. *Anesthesiology* **1996**, *85*, 1111−1119.

JM020546R