# Synthesis of Tropeines and Allosteric Modulation of Ionotropic Glycine Receptors

Gábor Maksay,*,† Péter Nemes,‡ and Tímea Bíró†

*Molecular Pharmacology Group, Institute of Biomolecular Chemistry, Chemical Research Center, Hungarian Academy of Sciences, H-1525, Budapest, Post Office Box 17, Hungary, and Department of Chemistry, Faculty of Veterinary Sciences, Szent István University, H-1400, Budapest, Post Office Box 2, Hungary*

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Twenty esters of 3α- and 3$\beta$-hydroxy(nor)tropanes and two amides of 3α-aminotropane were prepared with substituted benzoic acids. These (nor)tropeines inhibited [$^3$H]strychnine binding to glycine receptors in synaptosomal membranes of rat spinal cord. A ternary allosteric model was applied to determine the dissociation constants ($K_A$) of the tropeines having strong negative cooperativities with [$^3$H]strychnine binding ($\alpha > 10$). $K_A$ values about 10 nM are well below those of known allosteric agents. Low concentrations ($0.1K_A$) of the (nor)tropeines potentiated the displacing effects of glycine. Positive cooperativity with glycine ($\beta < 1$) decreased with the increase in concentration and binding affinity of tropeines. Displacing potencies were also measured for [$^3$H]granisetron binding to 5-HT$_3$ type serotonin receptors of rat cerebral cortex. Selectivities to glycine receptors versus 5-HT$_3$ receptors varied within 4 orders of magnitude. Nortropeines might serve as a lead to high-affinity selective allosteric modulators of glycine receptors.

## Introduction

Glycine is the major inhibitory neurotransmitter in mammalian spinal cord acting via ionotropic glycine receptors (GlyRs). Pentamers of $\alpha_{1-4}$ and $\beta$ GlyR subunits form chloride channels. Glycinergic neurotransmission plays predominant roles in muscle tone regulation and in the processing of sensory signals.[1] Since allosteric modulation is most suitable for the therapeutical fine-tuning of neurotransmitter receptors, positive modulators of GlyRs might exert beneficial muscle relaxant, anticonvulsant, analgesic, or anesthetic effects.[2] Still, GlyRs are referred to as "therapeutic orphans",[3] having no high-affinity allosteric modulators. Although GlyRs are modulated by $Zn^{2+}$,[4] alcohols,[5] and tropeines (esters of 3α-hydroxytropane and amides of 3α-aminotropane),[6] these agents act on other ionotropic receptors as well. Overlapping affinities to ionotropic receptors can be partly attributed to the structural similarities within the superfamily of GlyRs, nicotinic acetylcholine, 5-HT$_3$-type serotonin, and GABA$_A$ receptors. Thus it is a challenge to medicinal chemists to get high affinity and selective allosteric modulators of GlyRs. As to high-affinity agents, some tropeines potentiate GlyR activity in nanomolar concentrations, while they inhibit it in micromolar concentrations.[6] As to selectivity, subunit-specific modulation of GlyRs by some tropeines[7,8] and neurosteroids[9] has been promising. Inhibitory potencies of the tropeines (tropisetron and atropine) versus glycine activation of recombinant GlyRs vary for different $\alpha_{1-2}(\beta)$ subunits and $\alpha_1$ mutants by 4 orders of magnitude.[7] In subunit selectivity the $\beta$ subunit plays a critical role in the potentiation of GlyR ionophore function by tropisetron.[8] So tropeines seem to be a promising lead to develop high-affinity and subunit-selective allosteric agents of GlyRs. In vitro receptor assays can facilitate the development of such agents. GlyR binding[10] of the competitive antagonist [$^3$H]strychnine and chloride ionophore activity[11] can differentiate the structure−activity requirements of "Gly positive" and "Gly negative" agents with positive and negative cooperativity with glycine, respectively. "Gly positive" tropeines exert high-affinity (nanomolar) displacement of [$^3$H]strychnine binding potentiated by glycine.[10] We have recently applied a ternary allosteric model for the quantitative characterization of binding affinities and cooperativities for GlyRs.[12] This model permits the simultaneous binding of an allosteric agent and an orthosteric ligand, [$^3$H]strychnine or glycine. Here, we describe some nortropeines with binding affinities exceeding those of known potentiating agents of GlyRs by 1−2 orders of magnitude while they have lower activities on 5-HT$_3$ receptors.

## Synthesis

Tropane alkaloids occur as esters of relatively simple carboxylic acids and tropine, $\psi$-tropine, or nortropine. Due to their biological activity and pharmacological significance, they have been subject to intensive stereochemical and synthetic investigations. In this paper we describe the synthesis of substituted benzoates of tropine, $\psi$-tropine, and nor derivatives of some tropeines. The esters of tropine and $\psi$-tropine with substituted benzoic acids can be prepared in simple acylation processes,[13,14] which can be carried out in different solvents such as toluene, chloroform, dioxane, or pyridine. Acylation of tropine is more difficult because of the sterically hindered hydroxyl group and results in lower yields than the ester formation of $\psi$-tropine. In our synthesis we used the corresponding substituted benzoyl chlorides, which were added to a toluene solu-

* Corresponding author: phone (361) 325-7900/282; fax (361) 325-7554; e-mail maksay@chemres.hu.
† Chemical Research Center.
‡ Szent István University.

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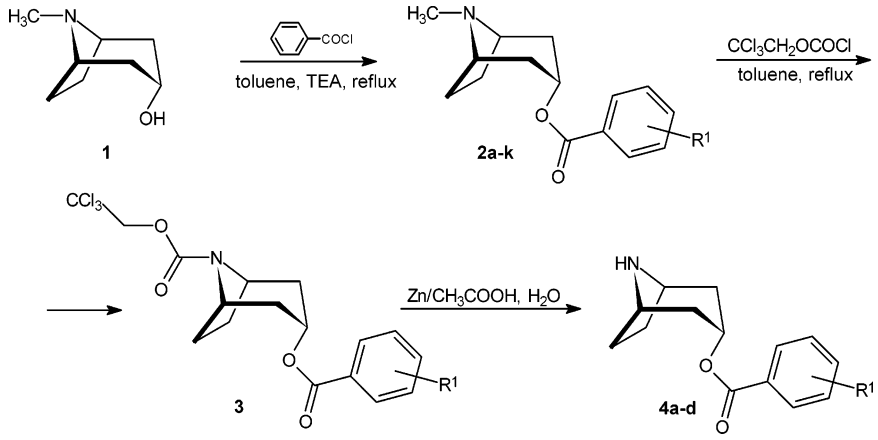
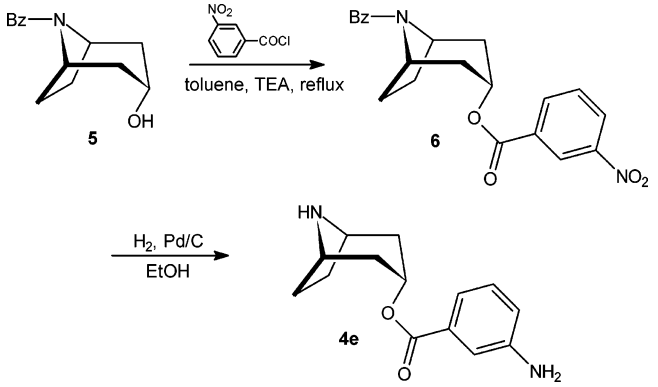
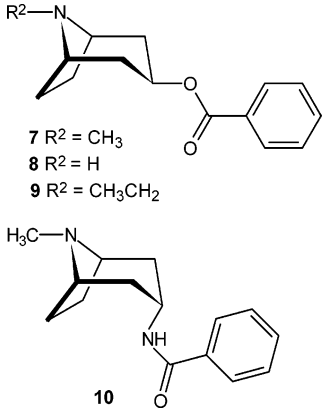
**Scheme 1**




**Scheme 2**




**Scheme 3**




tion of tropine in the presence of TEA. Several methods are known for the demethylation of tropane derivatives.[15,16] By use of ethyl chloroformate, demethylation takes place readily under the formation of methyl chloride and *N*-ethoxycarbonyl derivatives. However, the removal of the ethoxycarbonyl group requires vigorous reaction conditions. Therefore the use of 2,2,2-trichloroethyl chloroformate is much more appropriate for the demethylation of tropeine.[16] The removal of the trichloroethoxycarbonyl group can be achieved with zinc in acetic acid solution (Scheme 1). The procedure does not affect the ester group, and nortropeines can be obtained in good yield.

Since 3α-(3′-nitrobenzoyloxy)tropane did not undergo demethylation with 2,2,2-trichloroethyl chloroformate under the usual conditions, a different synthetic route was elaborated to obtain 3α-(3′-aminobenzoyloxy)nortropane (**4e**). *N*-Benzylnortropinone was prepared from benzylamine, acetonedicarboxylic acid, and succinic aldehyde following the classical Robinson−Schöpf biomimetic route.[17] The ketone was then hydrogenated stereoselectively in the presence of Raney-Ni catalyst under pressure, producing *N*-benzylnortropine (**5**).[18] Acylation of **5** gave the 3-nitrobenzoyl derivative **6**, which was subjected to repeated hydrogenation at ambient temperature, resulting in debenzylation and reduction of the nitro group simultaneously to yield directly **4e** under mild conditions (Scheme 2). 3β-Benzoyloxynortropane (**8**) was alkylated with ethyl bromide at room temperature to yield *N*-ethyl-3β-benzoyloxynortropane (**9**). 3α-Aminotropane was prepared from tropinone in a palladium-catalyzed one-pot stereoselective synthesis with ammonium formate as nitrogen and hydrogen source.[19] Acylation with benzoyl chloride was carried out at room temperature to result in the amide **10** in high yield[20] (Scheme 3).

## Receptor Binding

**Modulation of GlyRs.** The concentration-dependent displacing effects of the tropeines were examined on [$^3$H]-strychnine binding to GlyRs of rat spinal cord. All tropeines exerted great maximal displacements of specific [$^3$H]strychnine binding but possessed different potencies. This is illustrated in Figure 1 with three representative tropeines. According to the ternary allosteric model and eq 2, they have strong negative

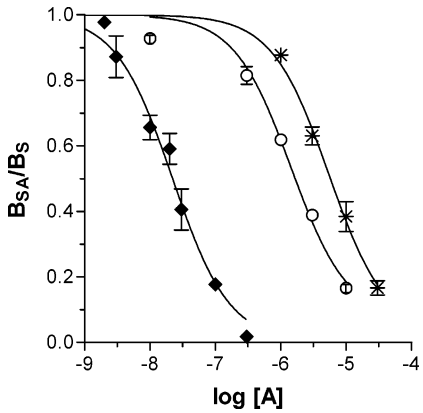



**Figure 1.** Displacement of [$^3$H]strychnine binding by three representative tropeines: **4d** (◆), **8** (○), and **2b** (∗). Points are mean ± SEM of 3−4 experiments. Curve fitting according to eq 2 resulted in $K_A$ and α values in Table 1.

**Table 1.** Binding Constants of (nor)Tropeines As Determined for [$^3$H]Strychnine Binding to GlyRs of Rat Spinal Cord and Displacing Potencies for [$^3$H]Granisetron Binding to 5-HT$_3$ Serotonin Receptors of Rat Cerebral Cortex

| | GlyR | | 5-HT$_3$R[a] | | |
|---|---|---|---|---|---|
| tropeines | -log $K_A$[b] | $\beta$[c] | $-\log IC_{50}$ | $n_H$ | selectivity, $IC_{50}/K_A$ |
| 3α-benzoyloxytropane (**2a**) | 6.387 ± 0.022 | 0.49 ± 0.09 | 6.525 ± 0.105 | 0.57 ± 0.09 | 0.78 |
| 3$\beta$-benzoyloxytropane (**7**) | 5.770 ± 0.037 | 0.57 ± 0.05 | 6.302 ± 0.047 | 0.88 ± 0.10 | 0.30 |
| 3α-(4′-ethylbenzoyloxy)tropane (**2b**) | 5.337 ± 0.063 | 0.15 ± 0.02 | 6.739 ± 0.083 | 1.05 ± 0.09 | 0.04 |
| 3α-(4′-nitrobenzoyloxy)tropane (**2c**) | 5.292 ± 0.055 | 0.20 ± 0.03 | 5.978 ± 0.018 | 1.07 ± 0.12 | 0.20 |
| 3α-(4′-*t*-butylbenzoyloxy)tropane (**2d**) | 4.532 ± 0.046 | 0.13 ± 0.02 | | | |
| 3α-(3′-methoxybenzoyloxy)tropane(**2e**) | 7.081 ± 0.056 | 0.27 ± 0.04 | 7.149 ± 0.032 | 1.26 ± 0.03 | 0.87 |
| 3α-(3′-chlorobenzoyloxy)tropane (**2f**) | 6.310 ± 0.057 | 0.12 ± 0.01 | 7.168 ± 0.102 | 1.05 ± 0.21 | 0.15 |
| 3α-(3′-nitrobenzoyloxy)tropane (**2g**) | 5.845 ± 0.041 | 0.20 ± 0.07 | | | |
| 3α-[3′-(trifluoromethyl)benzoyloxy]tropane (**2h**) | 5.824 ± 0.046 | 0.12 ± 0.01 | | | |
| 3α-(3′,4′,5′-trimethoxybenzoyloxy)tropane (**2i**) | 5.975 ± 0.034 | 0.09 ± 0.01 | 6.637 ± 0.086 | 0.95 ± 0.13 | 0.23 |
| 3α-(3′,5′-dichlorobenzoyloxy)tropane (bemesetron) (**2j**) | 5.991 ± 0.065[d] | 0.06 ± 0.004[d] | | | |
| 3$\beta$-benzoyloxynortropane (**8**) | 5.959 ± 0.068 | 4.3 ± 0.4 | 5.998 ± 0.119 | 1.00 ± 0.17 | 0.98 |
| 3α-benzoyloxynortropane (**4a**) | 7.983 ± 0.039 | 0.30 ± 0.04 | 5.806 ± 0.086 | 1.03 ± 0.23 | 161.1 |
| 3α-(3′-methoxybenzoyloxy)nortropane (**4b**) | 8.114 ± 0.035 | 0.39 ± 0.07 | 6.581 ± 0.063 | 0.90 ± 0.10 | 33.5 |
| 3α-(3′-chlorobenzoyloxy)nortropane (**4c**) | 7.646 ± 0.080 | 0.23 ± 0.02 | 6.160 ± 0.090 | 1.17 ± 0.18 | 33.7 |
| 3α-(3′-aminobenzoyloxy)nortropane (**4e**) | 7.233 ± 0.044 | 1.4 ± 0.4 | 6.239 ± 0.099 | 0.91 ± 0.02 | 10.3 |
| 3α-(2′,3′-benzofuran-5′,5′-dimethyl-8′-chloro-6′-carbonyloxo)tropane (**2k**) | 6.633 ± 0.142 | 0.06 ± 0.01 | 8.144 ± 0.148 | 0.87 ± 0.13 | 0.03 |
| 3α-(2′,3′-benzofuran-5′,5′-dimethyl-8′-chloro-6′-carbonyloxo)nortropane (**4d**) | 7.742 ± 0.106 | 0.13 ± 0.02 | 7.250 ± 0.127 | 0.90 ± 0.10 | 3.37 |
| 3$\beta$-*N*-ethylbenzoyloxynortropane (**9**) | 6.137 ± 0.064 | 0.55 ± 0.08 | 6.145 ± 0.025 | 1.01 ± 0.10 | 0.98 |
| 3α-benzoylamidotropane (**10**) | 4.796 ± 0.052 | 0.22 ± 0.03 | | | |
| 3α-(2′,3′-benzofuran-5′,5′-dimethyl-8′-chloro-6′-carbonylamido)tropane (zatosetron) | 6.569 ± 0.089[d] | | | | |

[a] Displacement curves were fitted with variable slopes ($n_H$). Data are mean ± SEM of 3−6 experiments. [b] $K_A$ values were determined with eq 2. [c] Tropeines were applied at a concentration of 0.1$K_A$ with different glycine concentrations for the determination of $\beta$ with eq 1. The values of α are ≫10 for all compounds except for **2d**, **2g**, and **8** with α = 14 ± 2, α = 14 ± 7, and α = 18 ± 9, respectively. [d] Taken from Maksay and Bíró.[12]

cooperativity with strychnine binding (α > 10). This is shown in Figure 1 for **4d** with maximal displacement approaching nonspecific [$^3$H]strychnine binding. Table 1 summarizes the dissociation constants of the tropeines with $K_A$ values between 8 nM and 30 $\mu$M. For most compounds the allosteric (eq 2) and competitive (eq 3) binding models result in identical $K_A$ values, with the exception of three tropeines with α < 20 (Table 1).

We concentrated on 3α-esters since (1) C3 showed marked stereoselectivity, that is, 100 times preference for 3α in **4a** over 3$\beta$ in **8**, and (2) the ester **2a** was about 30 times more potent than its amide analogue **10**. Ring substituents in the para position decreased the affinities parallel with size regardless of their electronic properties. Some substituents, for example, *m*-methoxy, were advantageous in **2e** and **4b**; most others were disadvantageous. Nortropeines exerted highest potency, as shown by the 40 times potency of N-demethylated **4a** over N-methylated **2a**.

The concentration-dependent displacement of [$^3$H]-strychnine binding by glycine was also examined because we have found this as an optimal test to evaluate the cooperativity with glycine ($\beta$).[11] Figure 2 shows the concentration-dependent positive cooperative effects of bemesetron **2j** with $\beta$ < 1. This is an extension of our previous analysis of the effect of **2j**. With increasing concentrations of "Gly positive" agents such as **2j**, potentiation turns into inhibition of GlyRs. This is accompanied with decreasing positive cooperativity with glycine and increasing $\beta$ values as shown for **2j** in Figure 3. Compound **2k**, an ester analogue of zatosetron with high (nanomolar) affinity, also shifted the displacement curve of glycine to indicate positive cooperativity (Figure 4). Even lower (2 nM and 20 nM) concentrations of its nor derivative **4d** displayed positive cooperativity with glycine ($\beta$ < 1, Figure 3). Since cooperativity with

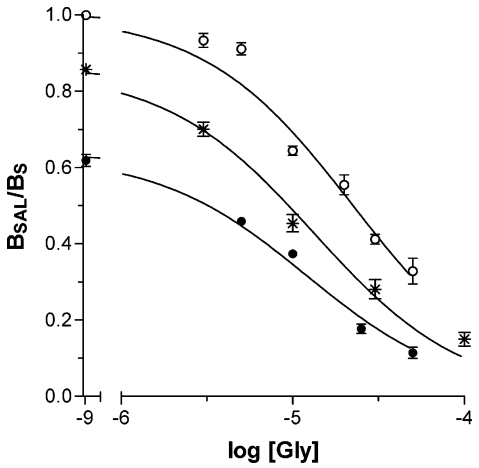



**Figure 2.** Displacement of [$^3$H]strychnine binding by glycine (control, ○) and the effects of 0.1 $\mu$M (∗) and 0.3 $\mu$M (●) **2j**. Points are mean ± SEM of 3−5 experiments. The data set for 0.1 $\mu$M **2j** is taken from Maksay and Bíró[12] and was determined under identical conditions. Curve fitting to control via eq 1 resulted in $K_L$ = 20.1 ± 1.0 $\mu$M glycine; for 0.3 $\mu$M **2j**, α ≫ 10 and $K_A$ = 0.4 $\mu$M. The $\beta$ values are shown in Figure 3. Control data (without glycine) are indicated on the abscissa at −9.

glycine ($\beta$) depended on the concentration of the allosteric agents, we compared the $\beta$ values at low identical occupancies by the tropeines (0.1$K_A$). Table 1 summarizes the $\beta$ values calculated with concentrations at 0.1$K_A$. Most tropeines have positive cooperativities with glycine ($\beta$ < 1). The 3$\beta$ nortropeine **8** not only has 40 times less affinity than 3α **4a** but also its cooperativity with glycine becomes negative (Table 1). The cooperativity of some nortropeines such as **4e** is about neutral (Table 1). Figure 5 shows a logarithmic plot of the affinities of (nor)tropeines ($K_A$) and cooperativities with glycine ($\beta$). It can be observed for some structural groups

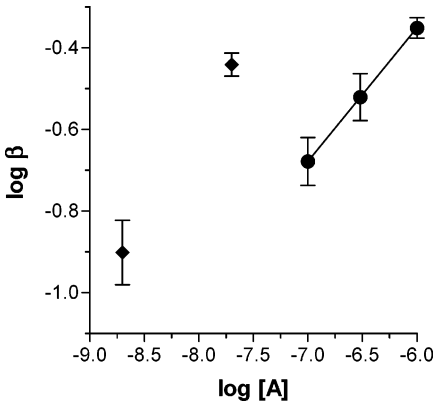



**Figure 3.** Concentration-dependent effects of **2j** (●) and **4d** (◆) on their positive cooperativities ($\beta$) with glycine.

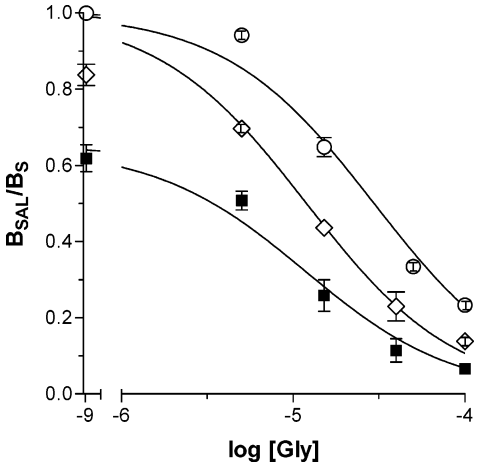



**Figure 4.** Displacement of [$^3$H]strychnine binding by glycine (control, ○) and the effects of 23 nM (◇) and 230 nM (■) **2k**. Points are mean ± SEM of 3−4 experiments. Curve fitting to control via eq 1 resulted in $K_L = 24.5 \pm 1.6$ $\mu$M glycine; for 23 nM **2k**, $\beta = 0.08 \pm 0.01$; for 230 nM **2k**, $\alpha = 5.8 \pm 2.4$ and $\beta = 0.26 \pm 0.06$. The effect of 23 nM **2k** without glycine was excluded from the fitting because of its high affinity displacing effect, and $\alpha \equiv 1$ was applied. Control data (without glycine) are indicated on the abscissa at −9.

that a decrease in binding affinity is accompanied with stronger positive cooperativity. The subset of para-substituted benzoate esters is replotted on the inset of Figure 5 and labeled with the para-substituents. Para-substitution of **2a** (with H) up to *tert*-butyl (**2d**) decreased the binding affinity but increased the cooperativity with glycine. This correlation ($r^2 = 0.88$) can be probably attributed mainly to steric effects because ethyl and nitro derivatives (**2b** and **2c**) have similar sizes and different electronic properties yet overlapping activities (Figure 5, inset).

**5-HT$_3$ Receptor Activity.** The displacing effects of selected (nor)tropeines were measured on [$^3$H]granisetron binding to 5-HT$_3$ type serotonin receptors of rat cerebral cortex. Table 1 summarizes the displacing potencies ($IC_{50}$). The slope factors $n_H$ of most tropeines were close to unity, supporting the view that the compounds are competitive antagonists of 5-HT$_3$ receptors. The selectivity ratios $IC_{50}/K_A$ vary by 4 orders of magnitude, demonstrating different structure−activity requirements for GlyRs versus 5-HT$_3$ receptors. N-Demethylation of **2a** leads to the greatest preference for GlyRs with a selectivity ratio of 161 for **4a**. All nortropeines have selectivity ratios beyond 10 and might thus serve as a promising lead toward selective allosteric modulators of GlyRs.

## Discussion

Allosteric interactions with glycine for [$^3$H]strychnine binding have been shown to correlate with the modulation of GlyR function.[10] This correlation between GlyR binding and function has been confirmed for various allosteric agents of known structures.[10−12] The ternary allosteric model enables us to describe structure−activity relationships for GlyR binding in a quantitative manner.[12] We have applied now this model for the development of new GlyR-selective allosteric modulators with tropeine structures. Most "Gly positive" allosteric agents such as tropeines exert biphasic effects on GlyRs. Potentiation at low concentrations is followed by inhibition at high (micromolar) concentrations of the tropeines.[11] This is manifested in a concentration-dependent shift in $\beta$ from positive to negative cooperativity with glycine binding. Therefore we measured this functionally most relevant parameter ($\beta$) at low identical occupancies ($0.1K_A$) of GlyRs. Allosteric potentiation of the chloride ionophore function of GlyRs also requires low occupancy by glycine.[8] Accordingly, some of these nortropeines potentiated the effects of low glycine

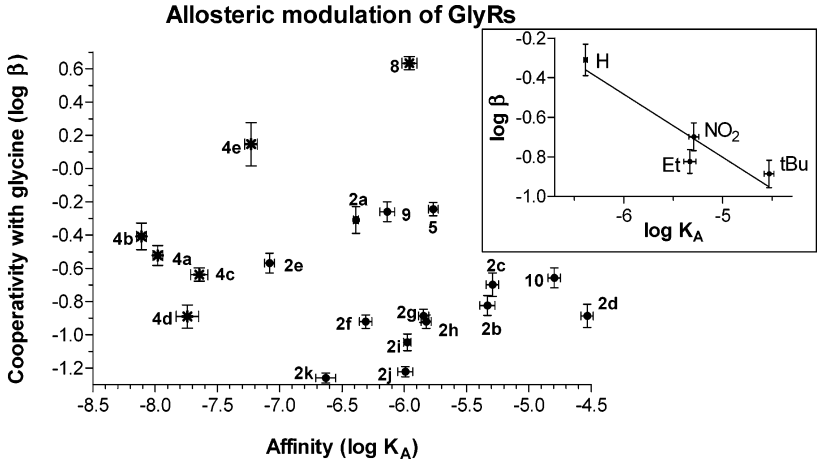



**Figure 5.** Correlation between the dissociation constants ($K_A$) of tropeines (●) and nortropeines (∗) and the extent of cooperativity ($\beta$) with glycine. (Inset) Subset of para-substituted 3α-benzoyloxytropane derivatives labeled with their moieties and the parent compound **2a** (H) show linear correlation ($r^2 = 0.88$).

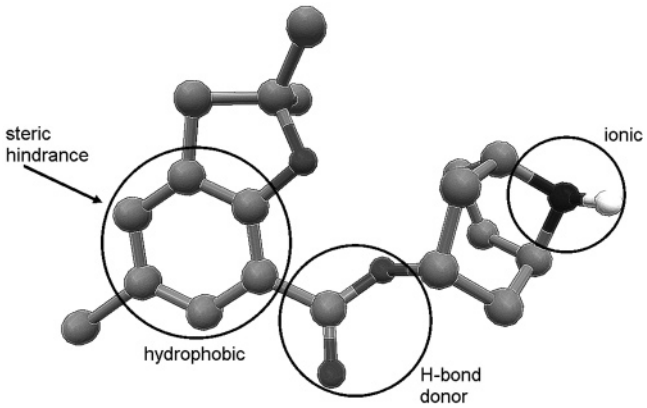



**Figure 6.** Pharmacophore model of tropeine binding to GlyRs: stick and ball representation of **4d** as a template. Circles indicate essential structural elements. The basic nitrogen may form an elecrostatic interaction, the carbonyloxy moiety accepts an H-bond, and the aromatic ring interacts with a hydrophobic region. Substituents are tolerated in the meta position, while para substituents create steric hindrance.

concentrations on recombinant human GlyRs (G. Maksay, unpublished results). Most (nor)tropeines have positive cooperativity with glycine ($\beta < 1$) and they possess most different binding affinities ($K_A$). However, the greatest affinities of the tropeines are accompanied by minor positive cooperativities with glycine.

Apparently full maximal displacement of specific [$^3$H]-strychnine binding by high concentrations of most tropeines can also be reconciled with apparently competitive interactions. Accordingly, eqs 2 and 3 resulted in identical $K_A$ values for tropeines with $\alpha \gg 10$. This means that strong negative cooperativity ($\alpha \gg 10$) between the tropeines and [$^3$H]strychnine binding cannot be distinguished from apparently competitive displacement. At high concentrations the tropeines compete apparently also with glycine bound in the same cavity as strychnine. Accordingly, atropine, a "Gly negative" agent, resulted in a parallel rightward shift of the chloride response curve of glycine for recombinant GlyRs.[7] With increasing concentrations even "Gly positive" tropeines become "Gly negative" in accordance with increasing $\beta$ values in the present binding assays. In conclusion, while high concentrations of the tropeines might apparently compete at the orthosteric binding site of GlyRs, low concentrations of "Gly positive" agents allosterically potentiate the binding and function of glycine.

A consensus structure of "Gly positive" tropeines has emerged from the structure−activity analysis of a limited number of well-known tropeines.[10] This highlights the importance of aromatic and tropane rings, linked via an ester or amide moiety.[10] The present data lead to the development of a pharmacophore model of tropeine binding to GlyRs, similar to those of 5-HT$_3$ receptor antagonists.[21] This is illustrated by Figure 6 showing **4d** as a template. The pharmacophore is composed of (a) an aromatic ring harbored by a lipophilic region of the binding site, (b) an attached ester group fixed via hydrogen bonds, and (c) a basic nitrogen of the tropane ring interacting electrostatically with the receptor. These three attachments form a triangle. Distortion of this triangle leads to serious deterioration of binding affinity (potency) and/or positive cooperativity (efficacy). The most striking example is the 3$\beta$-oriented nortropeine **8** with 40 times less affinity and opposite cooperativity in comparison to 3α **4a**. The hydrophobic interaction of the phenyl ring seems to be of low specificity because of its low sensitivity to the electronic properties of its para substituents. The phenyl ring seems to fit in a hydrophobic region sterically restricted toward the para position. The ester group might be close to a hydrogen-bond donor as suggested by the 30 times lower affinity of the amide analogue **10**. The tropane ring has structurally most distinctive interactions. It has been shown that its substitutions or replacement strongly decrease the binding affinity and/or positive cooperativity with glycine (efficacy).[10] Moreover, demethylation of the basic nitrogen leads to much more potent nortropeines. This is a feature distinctive from the pharmacophore models of 5-HT$_3$ receptor antagonists, where demethylation results in loss of activity.[21] Consequently, distinct structure−activity requirements of the pharmacophores of the (nor)tropeine modulators of GlyRs versus 5-HT$_3$ receptor antagonists lead to selectivity differences of 4 orders of magnitude between the two receptors. This is promising for the development of GlyR-selective allosteric agents.

## Experimental Section

**Chemistry.** The structures of the final products as free bases were confirmed by $^1$H and $^{13}$C NMR. Spectra were recorded on a Bruker Avance 250 (250 MHz) spectrometer, in $CDCl_3$ solutions. Chemical shifts ($\delta$) are expressed in parts per million (ppm) relative to the internal standard tetramethylsilane (TMS). Infrared spectra were obtained on a Perkin-Elmer 1605 FT-IR spectrometer. The purity of the compounds was controlled with microanalyses, which were carried out on a Heraeus Micro Rapid CHN. Melting points were determined on a Büchi SMP 20 apparatus.

Compounds **2a**−**d**, **2i**, **2j**, **4a**, **7**, **8**, and **9** are described in the literature,[14,22−27] while **2e**−**g**, **2h**, **2k**, **4b**−**e,** and **10** are new. 5-Chloro-2,3-dihydro-2,2-dimethylbenzofuran-7-carboxylic acid was synthesized according to a previously described procedure.[20]

**General Procedures: Acylation of Tropine.** Tropine (0.01 mol) and 0.011 mol of TEA were dissolved in 15 mL of toluene, and 0.011 mol of acyl chloride was added dropwise, at reflux temperature. The solution was then boiled for 3 h, cooled, and extracted with saturated $NaHCO_3$ solution. The organic phase was separated, dried with $Na_2SO_4$, and evaporated at reduced pressure. The oily residue was crystallized from appropriate solvent, or it was converted into the hydrochloride salt in acetone with ethereal HCl solution. Yield: 40−55%.

**Demethylation of Tropeines.** Tropeine (0.005 mol) was dissolved in 10 mL of toluene, and a catalytic amount of $K_2CO_3$ was added. The solution was boiled and 0.0075 mol of trichloroethyl chloroformate in 5 mL of toluene was added dropwise in 20 min while stirring. The mixture was refluxed for additional 2 h, cooled, and extracted twice with 10% acetic acid solution. The organic phase was separated, dried over $Na_2SO_4$, and evaporated. The oily material was crystallized from diisopropyl ether and used without further purification. Yield: 70−80%.

**Removal of the Trichlorocarboethoxy Group.** *N*-(Trichlorocarboethoxy)nortropeine (0.0047 mol) dissolved in 47 mL of acetic acid was added dropwise to a suspension of 1.46 g (0.022 mol) of zinc dust at room temperature. After being stirred for 2 h, the mixture was cooled to 10 °C and was made alkaline by addition of 50 g of NaOH and 15 g of potassium−sodium tartarate dissolved in 300 mL of water. The solution was then saturated with $K_2CO_3$, and extracted three times with $CH_2Cl_2$. The organic phases were combined, and the

solution was dried and evaporated to give oily materials that could be either crystallized or converted into their hydrochloride salts. Yield: 50−61%.

**NMR Data of the New Compounds. 3α-Benzoyloxytropane (2a):** mp (hydrochloride) 248 °C; Anal. ($C_{15}H_{20}ClNO_2$) C, H, N; $^1$H NMR ($CDCl_3$), δ 7.90 (m, 2H), 7.31−7.60 (m, 3H), 5.33 (t, 1H), 3.82 (bs, 2H), 2.27 (s, 3H), 1.71−2.15 (m, 8H); $^{13}$C NMR δ 166.44 (C=O), 133.28, 131.61, 128.59, 128.42 (aromatics), 68.37 ($C_3$), 60.55 ($C_{1,5}$), 40.58 (N−$CH_3$) 37.33 ($C_{2,4}$), 26.23 ($C_{6,7}$).

**3α-(4′-Ethylbenzoyloxy)tropane (2b):** mp 56 °C; Anal. ($C_{17}H_{23}NO_2$) C, H, N; $^1$H NMR δ 7.92 (d, 2H), 7.24 (d, 2H), 5.22 (t, 1H), 3.11 (bs, 2H), 2.67 (q, 2H), 2.28 (s, 3H), 1.76−2.15 (m, 8H), 1.22 (t, 3H); $^{13}$C NMR, δ 166.24 (C=O), 149.99, 129.91, 128.60, 128.31 (aromatics), 68.16 ($C_3$), 60.18 ($C_{1,5}$), 40.85 (N−$CH_3$) 37.12 ($C_{2,4}$), 29,29 (4′-$CH_2$$CH_3$) 26.17 ($C_{6,7}$), 15.61 (4′-$CH_2$$CH_3$).

**3α-(4′-Nitrobenzoyloxy)tropane (2c):** mp 133 °C; Anal. ($C_{15}H_{18}N_2O_4$) C, H, N; $^1$H NMR δ 8.22 (d, 2H), 8.11 (d, 2H), 5.22 (t, 1H), 3.12 (br s, 2H), 2.24 (s, 3H), 1.76−2.18 (m, 8H); $^{13}$C NMR δ 164.25 (C=O), 150.73, 136.46, 130.81, 123.94 (aromatics), 69.78 ($C_3$), 59.98 ($C_{1,5}$), 40.76 (N−$CH_3$) 36.95 ($C_{2,4}$), 26.13 ($C_{6,7}$).

**3α-(4′-*t*-Butylbenzoyloxy)tropane (2d):** mp 79−80 °C; Anal. ($C_{19}H_{27}NO_2$) C, H, N; $^1$H NMR δ 7.89 (d, 2H), 7.40 (d, 2H), 5.18 (t, 1H), 3.08 (br s, 2H), 2.24 (s, 3H), 1.72−2.21 (mm, 8H), 1.27 (s, 9H); $^{13}$C NMR δ 166.20 (C=O), 156.83, 129.68, 128.60, 125.78 (aromatics), 68.11 ($C_3$), 60.23 ($C_{1,5}$), 40.86 (N−$CH_3$), 37.14 ($C_{2,4}$), 35.43 [4′-*C*($CH_3$)$_3$], 31.49 [4′-C(*C*$H_3$)$_3$], 26.18 ($C_{6,7}$).

**3α-(3′-Methoxybenzoyloxy)tropane (2e):** mp 113 °C; Anal. ($C_{16}H_{21}NO_3$) C, H, N; $^1$H NMR δ 7.61−7.69 (m, 3H), 7.40 (m, 1H), 5.33 (t, 1H), 3.94 (s, 3H), 3.25 (br s, 2H), 2.27 (s, 3H), 1.74−2.25 (m, 8H); $^{13}$C NMR δ 165.38 (C=O), 159.90, 131.21, 130.03, 121.64, 119.62, 114.59 (aromatics), 65.50 ($C_3$), 62.41 ($C_{1,5}$), 55.69 ($OCH_3$), 39.47 (N−$CH_3$), 34.85 ($C_{2,4}$), 24.75 ($C_{6,7}$).

**3α-(3′-Chlorobenzoyloxy)tropane (2f):** mp 71 °C; Anal. ($C_{15}H_{18}ClNO_2$) C, H, N; $^1$H NMR δ 7.90 (t, 1H), 7.82 (m, 1H), 7.45 (m, 1H), 7.32 (t, 1H), 5.17 (t, 1H), 3.11 (br s, 2H), 2.25 (s, 3H), 1.74−2.21 (m, 8H); $^{13}$C NMR δ 164.99 (C=O), 134.95, 133.23, 132.90, 130.14, 129.87, 127.84 (aromatics), 69.02 ($C_3$), 60.13 ($C_{1,5}$), 40.74 (N−$CH_3$), 36.94 ($C_{2,4}$), 26.15 ($C_{6,7}$).

**3α-(3′-Nitrobenzoyloxy)tropane (2g):** mp 204 °C; Anal. ($C_{15}H_{18}N_2O_4$) C, H, N; $^1$H NMR δ 8.74 (s, 1H), 8.34 (m, 2H), 7.55 (t, 1H) 5.24 (t, 1H), 3.16 (br s, 2H), 2.26 (s, 3H), 1.74−2.24 (mm, 8H); $^{13}$C NMR δ 164.35 (C=O), 148.72, 135.23, 132.92, 130.25, 12.90, 127.68 (aromatics), 69.90 ($C_3$), 58.90 ($C_{1,5}$), 40.65 (N−$CH_3$), 37.45 ($C_{2,4}$), 26.40 ($C_{6,7}$).

**3α-[3′-(Trifluoromethyl)benzoyloxy]tropane (2h):** mp 71 °C; Anal. ($C_{16}H_{18}F_3NO_2$) C, H, N; $^1$H NMR δ 8.21 (s, 1H), 8.13 (d, 1H), 7.74 (d, 1H), 7.53 (t, 1H), 5.22 (t, 1H), 3.12 (br s, 2H), 2.25 (s, 3H), 1.76−2.24 (m, 8H); $^{13}$C NMR δ (ppm) 164.86 (C=O), 132.86, 132.04 (aromatics), 131.6 (*C*-$CF_3$, q, $^2J_{C,F}$ = 81 Hz), 129.7, (q, $^3J_{C,F}$ = 3.6 Hz), 129.6 (aromatic), 126.7 (q, $^3J_{C,F}$ = 3.6 Hz), 124.05 ($CF_3$,q, $^1J_{C,F}$ = 275 Hz), 69.02 ($C_3$), 60.13 ($C_{1,5}$), 40.74 (N−$CH_3$), 36.94 ($C_{2,4}$), 26.15 ($C_{6,7}$).

**3α-(3′,4′,5′-Trimethoxybenzoyloxy)tropane (2i):** mp 116 °C; Anal. ($C_{18}H_{25}NO_5$) C, H, N; $^1$H NMR δ 7.24 (s, 2H), 5.17 (t, 1H), 3.84 (s, 9H), 3.10 (br s, 2H), 2.24 (s, 3H), 1.73−2.20 (m, 8H); $^{13}$C NMR δ 165.62 (C=O), 153.27, 142.35, 126.17, 107.12 (aromatics), 68.47 ($C_3$), 61.21 ($OCH_3$), 60.16 ($C_{1,5}$), 56.45 ($OCH_3$), 40.82 (N−$CH_3$), 37.04 ($C_{2,4}$), 26.06 ($C_{6,7}$).

**3α-(3′,5′-Dichlorobenzoyloxy)tropane (2j):** mp 165 °C; Anal. ($C_{15}H_{17}Cl_2NO_2$) C, H, N; $^1$H NMR δ 7.87 (s, 2H), 7.46 (s, 1H), 5.21 (t, 1H), 3.19 (br s, 2H), 2.27 (s, 3H), 1.75−2.22 (m, 8H); $^{13}$C NMR δ 164.88 (C=O), 135.14, 133.91, 133.32, 128.37 (aromatics), 69.25 ($C_3$), 60.23 ($C_{1,5}$), 40.94 (N−$CH_3$) 36.90 ($C_{2,4}$), 26.25 ($C_{6,7}$).

**3α-(2′,3′-Benzofuran-5′,5′-dimethyl-8′-chloro-6′-carbonyloxo)tropane (2k):** mp 141−142 °C; Anal. ($C_{19}H_{24}ClNO_3$) C, H, N; $^1$H NMR δ 7.65 (s, 1H), 7.28 (s, 1H), 5.22 (t, 1H), 3.95 (br s, 2H), 2.98 (s, 2H), 2.27 (s, 3H), 1.0−2.7 (m, 8H), 1.43 (s, 6H); $^{13}$C NMR δ 165.44 (C=O), 158.23, 132.36, 130.47, 129.81, 125.24, 113.65 (aromatics), 89.69 ($C_{2'}$−O), 66.18 ($C_3$), 60.25 ($C_{1,5}$), 42.33 ($C_{3'}$), 40.31 (N−$CH_3$), 33,95 ($C_{2,4}$), 28.53 (2$CH_3$), 26.09 ($C_{6,7}$).

**3α-Benzoyloxynortropane (4a):** mp 232 °C (hydrochloride); Anal. ($C_{14}H_{18}ClNO_2$) C, H, N; $^1$H NMR δ 9.28 (br s, 1H), 7.85 (m, 2H), 7.3−7.6 (m, 3H), 5.22 (t, 1H), 3.98 (br s, 2H), 2.48 (m, 2H), 1.97−2.14 (m, 6H); $^{13}$C NMR δ 165.27 (C=O), 133.20, 131.42, 128.98, 128.62 (aromatics), 67.28 ($C_3$), 55.02 ($C_{1,5}$), 34.22 ($C_{2,4}$), 26,62 ($C_{6,7}$).

**3α-(3′-Methoxybenzoyloxy)nortropane (4b):** mp 255 °C (hydrochloride); Anal. ($C_{15}H_{20}ClNO_3$) C, H, N; $^1$H NMR δ 9.22 (br s, 1H), 7.68 (m, 3H), 7.38 (m, 1H), 5.24 (t, 1H), 3.94 (s, 3H), 3.85 (br s, 2H), 1.70−2.26 (m, 8H); $^{13}$C NMR δ 164.98 (C=O), 159.66, 131.43, 130.51, 121.59, 119.60, 114.28 (aromatics), 66.37 ($C_3$), 55.66 ($C_{1,5}$), 53,23 ($OCH_3$), 33.34 ($C_{2,4}$), 26.12 ($C_{6,7}$).

**3α-(3′-Chlorobenzoyloxy)nortropane (4c):** mp 215 °C (hydrochloride); Anal. ($C_{14}H_{17}Cl_2NO_2$) C, H, N; $^1$H NMR δ 9.60 (br s, 1H), 7.85 (m, 2H), 7.71 (m, 1H), 7.58 (m, 1H), 5.16 (t, 1H), 3.97 (br s, 2H), 1.97−2.56 (m, 8H); $^{13}$C NMR δ 164.04 (C=O), 133.88, 133.59, 132.18, 128.91, 128.91, 128.04 (aromatics), 67.20 ($C_3$), 52.91 ($C_{1,5}$), 33.15 ($C_{2,4}$), 26.18 ($C_{6,7}$).

**3α-(2′,3′-Benzofuran-5′,5′-dimethyl-8′-chloro-6′-carbonyloxo)nortropane (4d):** mp 247 °C (hydrochloride); Anal. ($C_{18}H_{23}Cl_2NO_3$) C, H, N; $^1$H NMR δ 9.68 (br s, 1H), 7.63 (s, 1H), 7.21 (s, 1H), 5.33 (t, 1H), 4.05 (br s, 2H), 2.95 (s, 2H), 2.0−2.7 (m, 8H) 1.46 (s, 6H); $^{13}$C NMR δ (ppm) 164.37 (C=O), 158.15, 132.12, 130.37, 129.85, 125.03, 113.57 (aromatics), 89.64 ($C_{2'}$−O), 66.00 ($C_3$), 54.02 ($C_{1,5}$), 42.27 ($C_{3'}$), 34.05 ($C_{2,4}$), 28.51 (2$CH_3$), 26.38 ($C_{6,7}$).

***N*-Benzyl-(3′-nitrobenzoyloxy)nortropane (6).** The compound was prepared from *N*-benzylnortropine (**5**) and 3-nitrobenzoyl chloride according to the standard acylation procedure described above: mp 105 °C; Anal. ($C_{21}H_{22}N_2O_4$) C, H, N; $^1$H NMR δ 8.76 (s, 1H), 8.25−8.35 (m, 2H), 7.59 (t, 1H), 7.16−7.33 (m, 5H), 5.27 (t, 1H), 3.51 (s, 2H), 3.18 (br s, 2H), 1.75−2.26 (m, 8H); $^{13}$C NMR δ 164.18 (C=O), 148.74, 139.82, 135.42, 132.95, 130.14, 128.99, 128.68, 127.68, 127.37, 124.80 (aromatics), 70.58 ($C_3$), 58.19 ($C_{1,5}$), 57.13 (N−$CH_2$), 37.38 ($C_{2,4}$), 26.66 ($C_{6,7}$).

**3α-(3′-Aminobenzoyloxy)nortropane (4e).** Compound **6** (0.005 mol, 1.83 g) was hydrogenated in 20 mL of ethanol in the presence of palladium catalyst on charcoal (10%) at atmospheric pressure and room temperature. After consumption of the calculated amount of hydrogen the catalyst was filtered, and the solvent was evaporated to yield 1.80 g of **4** as an oil, which was converted into its hydrochloride: mp 256 °C; Anal. ($C_{14}H_{20}Cl_2N_2O_2$) C, H, N; $^1$H NMR δ 9.55 (br s, 1H), 7.13−7.37 (m, 3H), 6.80 (m, 1H), 5.23 (t, 1H), 3.78 (br s, 2H), 3.50 (br s, 2H), 1.78−2.15 (m, 8H); $^{13}$C NMR δ 164.21 (C=O), 144.72, 13.01, 127.528, 117.82, 117.46, 113.78 (aromatics), 66.75 ($C_3$), 52.53 ($C_{1,5}$), 35.67 ($C_{2,4}$), 27.56 ($C_{6,7}$).

**3β-Benzoyloxytropane (7):** mp 52 °C; Anal. ($C_{15}H_{19}NO_2$) C, H, N; $^1$H NMR δ 7.93 (m, 2H), 7.30−7.52 (m, 3H), 5.17 (m, 1H), 3.18 (br s, 2H), 2.28 (s, 3H), 1.6−2.1 (m, 8H); $^{13}$C NMR δ 166.45 (C=O), 133.17, 130.90, 129.02, 128.63 (aromatics), 68.16 ($C_3$), 60.65 ($C_{1,5}$), 39.16 (N−$CH_3$), 36.16 ($C_{2,4}$), 26,89 ($C_{6,7}$).

**3β-Benzoyloxynortropane (8):** mp 252 °C (hydrochloride); Anal. ($C_{14}H_{18}ClNO_2$) C, H, N; $^1$H NMR δ 9,32 (br s, 1H), 7.90 (m, 2H), 7.35−7.60 (m, 3H), 5.12 (m, 1H), 3.88 (br s, 2H), 1.97−2.34 (m, 8H); $^{13}$C NMR δ 165.88 (C=O), 133.41, 131.82, 129.07, 128.75 (aromatics), 68.19 ($C_3$), 55.45 ($C_{1,5}$), 35.21 ($C_{2,4}$), 27,62 ($C_{6,7}$).

***N*-Ethyl-3β-benzoyloxynortropane (9):** mp 55 °C; Anal. ($C_{16}H_{21}NO_2$) C, H, N; $^1$H NMR δ 7.97 (m, 2H), 7.32−7.49 (m, 3H), 5.25 (m, 1H), 3.34 (br s, 2H), 2.48 (q, 2H), 1.65−2.01 (m, 8H), 1.08 (t, 3H); $^{13}$C NMR δ 166.37 (C=O), 133.10, 131.01, 129.84, 128.61 (aromatics), 68.58 ($C_3$), 57.92 ($C_{1,5}$), 44.41 (N−$CH_2$), 35.53 ($C_{2,4}$), 27,24 ($C_{6,7}$), 14.27 (N−$CH_2$$CH_3$).

**3α-Benzoylamidotropane (10):** mp 138 °C; Anal. ($C_{15}H_{20}N_2O$) C, H, N; $^1$H NMR δ 7.62 (m, 2H), 7.30 (m, 3H),

6.51 (d, 1H), 4.13 (q, 1H), 3.10 (br s, 2H), 2.22 (s, 3H), 1.65−2.22 (m, 8H); $^{13}$C NMR $\delta$ 166.83 (C=O), 135.31, 131.67, 128.95, 127.01 (aromatics), 60.35 ($C_{1,5}$), 42.20 ($C_3$), 40.63 (N−$CH_3$), 36.71 ($C_{2,4}$), 26.17 ($C_{6,7}$).

**Receptor Binding: GlyRs.** Synaptosomal membranes were prepared from rat spinal cord as described.[10] Briefly, spinal cords of male Wistar rats were homogenized in 5 mM Tris-HCl buffer (pH 7.4) by Ultra-Turrax for 2 × 10 s. The homogenates were centrifuged at 30000*g* for 20 min, and the pellets were suspended in 50 mM Tris-HCl buffer (pH 7.4), washed by four similar centrifugations, and frozen. Before the binding assay, the thawed suspensions were centrifuged in 50 mM Tris-HCl buffer containing 200 mM KSCN (pH 7.4) at 10000*g* for 10 min. Membrane suspensions (about 0.1 mg of protein/mL) in 50 mM Tris-HCl buffer containing 200 mM KSCN were incubated with 3 nM [$^3$H]strychnine (10 $\mu$Ci/mmol, DuPont-NEN) for 40−50 min at 0 °C. Different concentrations of the tropeines were coincubated to measure cooperativity with [$^3$H]strychnine binding ($\alpha$). Different concentrations of glycine were also incubated in the presence and absence of tropeine concentrations at 0.1$K_A$ to measure cooperativity with glycine ($\beta$). Nonspecific binding was determined in the presence of 2 mM glycine. Duplicate aliquots were filtered on Whatman GF/B filters under vacuum.

**5-HT$_3$ Type Serotonin Receptors.** Synaptosomal membranes were prepared from cerebral cortex plus hippocampus of male Wistar rats as described.[28] Briefly, tissues were homogenized in 10 mM HEPES buffer containing 140 mM NaCl (pH 7.5) in an Ultra-Turrax for 2 × 10 s, centrifuged at 30000*g* for 20 min, washed by centrifugation at 30000*g* for 10 min, and frozen. Before the binding assay, the thawed suspensions were centrifuged in 10 mM HEPES buffer containing 140 mM NaCl (pH 7.5) at 10000*g* for 10 min, incubated with 0.3 nM [$^3$H]granisetron (85 $\mu$Ci/mmol [$^3$H]BRL 43694, DuPont−NEN) for 2.5 h on ice. Different concentrations of the tropeines were applied to measure their displacing potencies and 10 $\mu$M granisetron was used for nonspecific binding. Duplicate aliquots were filtered under vacuum on Whatman GF/B filters presoaked in 0.1% poly(ethylenimine) solution.

**Data Analysis.** Nonlinear statistical regression program NLREG (PH Sherrod, Nashville, TN) and GraphPad Prism Version 4 (San Diego, CA) were used for fitting. The ternary allosteric model applied was described previously.[12] It contains three dissociation constants ($K_S$, $K_L$, and $K_A$) for the binding of [$^3$H]strychnine (S), glycine (L), and the allosteric agents (A) as well as the cooperativity factors $\alpha$ and $\beta$. The cooperativity factors greater or smaller than unity increase or decrease, respectively, the dissociation of the ligands. Thus, $\alpha$ and $\beta$ values greater than unity represent negative cooperativity of the allosteric agents with [$^3$H]strychnine and glycine binding, respectively. Equation 1 expresses the ratio of specific [$^3$H]-strychnine binding in the presence of three ligands ($B_{SAL}$) over control, in the presence of [$^3$H]strychnine ($B_S$):

$$\frac{B_{SAL}}{B_S} = \frac{[S] + K_S}{[S] + K_S \dfrac{[L](K_A + [A]/\beta) + K_L(K_A + [A])}{K_L(K_A + [A]/\alpha)}} \quad (1)$$

In the absence of glycine, the equation is simplified:

$$\frac{B_{SA}}{B_S} = \frac{[S] + K_S}{[S] + \dfrac{K_S(K_A + [A])}{K_A + [A]/\alpha}} \quad (2)$$

$K_S$ values of 13 nM [$^3$H]strychnine were determined via saturation analysis.[10] Concentration-dependent effects of the allosteric agents were fitted to eq 2 to determine $K_A$ and $\alpha$ values. Displacements by different concentrations of glycine were measured in the absence (control) and presence of constant concentrations of the allosteric agents to determine $\beta$ values. Alternatively, dissociation constants of the tropeines ($K_A$) were also calculated according to the Cheng−Prusoff equation:

$$K_A = \frac{IC_{50}}{1 + [S]/K_S} \quad (3)$$

where $IC_{50}$ values represent 50% displacement of [$^3$H]strychnine binding by the tropeines.

Displacement of [$^3$H]granisetron binding was fitted via GraphPad Prism 4 to get $IC_{50}$ and slope values ($n_H$) of displacement.

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**Supporting Information Available:** Results from elemental analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

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