Enaminone Amides as Novel Orally Active $GABA_A$ Receptor Modulators

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A series of enaminone esters and amides have been developed as potent allosteric modulators of γ-aminobutyric $acid_A$ ($GABA_A$) receptors. The compounds bind to a novel modulatory site that is independent of the benzodiazepine (BZ), isosteric GABA, and neuroactive steroid binding sites. Structure−activity relationship (SAR) studies resulted in the synthesis of the *c*-Bu amide **16h** with an in vitro potency of 7 nM based on inhibition of [^{35}S]TBPS binding. The activity of the enaminones as positive allosteric modulators was confirmed with electrophysiological measurements in oocytes expressing $\alpha_1\beta_2\gamma_{2L}$ $GABA_A$ receptors. The *i*-Pr, *s*-Bu, *c*-Pr, and *c*-Bu amides (**16e**−**h**) were orally active in mice with profound central nervous system depressant effects. The *i*-Pr amide **16e** was an orally active anxiolytic in the mouse light−dark paradigm.

γ-Aminobutyric acid (GABA[a]) is the major inhibitory neurotransmitter in the mammalian brain. There are three types of GABA receptors, termed $GABA_A$, $GABA_B$, and $GABA_C$ receptors.[1] $GABA_A$ and $GABA_C$ receptors are ligand gated ion channels that conduct chloride ions, whereas $GABA_B$ receptors are G-protein coupled receptors. $GABA_A$ receptors are heteropentameric in structure and belong to the cys-loop receptor family that includes α7 nicotinic acetylcholine, glycine, and serotonin-3A receptors. Allosteric modulators of $GABA_A$ receptors[2] such as benzodiazepines (BZ),[3] neuroactive steroids,[4] and barbiturates[5] have been identified that are useful as anxiolytics, anticonvulsants, anesthetics, and sedative-hypnotics. Numerous non-BZ ligands that bind to the BZ-site on the $GABA_A$ receptor have also been described, including imidazopyridines, pyrazolopyrimidines, and triazolopyrimidines.[6] Side-effects associated with BZ-site ligands include dependence, tolerance, strong interactions with alcohol, and amnesic and myorelaxant effects.[7] Novel allosteric modulators[8] that bind to the $GABA_A$ receptor at sites other than the BZ-site may offer an opportunity to discover central nervous system (CNS) agents with improved side effect profiles.

As part of a program to develop novel quinolones as modulators of $GABA_A$ receptors, 7-chloro-1-ethyl-6-[(1,2,3,4-tetrahydro-1-naphthylenyl)amino]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (**1**, Chart 1) was identified as an allosteric modulator of the $GABA_A$ receptor with an anxioselective profile in vivo.[9] An intermediate in the synthesis of N-1 aryl substituted analogs of **1**, ethyl 2,4-dichloro-5-fluoro-α-[[(4-fluorophenyl)-amino]methylene]-*β*-oxobenzenepropanoate (**2a**), was found to have $GABA_A$ receptor agonist activity based on its ability to allosterically inhibit the binding of [^{35}S]-*tert*-butylbicyclophosphorothionate ([^{35}S]TBPS)[10] to rat brain cortical homogenates with an IC_{50} = 150 nM (I_{max} 80%). The synthesis of **2a** and its analogs is shown in Scheme 1.[11] Reaction of 2,4-dichloro-5-fluorobenzoyl chloride (**3a**) with ethyl 2,2-dimethylaminoacrylate in the presence of diisopropylethyl- or triethylamine afforded

Chart 1. Structures of **1** and **2a**

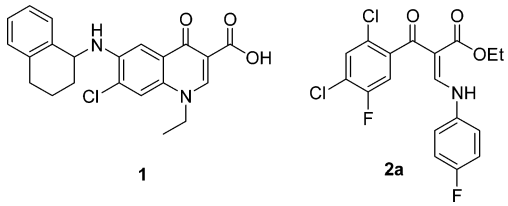
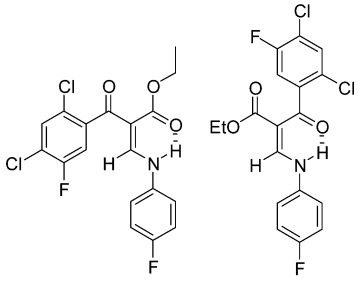


Chart 2. *Z*- and *E*-Isomers of **2a**



the dimethylenaminone (**4a**), which underwent substitution with 4-fluoroaniline at room temperature in EtOH to afford **2a**.[12] The ^{1}H NMR of **2a** in $CDCl_3$ indicates that the compound is a 1:1 mixture of double bond isomers. The chemical shifts are very different for the aniline NH in the two isomers. In one isomer the aniline NH is a doublet at 12.7 ppm (coupled to the vinyl proton) and in the second isomer the aniline NH is a doublet at 11.3 ppm. The coupling constant between the NH and the vinyl proton in both isomers is 13 Hz, strongly suggesting an antiperiplanar relationship for the two protons.[13] The isomer with the aniline NH at 12.7 ppm incorporates a hydrogen bond (H-bond) between the aniline NH and the ester carbonyl (**2aZ**, Chart 2), and the second isomer has an H-bond between the aniline NH and the ketone carbonyl (**2aE**). These structure−NMR correlations are supported by assignments in related systems.[14]

Analogs of **2a** were synthesized with modifications to the substituents on the aryl group of the ketone (Table 1). For comparison, data for the endogenous neurosteroid 5α-pregnan-3α-ol-20-one (3α,5α-P) are included.[15] The 2- and 3-chloroaryl ketones (**2b** and **2c**) show 2- and 7-fold losses, respectively, in

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[a] Abbreviations: GABA, γ-aminobutyric acid; TBPS, *tert*-butylbicyclophosphorothionate; LRR, loss-of-righting reflex; 5α-pregnan-3α-ol-20-one, 3α,5α-P; *N*,*N*-dimethylformamide dimethyl acetal, DMFDMA; hydrogen bond, H-bond; MED, minimum effective dose; TI, therapeutic index; PTZ, pentylenetetrazole; 3α,20α-diol, 5α-pregnane-3α,20α-diol.

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Scheme 1. Synthesis of Enaminones **2a**−**d**

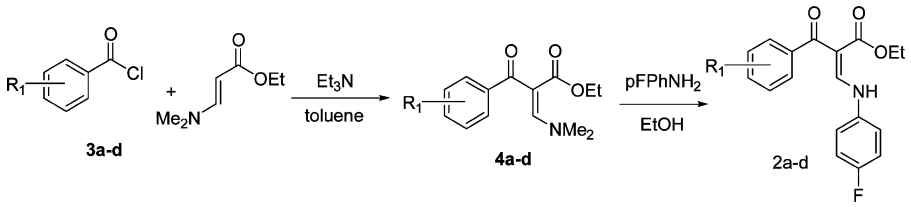
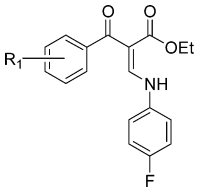


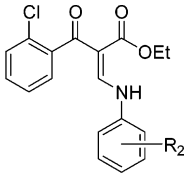
Table 1. In Vitro Potency of Ethyl α-[[(4-Fluorophenyl)amino]methylene]-*β*-oxophenylpropanoates[a]



compd	R_1	IC_{50} for inhibn of [^{35}S]TBPS binding (nM)[b]	I_{max} (%)
3α,5α-P[c]	-	50 ± 5	95 ± 1
2a	2,4-diCl, 5-F	130 ± 27	87 ± 6
2b	2-Cl	300 ± 55	93 ± 7
2c	3-Cl	900 ± 370	90 ± 16
2d	4-Cl	490 ± 84	100 ± 8

[a] Values are means and SEMs of three indpendent experiments. [b] The concentration of test compound inhibiting 50% specific binding (IC_{50}) and the maximal extent of inhibition (I_{max}) were calculated by fitting the data to the sigmodial function. [c] 5α-Pregnan-3α-ol-20-one (3α,5α-P) data are taken from ref 15.

Table 2. In Vitro Potency of Ethyl 2-Chloro-*β*-oxo-α-[(phenylamino)-methylene]benzenepropanoates

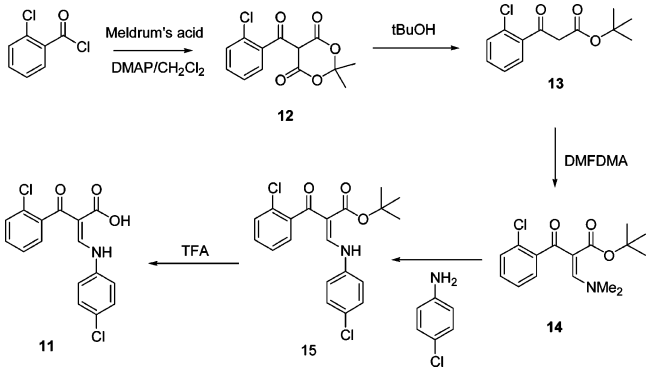


compd	R_2	IC_{50} for inhibn of [^{35}S]TBPS binding (nM)	I_{max} (%)
2b	4-F	300 ± 55	93 ± 7
5	4-Cl	90 ± 10	95 ± 10
6	2-Cl	700 ± 110	100 ± 7
7	3-Cl	600 ± 130	100 ± 8
8	4-Me	450 ± 150	93 ± 12
9	4-iPr	360 ± 75	94 ± 8
10	4-CCH	8 ± 1	100 ± 7

potency compared to **2a**, while the 4-chloroaryl ketone (**2d**) shows almost a 4-fold loss in activity. All of the esters were mixtures of isomers by ^{1}H NMR.

Substitutions to the aniline ring were targeted because the initial SAR on the aryl ketone did not lead to increases in potency. For ease of synthesis, the SAR around the 2-chloride (**2b**) was investigated further (Table 2). Within the halogen series, the in vitro potency was found to increase to 90 nM for the 4-chloroaniline **5**. The 2- and 3-chloroanilines, **6** and **7**, were less potent than the 4-isomer, with IC_{50} values of 700 and 600 nM, respectively. Small alkyl groups at the 4-position resulted in a loss in activity compared to **2b** with the 4-methyl and 4-isopropyl compounds (**8** and **9**) having IC_{50} values of 450 and 360 nM, respectively. The 4-ethynyl compound **10** was the most potent compound in this series, with an IC_{50} of 8 nM. Increases in potency did not come at the expense of efficacy,

Scheme 2. Synthesis of Acid **11**



with **10** showing full displacement of [^{35}S]TBPS binding. Overall, the SAR indicates that adding steric bulk at the 4-position of the aniline does not improve in vitro potency in the series where R_2 = F, Me, and *i*-Pr. The increased activity for the 4-chloroaniline **5** is thus not due to its size but potentially is related to its ability to act as a resonance donor to the aniline ring. The influence of an H-bonding interaction with the halogen at the 4-position of the aniline is unlikely because of the known decrease in the strength of H-bonds when fluorine is replaced with chlorine.[16] Potency is reduced when the chlorine is shifted to the 2- or 3-position of the aniline (**6** and **7**) presumably because of unfavorable steric interactions with the receptor. The increase in potency observed with 4-ethynyl substitution is likely related to a specific interaction of the triple bond π-system with the receptor.[17]

For comparison with the ethyl ester **5**, the corresponding acid **11** was prepared as shown in Scheme 2. Meldrum's acid was acylated with 2-chlorobenzoyl chloride to give the expected adduct (**12**), which was conveniently purified and stored by conversion to the isopropylamine salt (**12a**).[18] Partitioning the salt between EtOAc and a 1 M aqueous HCl solution re-formed the acid **12**. The isolated acid was then heated with excess *tert*-butyl alcohol to form the desired *β*-keto ester (**13**).[19] Addition of *N*,*N*-dimethylformamide dimethyl acetal (DMFDMA) then gave the corresponding enaminone **14**. Reaction of **14** with 4-chloroaniline afforded the *tert*-butyl ester **15**, and subsequent cleavage of the ester with trifluoroacetic acid gave the desired acid **11**.

The *tert*-butyl ester **15** was active in vitro ([^{35}S]TBPS IC_{50} = 320 nM), while the acid **11** was essentially inactive ([^{35}S]-TBPS IC_{50} = 7000 nM). Because of the poor activity of the acid, it is very unlikely that the ethyl esters are simply prodrugs that are converted to the acid under the [^{35}S]TBPS assay conditions. Compound **5** was selected for initial profiling in vivo because of its good in vitro potency when compared to known modulators of the $GABA_A$ receptor (e.g., 3α,5α-P) and the hope that the chloride substitution on the aryl ketone and aniline would retard metabolism of these two rings. The ethyl ester **5** caused all animals tested to lose their righting reflex (LRR)[9] for 40 min when dosed intraperitoneally (ip) at 50 mg/kg in mice. No mortality was observed at this dose after 24 h. Not

Scheme 3. Synthesis of Enaminone Amide **16a**

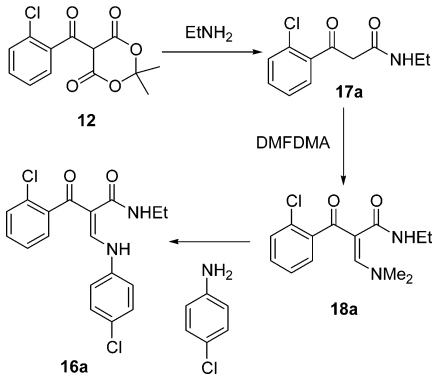
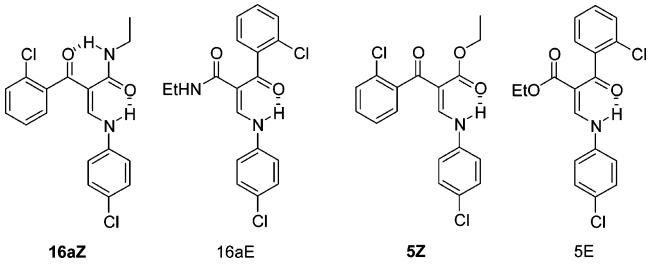


Chart 3. Comparison of Hydrogen Bonding within Enaminone Amides and Esters



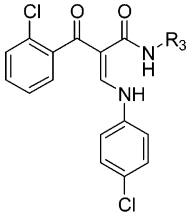
surprisingly, however, the ethyl ester **5** was not active in inducing LRR when tested orally (po) at 50 mg/kg in mice. **5** was inactive at this dose when evaluated for its ability to suppress locomotor activity. It was likely that the ester was rapidly being converted to the inactive acid **11** when dosed orally.

On the basis of these results, the ethyl ester in **5** was replaced with an ethyl amide as a potential metabolically stable bioisostere. The ethyl amide **16a** was prepared as shown in Scheme 3. Reaction of 2-chlorobenzoyl Meldrum's acid (**12**) with ethylamine afforded the expected β-ketoamide **17a**.[20] The corresponding enaminone **18a** was prepared as in Scheme 2, and addition of 4-chloroaniline at reflux in toluene gave the desired enaminone amide **16a**.

The amide **16a** was found to be more potent in vitro than the corresponding ester **5** ([^{35}S]TBPS IC$_{50}$ = 50 and 90 nM, respectively). The ^{1}H NMR of **16a**, unlike the corresponding ester, did not show a mixture of isomers. Only a single aniline NH and vinyl proton were apparent. This difference between the esters and amides can be understood if the amide exists as the *Z*-isomer (**16aZ**, Chart 3), where two H-bonds can form, one between the aniline NH and the carbonyl of the amide and a second between the amide NH and the ketone carbonyl. The corresponding *E*-isomer (**16aE**) can benefit from only one H-bond, between the aniline NH and the ketone carbonyl, making it less favored energetically than the *Z*-isomer. In the esters, both the *Z*- and *E*-isomers have a single H-bond (**5Z** and **5E**, Chart 3), and the two isomers are closer in energy than in the enaminone amides. Enaminones amides related to **16a** have been reported to exist as single isomers.[21]

The ethyl amide **16a** was dosed in mice as described for the corresponding ester. While all mice tested showed LRR at 50 mg/kg ip, no LRR or rotarod[9] deficit was apparent orally. The amide side chain (R$_3$, Table 3) was systematically varied in order to better understand this result. A more convergent method for the synthesis of analogs of amide **16a** was employed where the acid **11** was converted to the corresponding acid chloride with thionyl chloride and then treated with the desired amine (Scheme 4). This method worked well for the preparation of most amides. However, when the crude acid chloride derived from **11** was treated with isopropyl-, cyclopropyl-, or cyclobutylamine, only very low yields of the desired amides were isolated. These compounds (**16e**, **16g**, and **16h**) and the propyl amide **16d** were prepared by using the route in Scheme 3 but using an alternative route to the intermediate β-ketoamide **17** given in Scheme 5. The *tert*-butyl ester **13** was prepared as in Scheme 2 and then cleaved to the β-keto acid **19**. Amide bond formation with dicyclohexyl carbodiimide (DCC) or via the corresponding acid chloride gave the β-ketoamide **17**. Conversion to the desired product was accomplished as in Scheme 3. In each case, ^{1}H NMR showed the amides to exist as single isomers.

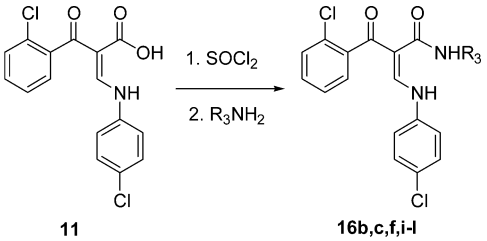
Table 3. In Vitro Potency of *N*-Alkyl-2-chloro-α-[[(4-chlorophenyl)-amino]methylene]-β-oxobenzenepropanamides[a]



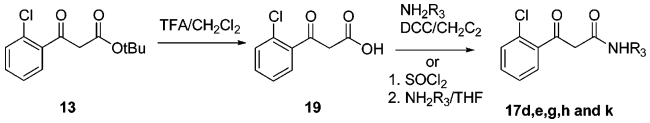
compd	R$_3$	IC$_{50}$ for inhibn of [^{35}S]TBPS binding (nM)	I_{max} (%)
16b	H	1700 ± 770	40 ± 18
16c	Me	160 ± 27	74 ± 8
16a	Et	50 ± 5	82 ± 4
16d	Pr	45 ± 7	90 ± 7
16e	i-Pr	40 ± 13	80 ± 10
16f	s-Bu	20 ± 2	86 ± 4
16g	c-Pr	30 ± 4	92 ± 5
16h	c-Bu	7 ± 2	88 ± 6
16i	c-Pentyl	30 ± 4	88 ± 5
16j	1-ethylpropyl	80 ± 9	86 ± 6
16k	t-Bu	3000	100
16l	1,2-diMePr	400 ± 42	94 ± 7

[a] Values are means and SEMs of three independent experiments, except for **16k** (n = 1).

Scheme 4. Synthesis of Amides **16b,c,f,** and **i**−**l** from Acid **11**



Scheme 5. Alternative Synthesis of β-Ketoamides **17d,e,g,h,** and **k**



The unsubstituted amide **16b** was a weak inhibitor of [^{35}S]-TBPS binding, exhibiting an 34-fold loss in potency compared to the ethyl amide **16a**. The methyl amide (**16c**) was 3-fold less potent in vitro than the ethyl amide. The lack of oral activity for the ethyl amide may be due to dealkylation to the weakly active unsubstituted amide **16b**. The corresponding *tert*-butyl amide **16k** was prepared to eliminate this possibility. Surprisingly, given the activity of the corresponding *tert*-butyl ester (**15**, [^{35}S]TBPS IC$_{50}$ = 320 nM), the *tert*-butyl amide was only

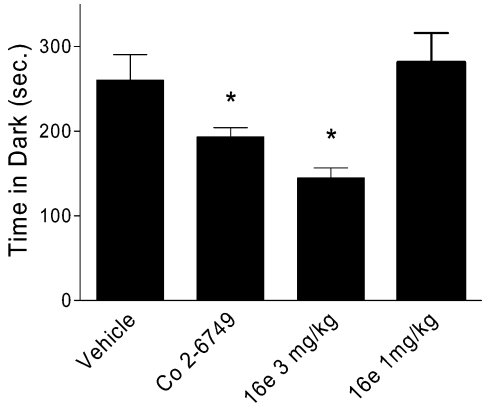


Figure 1. Dose-dependent effect of 2-chloro-α-[[(4-chlorophenyl)-amino]methylene]-*N*-isopropyl-*β*-oxobenzenepropanamide (**16e**, 1 and 3 mg/kg po, $N = 10$) and 3α,21-dihydroxy-3*β*-trifluoromethyl-5*β*-19-norpregnan-20-one (Co 2-6749; 10 mg/kg po, $N = 59$) compared to vehicle (3:1 PEG 400/5% dextrose in water, $N = 19$) on time spent in the dark chamber in the mouse light−dark paradigm. *Standard deviation from vehicle $P < 0.001$ Anova, <0.5 Dunnett's multiple comparison test.

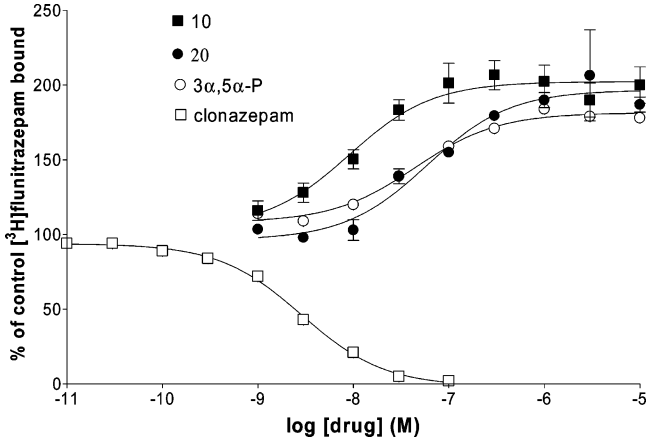
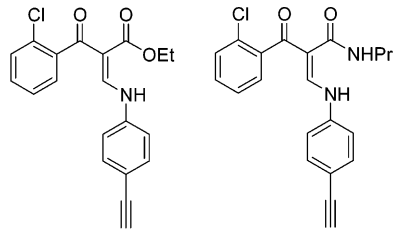


Figure 2. Dose response of ethyl 2-chloro-α-[[(4-ethynylphenyl)amino]-methylene]-*β*-oxobenzenepropanoate (**10**), 2-chloro-α-[[(4-ethynylphenyl)amino]methylene]-*β*-oxo-*N*-propylbenzenepropanamide (**20**), 3α,5α-P, and clonazepam on 0.2 nM [^{3}H]flunitrazepam binding in rat cortex.

Chart 4. Structures of **10** and 2-Chloro-α-[[(4-ethynylphenyl)-amino]methylene]-*β*-oxo-*N*-propylbenzenepropanamide (**20**)



10 **20**

weakly active in vitro ([^{35}S]TBPS $IC_{50} = 3000$ nM). The propyl amide (**16d**) was prepared with the goal of adding bulk to the ethyl amide without compromising in vitro activity. We found **16d** to be equipotent to the ethyl amide **16a**. Amide **16d** exhibited an in vivo profile identical to that of the ethyl amide: mice showed LRR when dosed ip at 50 mg/kg but not orally at 50 mg/kg. To further increase the steric bulk of R_3, the isopropyl, *sec*-butyl, and cyclopentyl amides **16e**, **16f**, and **16i** were prepared. All three compounds were similar in potency to **16a**. The 1-ethylpropyl amide **16j** was also targeted and found to be 1.5-fold less potent than **16a**. The 1,2-dimethylpropyl homolog of **16f** (**16l**) resulted in a 8-fold loss in activity. The cyclopropyl amide **16g** inhibited [^{35}S]TBPS binding with an IC_{50} of 30 nM. The cyclobutyl amide **16h** was the most potent enaminone amide tested with an IC_{50} of 7 nM. The in vitro data indicate a positive role for lipophilicity in the series R_3 = H, Me, and Et. The propyl amide **16d** does not have improved potency. Within the branched amides, the isopropyl amide **16e** is similar in potency to the ethyl amide. Adding bulk to give the *sec*-butylamide **16f** doubles potency, while the addition of an additional methyl group in the 1-ethylpropyl amide **16j** results in a 4-fold loss relative to **16f**. The activity of the cyclic amides shows a preference for the cyclobutyl amide **16h**. Ring contraction or expansion results in a 4-fold loss in activity. Taken together, these data support the presence of a lipophilic pocket in the receptor of limited size that accommodates bulk only in specific directions.

The isopropyl, *sec*-butyl, cyclopropyl, and cyclobutylamides (**16e**, **16f**, **16g**, and **16h**) were found to cause LRR orally in mice at 50 mg/kg. The anxiolytic activity of the isopropylamide **16e** was determined in the mouse light−dark paradigm.[23] When dosed orally at 3 mg/kg, **16e** significantly reduced the time mice spent in the dark (Figure 1) compared to vehicle alone. No effect was observed for **16e** orally at 1 mg/kg. The neurosteroid 3α,-21-dihydroxy-3*β*-trifluoromethyl-5*β*-19-norpregnan-20-one (Co 2-6749) was used as a positive control and was active orally at 10 mg/kg.[24] The CNS depressant potential of **16e** was evaluated in the rotarod test. No rotarod deficit was observed orally at 3 mg/kg, and only one of seven animals was found to fail the test at 30 mg/kg. On the basis of these data, **16e** has a therapeutic index (TI) of >10 (TI = light-dark MED/rotarod TD_{50}).

The oral activity observed with the amides tested with branching at the carbon atom bonded to the amide nitrogen (**16e**−**h**) is likely due to reduced metabolism to the inactive unsubstituted amide **16b** or acid **11** when dosed orally.

None of the amides were found to be active as anticonvulsants when tested ip at 50 mg/kg prior to sc dosing of 85 mg/kg of the chemical convulsant pentylenetetrazole (PTZ).

In order to confirm that the enaminones are positive allosteric modulators of $GABA_A$ receptors in a functional assay, **16e** was evaluated for its ability to potentiate GABA currents in human $\alpha_1\beta_2\gamma_{2L}$ $GABA_A$ receptors expressed in *Xenopus* oocytes.[25] Amide **16e** showed robust activity as a modulator electrophysiologically, with an EC_{50} of 34 ± 2 nM and modulation of the GABA EC_{10} to 88% of the maximum GABA response. In the absence of GABA, **16e** did not elicit a response up to a concentration of 10 *μ*M (limit of solubility), confirming its mode of action as an allosteric modulator.

To more fully define the in vitro pharmacological profile of the enaminones, the ethyl ester **10** ([^{35}S]TBPS $IC_{50} = 8$ nM) and the corresponding propyl amide, 2-chloro-α-[[(4-ethynylphenyl)amino]methylene]-*β*-oxo-*N*-propylbenzenepropanamide (**20**, Chart 4), were tested for their ability to interact with the BZ binding site on the $GABA_A$ receptor. The amide **20** was prepared by using the general method in Scheme 3 and was a potent modulator of [^{35}S]TBPS binding with $IC_{50} = 54 \pm 1$ nM ($I_{max} = 91 \pm 3\%$). Both **10** and **20** dose-dependently enhance the binding of [^{3}H]flunitrazepam ($EC_{50} = 6 \pm 2$ and 60 ± 2 nM, respectively), indicating that the enaminones do not bind directly to the BZ-site on the $GABA_A$ receptor (Figure 2). As expected, the neuroactive steroid 3α,5α-P also dose-dependently enhanced the binding of [^{3}H]flunitrazepam, while the BZ-site ligand clonazepam dose-dependently inhibited the binding of [^{3}H]flunitrazepam in the same assay. Both **10** and **20** enhance the binding of [^{3}H]muscimol, ruling out activity for the enaminones at the isosteric GABA site on the $GABA_A$ receptor (Figure 3).

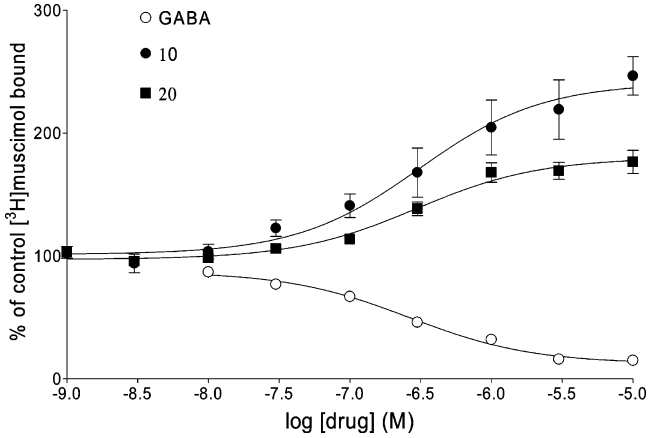


Figure 3. Dose response of ethyl 2-chloro-α-[[(4-ethynylphenyl)amino]-methylene]-*β*-oxobenzenepropanoate (**10**), 2-chloro-α-[[(4-ethynylphenyl)amino]methylene]-*β*-oxo-*N*-propylbenzenepropanamide (**20**), and GABA on 5 nM [^{3}H]muscimol binding in rat cortex.

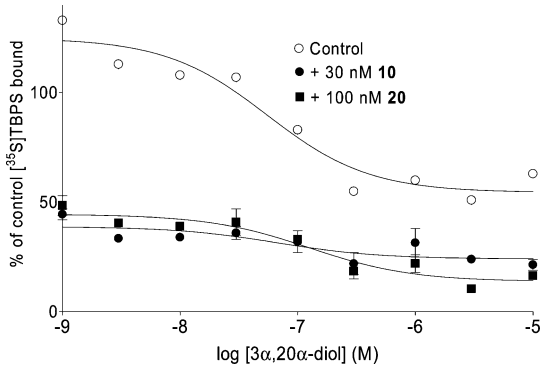


Figure 4. Dose response of 3α,20α-diol in the absence and presence of 30 nM ethyl 2-chloro-α-[[(4-ethynylphenyl)amino]methylene]-*β*-oxobenzenepropanoate (**10**) or 100 nM 2-chloro-α-[[(4-ethynylphenyl)-amino]methylene]-*β*-oxo-*N*-propylbenzenepropanamide (**20**) on 2 nM [^{35}S]TBPS binding in rat cortex.

The [^{35}S]TBPS dose response for the partial agonist neuroactive steroid 5α-pregnane-3α,20α-diol (3α,20α-diol) in the presence of **10** or **20** (Figure 4) shows that the effects of the enaminones and the steroid are additive. Thus, the enaminones do not interact directly with the neuroactive steroid site of the GABA$_A$ receptor.

In conclusion, a series of enaminone esters and amides has been identified as novel allosteric modulators of the GABA$_A$ receptor. In vitro binding studies indicate that this class of modulators likely interacts with a novel site on the GABA$_A$ receptor distinct from the BZ, GABA, and neuroactive steroid binding sites. The cyclobutylamide (**16h**) was identified from SAR studies with low nanomolar in vitro potency as a modulator of [^{35}S]TBPS binding. Electrophysiological studies in oocytes confirmed that the enaminone esters and amides are positive allosteric modulators of human GABA$_A$ receptors. The isopropyl, *sec*-butyl, cyclopropyl, and cyclobutyl amides (**16e**−**h**) may have use as sedative-hypnotics because they were found to cause LRR orally in mice. Compound **16e** was orally active as an anxiolytic in the mouse light−dark paradigm with a MED of 3 mg/kg and TI of >10. These modulators have no apparent anticonvulsant activity, despite their robust modulation of GABA$_A$ receptors. The in vivo profile of **16e** (inactive against PTZ-induced seizures and active as an anxiolytic) is similar to that reported for the quinolone **1**.[9] Additional studies are underway to more fully probe the interactions of this novel class of compounds with GABA$_A$ receptors in order to characterize their pharamacological profile and to elucidate the basis for their, thus far, atypical profile as GABA$_A$ receptor modulators.

Experimental Section

Chemistry. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Unity Inova spectrometer at 400 and 100 MHz, respectively, in $CDCl_3$ referenced to $CHCl_3$ (7.26 ppm) or to tetramethylsilane (0.00 ppm) and to $CDCl_3$ at 77.00 ppm. ^{1}H and ^{13}C NMR spectra in DMSO-d_6 were referenced to DMSO-d_5 (2.50 ppm) and to DMSO-d_6 (39.51 ppm), respectively. Melting points were determined on an Electrothermal MEL-TEMP 3.0 apparatus (Barnstead International, Dubuque, IA) and are not corrected. Elemental analyses were performed by Robertson Microlit Laboratories, Madison, NJ. Flash chromatography was carried out by using the method of Still et al.,[26] on 230−400 mesh silica gel (silica gel 60, Geduran) obtained from EMD. Reverse phase high performance liquid chromatography (RPHPLC) was performed on a Shimatzu system with CH_3CN/water mixtures. Solvents were HPLC grade and were obtained from EMD. DMSO, GABA, and pentylenetetrazole (PTZ) were obtained from Sigma Chemical Co. Anhydrous solvents were obtained from Aldrich Chemical Co. (Milwaukee, WI). Other synthetic reagents were obtained from Aldrich or Lancaster Synthesis (Windham, NH) and were used as received unless otherwise indicated. 4-Fluoroaniline (Lancaster) was purified by bulb-to-bulb distillation before use. [^{3}H]Flunitrazepam, [^{35}S]TBPS, [^{3}H]muscimol, and unlabeled TBPS were obtained from Perkin-Elmer Bioscience (Boston, MA). The neuroactive steroid 3α,21-dihydroxy-3*β*-trifluoromethyl-5*β*-19-norpregnan-20-one (Co 2-6749) was prepared as described in the literature.[24b]

Ethyl 2,4-Dichloro-α-[(dimethylamino)methylene]-5-fluoro-*β*-oxobenzenepropanoate (**4a**). A mixture of ethyl 3,3-dimethylaminoacrylate (3.10 g, 21.6 mmol) and *N*,*N*-diisopropylethylamine (8.0 mL, 5.94 g, 45.9 mmol) was stirred at room temperature and a solution of 2,4-dichloro-5-fluorobenzoyl chloride (Lancaster; 4.92 g, 21.6 mmol) was added dropwise via addition funnel over 20 min. The cloudy yellow solution that formed was placed in an oil bath at 85−90 °C. After 3 h, the mixture that formed was filtered and the solid was washed with benzene. The dark filtrate was concentrated and the residue was triturated with hexanes (50 mL). The solid that formed was collected and washed with hexanes (20 mL) and partitioned between water and EtOAc. The EtOAc layer was washed with water (3 × 25 mL) and brine, dried (Na_2SO_4), filtered, and concentrated to 5.0 g (69%) of **4a**. Recrystallization from 4:1 hexanes/EtOAc gave the product as an off-white solid. Mp: 94.5−95.5 °C (lit[27] mp: 94−95 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 (s, 1H), 7.39 (d, 1H, $J_{H,F}$ = 6.4 Hz), 7.20 (d, 1H, $J_{H,F}$ = 8.7 Hz), 3.97 (q, 2H, J = 7.1 Hz), 3.37 (s, 3H), 2.97 (s, 3H), 0.96 (t, 3H, J = 7.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) 187.59, 167.00, 159.27, 156.54 (d, $J_{C,F}$ = 250 Hz), 142.39 (d, $J_{C,F}$ = 5.3 Hz), 130.72, 126.06 (d, $J_{C,F}$ = 3.8 Hz), 121.78 (d, $J_{C,F}$ = 19.1 Hz), 116.51 (d, $J_{C,F}$ = 23.7 Hz), 101.73, 59.91, 48.03, 42.79, 13.72 ppm. Anal. ($C_{14}H_{14}Cl_2FNO_3$) C, H, N.

Ethyl 2-Chloro-α-[(dimethylamino)methylene]-*β*-oxobenzenepropanoate (**4b**). A mixture of ethyl 3,3-dimethylaminoacrylate (Acros; 4.68 g, 32.7 mmol) and *N*,*N*-diisopropylethylamine (12 mL, 8.9 g, 69 mmol) was stirred at room temperature and a solution of 2-chlorobenzoyl chloride (5.72 g, 32.7 mmol) in 30 mL of toluene was added over 5 min. The yellow solution that formed was placed in an oil bath at 85−90 °C. After 3 h, the mixture that formed was filtered and the solid was washed with toluene (4 × 25 mL). The pooled toluene washes were extracted with water (3 × 50 mL) and brine (1 × 30 mL), dried (Na_2SO_4), filtered, and concentrated. The dark filtrate was concentrated and the oily residue was triturated with hexanes (100 mL). The solid that formed was isolated by filtration and washed with hexanes (25 mL). The crude product was dissolved in a minimum volume of EtOAc and added to 16.5 cm of flash silica gel in a 5 cm diameter column. Elution with 100% EtOAc afforded an oil that solidified after trituration with hexanes to give **4b** (5.68 g, 62%). Mp: 70−71.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (br s, 1H), 7.34−7.23 (m, 4H), 3.89

(q, 2H, $J = 7.2$ Hz), 3.32 (br s, 3H), 2.96 (br s, 3H), 0.83 (t, 3H, $J = 7.2$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.33, 167.45, 158.23, 142.29, 130.80, 129.69, 129.34, 128.61, 126.26, 102.92, 59.72, 47.76 (br), 42.31 (br), 13.46 ppm. Anal. ($C_{14}H_{16}ClNO_3$) C, H, N.

Ethyl 3-Chloro-α-[(dimethylamino)methylene]-β-oxobenzenepropanoate (**4c**). A mixture of 3,3-dimethylaminoacrylate (1.44 g, 10.0 mmol) and triethylamine (3.0 mL, 2.2 g, 22 mmol) was treated with a solution of 3-chlorobenzoyl chloride (1.78 g, 10.2 mmol) in 10 mL of toluene. The resulting mixture was heated at 95 °C for 4.5 h. Workup as described for the 2-isomer gave the crude product as a dark orange oil. Column chromatography (1:1 EtOAc/hexanes) and trituration of the resulting light yellow oil with hexanes gave 902 mg (32%) of **4c** as a light yellow solid. Mp: 65−66 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (br s, 1H), 7.63 (br s, 1H), 7.44−7.29 (m, 4H), 3.97 (q, 2H, $J = 7.0$ Hz), 3.05 (2 br s, 6H), 0.92 (t, 3H, $J = 7.0$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.08, 168.19, 156.24, 143.06, 134.09, 131.06, 129.15, 128.55, 126.60, 99.89 (br), 59.73, 44.41 (br), 13.80 ppm.[28] Anal. ($C_{14}H_{16}ClNO_3$) C, H, N.

Ethyl 4-Chloro-α-[(dimethylamino)methylene]-β-oxobenzenepropanoate (**4d**) was prepared as described above for **4c** as a light yellow solid. Mp: 78.5−79.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (br m, 3H), 7.35 (d, 2H, $J = 8.5$ Hz), 3.96 (q, 2H, $J = 7.1$ Hz), 3.00 (br s, 6H), 0.93 (t, 3H, $J = 7.2$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.40, 168.30, 156.15, 139.48, 137.45, 129.95, 128.09, 99.89, 46.50 (br), 42.20 (br), 59.72, 13.85 ppm.[28] Anal. ($C_{14}H_{16}ClNO_3$) C, H, N.

Ethyl 2,4-Dichloro-5-fluoro-α-[[(4-fluorophenyl)amino]methylene]-β-oxobenzenepropanoate (**2a**). A suspension of **4a** (512 mg, 1.53 mmol) in 5 mL of EtOH was treated with neat 4-fluoroaniline (172 μL, 1.55 mmol). After stirring overnight, the precipitate that formed was isolated and washed with 1.5 mL of EtOH, affording 311 mg (51%) of **2a** as a white solid. Mp: 119−120 °C, as a 55:45 mixture of isomers (lit.[11a] mp: 111−112 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ (major isomer) 12.70 (d, 1H, $J = 13.1$ Hz), 8.59 (d, 1H, $J = 14.0$ Hz), 7.41 (dd, 1H, $J = 6.3$, 2.3 Hz), 7.28−7.20 (m, 4H), 7.06 (d, 1H, $J = 8.5$ Hz), 4.07 (q, 2H, $J = 7.0$ Hz), 1.06 (t, 3H, $J = 7.0$ Hz). Anal. ($C_{18}H_{13}Cl_2FNO_3$) C, H, N.

Ethyl 2-Chloro-α-[[(4-fluorophenyl)amino]methylene]-β-oxobenzenepropanoate (**2b**) was prepared as described above for **2a**. Mp: 111−112 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (major isomer) 12.75 (d, 1H, $J = 13.7$ Hz), 8.56 (d, 1H, $J = 13.4$ Hz), 7.37−7.24 (m, 6H), 7.14 (t, 2H, $J = 8.4$ Hz), 4.01 (q, 2H, $J = 7.1$ Hz), 0.93 (t, 3H, $J = 7.0$ Hz). Anal. ($C_{18}H_{15}ClFNO_3$) C, H, N.

Ethyl 3-Chloro-α-[[(4-fluorophenyl)amino]methylene]-β-oxobenzenepropanoate (**2c**). A mixture of ethyl 3-chloro-α-[(dimethylamino)methylene]-β-oxobenzenepropanoate (**4c**, 204 mg, 0.724 mmol) and 4-fluoroaniline (80 mg, 0.72 mmol) in 4 mL of EtOH was allowed to stand at room temperature for 5 d. The resulting yellow solution was concentrated in vacuo. The residue was dissolved in 10 mL of EtOAc and extracted with a 1 M HCl solution (3 × 10 mL), a saturated $NaHCO_3$ solution, and brine (10 mL of each). The EtOAc layer was dried (Na_2SO_4), filtered, and concentrated. The oil that remained was subjected to flash chromatography (4:1 hexanes/EtOAc), affording 162 mg (65%) of **2c** as a light yellow oil. Trituration with hexanes gave a white solid. Mp: 70−80 °C. By ^{1}H NMR, **2c** is a 1.4:1 mixture of isomers. ^{1}H NMR (major isomer, 400 MHz, $CDCl_3$): δ 12.23 (d, 1H, $J = 13.1$ Hz), 8.49 (d, 1H, $J = 13.4$ Hz), 7.52−7.30 (m, 4H), 7.24−7.08 (m, 4H), 4.06 (q, 2H, $J = 7.1$ Hz), 1.02 (t, 3H, $J = 7.2$ Hz). Anal. ($C_{18}H_{15}ClFNO_3$) C, H, N.

Ethyl 4-Chloro-α-[[(4-fluorophenyl)amino]methylene]-β-oxobenzenepropanoate (2d) was isolated as a white solid in 28% yield. Mp: 110−111 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (major isomer) 12.70 (d, 1H, $J =$ Hz), 8.47 (d, 1H, $J = 13.1$ Hz), 7.59 (d, 1H, $J = 8.2$ Hz), 7.46−7.07 (m, 7H), 4.07 (q, 2H, $J = 7.0$ Hz), 1.05 (t, 3H, $J = 7.2$ Hz). Anal. ($C_{18}H_{15}ClFNO_3$) C, H, N.

Compounds **5**−**10** were prepared by using the method used above for the synthesis of **2a**−**d.**

Ethyl 2-Chloro-α-[[(4-chlorophenyl)amino]methylene]-β-oxobenzenepropanoate (**5**). A precipitate formed as the reaction was stirred in EtOH. The product was isolated by filtration and washed with EtOH, affording a 47% yield of the dichloride as a solid. Mp: 121.5−122.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (major isomer) 12.71 (d, 1H, $J = 12.8$ Hz), 8.58 (d, 1H, $J = 13.4$ Hz), 7.40 (d, 2H, $J = 8.9$ Hz), 7.37−7.28 (m, 4H), 7.22 (d, 2H, $J = 8.9$ Hz), 4.01 (q, 2H, $J = 7.1$ Hz), 0.93 (t, 3H, $J = 7.0$ Hz). Anal. ($C_{18}H_{15}Cl_2NO_3$) C, H, N.

Ethyl 2-Chloro-α-[[(2-chlorophenyl)amino]methylene]-β-oxobenzenepropanoate (**6**) was isolated as a viscous oil after chromatography on silica gel eluting with 6:1 hexanes/EtOAc. The oil solidified on standing to give a white solid. Mp: 92−95 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (major isomer) 12.99 (d, 1H, $J = 13.1$ Hz), 8.66 (d, 1H, $J = 13.4$ Hz), 7.48 (d, 1H, $J = 8.5$ Hz), 7.45−7.31 (m, 6H), 7.19−7.12 (m, 1H), 4.03 (q, 2H, $J = 7.1$ Hz), 0.94 (t, 3H, $J = 7.2$ Hz). Anal. ($C_{18}H_{15}Cl_2NO_3$) C, H, N.

Ethyl 2-Chloro-α-[[(3-chlorophenyl)amino]methylene]-β-oxobenzenepropanoate (**7**). Mp: 107−108 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (major isomer) 12.65 (d, 1H, $J = 13.4$ Hz), 8.59 (d, 1H, $J = 13.1$ Hz), 7.38−7.21 (m, 7H), 7.17 (dt, 1H, $J = 7.8$, 2.0 Hz), 4.02 (q, 2H, $J = 7.0$ Hz), 0.94 (t, 3H, $J = 7.0$ Hz). Anal. ($C_{18}H_{15}Cl_2NO_3$) C, H, N.

Ethyl 2-Chloro-α-[[(4-methylphenyl)amino]methylene]-β-oxobenzenepropanoate (**8**). Mp: 106−108 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.74 (d, 1H, $J = 13.7$ Hz), 8.62 (d, 1H, $J = 13.4$ Hz), 2.37 (s, 3H), 7.37−7.25 (m, 4H), 7.23 (d, 2H, $J = 8.8$ Hz), 7.17 (d, 2H, $J = 8.5$ Hz), 4.00 (q, 2H, $J = 7.1$ Hz), 0.93 (t, 3H, $J = 7.0$ Hz). Anal. ($C_{19}H_{18}ClNO_3$) C, H, N.

Ethyl 2-Chloro-α-[[(4-isopropylphenyl)amino]methylene]-β-oxobenzenepropanoate (**9**). Mp: 87−88 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (major isomer) 12.74 (d, 1H, $J = 13.4$ Hz), 8.63 (d, 1H, $J = 13.4$ Hz), 7.37−7.25 (m, 6H), 7.21 (d, 2H, $J = 8.5$ Hz), 4.00 (q, 2H, $J = 7.2$ Hz), 2.93 (heptet, 1H, $J = 7.0$ Hz), 1.26 (d, 6H, $J = 7.0$ Hz), 0.93 (t, 3H, $J = 7.0$ Hz). Anal. ($C_{21}H_{22}ClNO_3$) C, H, N.

Ethyl 2-Chloro-α-[[(4-ethynylphenyl)amino]methylene]-β-oxobenzenepropanoate (**10**). Mp: 131−132.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (major isomer) 12.70 (d, 1H, $J = 13.4$ Hz), 8.62 (d, 1H, $J = 13.4$ Hz), 7.55 (d, 2H, $J = 8.9$ Hz), 7.36−7.27 (m, 4H), 7.24 (d, 2H, $J = 8.9$ Hz), 4.02 (q, 2H, $J = 7.1$ Hz), 3.14 (s, 1H), 0.94 (t, 3H, $J = 7.2$ Hz). Anal. ($C_{20}H_{16}ClNO_3$) C, H, N.

5-(2-Chlorobenzoyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (12). A solution of 2,2-dimethyl-1,3-dioxane-4,6-dione (24.0 g, 166.5 mmol) and 4-(dimethylamino)pyridine (DMAP, 47.47 g, 209 mmol) in CH_2Cl_2 (500 mL) was cooled in an ice−salt bath to −10 °C, and a solution of 2-chlorobenzoyl chloride (32.44 g, 185 mmol) in CH_2Cl_2 (125 mL) was added dropwise via addition funnel over 2 h. The resulting yellow solution was kept in the cooling bath for 4 h and allowed to stir at room temperature overnight. The orange-yellow solution was then cooled in an ice−water bath and washed with 3 × 100 mL of a 1 M aqueous HCl solution and water. The organic layer was dried over $MgSO_4$ and filtered, and the filtrate was evaporated to dryness. The residue was triturated with hexanes (500 mL), and the resulting yellow solid was collected by filtration, washed with hexanes (100 mL), and dried under vacuum to give 45.08 (96%) of **12** as a yellow powder. The organic layer was extracted with EtOAc (3 × 50 mL), and the pooled organic layers were washed with water and brine, dried ($MgSO_4$), filtered, and concentrated to afford an additional 2.19 g of crude product. A suspension of 23 g (81 mmol) of crude **12** in 800 mL of toluene was stirred at room temperature for 45 min and then filtered to remove insoluble material. The toluene solution was then treated with neat isopropylamine (6.0 mL, 4.2 g, 70 mmol) added dropwise via syringe. The resulting precipitate was isolated by filtration and washed with toluene (3 × 50 mL) and hexanes (2 × 50 mL) to afford the salt **12a** as a yellow solid. Mp: 147−149 °C (dec). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.75 (br s, 3H), 7.24−7.15 (m, 3H), 7.02 (dd, 1H, $J = 7.0$, 2.1 Hz), 3.26 (heptet, 1H, $J = 6.4$ Hz), 1.53 (s, 6H), 1.16 (d, 6H, $J = 6.4$ Hz). ^{13}C NMR (100 MHz, DMSO-d_6) 187.51, 163.59, 145.71, 128.28, 128.19, 127.33, 126.94,

126.05, 99.50, 88.32, 42.85, 26.14, 20.20 ppm. Anal. ($C_{16}H_{20}ClNO_5$) C, H, N. The salt was then suspended in CH_2Cl_2 and washed a 1 M aqueous HCl solution. The organic layer was separated, dried ($MgSO_4$), filtered, and concentrated to give **12** as a yellow solid. Mp: 88.5−91 °C (dec). ^{1}H NMR (400 MHz, $CDCl_3$): δ 15.10 (br s, 1H), 7.54−7.38 (m, 4H), 1.81 (s, 6H).

1,1-Dimethylethyl 2-Chloro-β-oxobenzenepropionate (13). A mixture of **12** (11.5 g, 41.0 mmol) and *t*-BuOH (15 mL) was refluxed for 5 h and then concentrated to dryness. The residue was purified by silica gel chromatography. Elution with 1:9 EtOAc/hexanes gave 7.23 g (70%) of ester **13** as a viscous yellow oil that was carried on without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ (mixture of keto and enol forms, ratio 1.9:1) 12.62 (s, 1H, enol OH), 7.61−7.30 (m, 4H), 5.45 (s, 1H, enol =CH), 3.94 (s, 2H, keto CH_2), 1.54 (s, 9H, enol tBu), 1.39 (s, 9H, keto tBu). Anal. ($C_{13}H_{15}ClO_3$) C, H, N.

1,1-Dimethylethyl 2-Chloro-α-[(dimethylamino)methylene]-β-oxobenzenepropanoate (14). A solution of the 1,1-dimethylethyl ester **13** (2.00 g, 7.86 mmol) and 1.20 g (10 mmol) of DMFDMA in toluene (25 mL) was stirred at 80 °C for 16 h. The reaction was concentrated in vacuo and the residue was subjected to column chromatography. Elution with 3:2 hexanes/EtOAc afforded 1.96 g (80%) of **14** as an oil that solidified on standing. Mp: 97−99 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (s, 1H), 7.40 (br s, 1H), 7.35−7.23 (m, 4H), 3.31 (br s, 3H), 2.94 (br s, 3H), 1.10 (s, 9H). Anal. ($C_{16}H_{20}ClNO_3$) C, H, N.

1,1-Dimethylethyl 2-Chloro-α-[[(4-chlorophenyl)amino]methylene]-β-oxobenzenepropanoate (**15**). A solution **14** (3.86 g, 12.5 mmol) and 4-chloroaniline (1.59 g, 12.5 mmol) in EtOH (25 mL) was stirred at room temperature for 45 h. The resulting precipitate was isolated and washed with EtOH, giving 2.91 g of **15** as a white solid. Mp: 129−132 °C. The EtOH mother liquor was concentrated in vacuo and the residue was purified by flash chromatography, affording an additional 1.55 g of **15** (91% total yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.56 (d, 1H, J = 13.4 Hz), 8.54 (d, 1H, J = 13.4 Hz), 7.38 (d, 2H, J = 8.5 Hz), 7.36−7.24 (m, 4H), 7.20 (d, 2H, J = 8.9 Hz), 1.16 (s, 9H). Anal. ($C_{20}H_{19}Cl_2NO_3$) C, H, N.

2-Chloro-α-[[(4-chlorophenyl)amino]methylene]-β-oxobenzenepropanoic Acid (**11**). To a solution of *tert*-butyl ester **15** (1.30 g, 3.30 mmol) in CH_2Cl_2 (20 mL) was added trifluoroacetic acid at room temperature, and the solution was stirred at room temperature for 16 h. The resulting yellow reaction was evaporated to dryness and the residue was dissolved in toluene and concentrated in vacuo. The residual solid was triturated with hexanes, filtered, washed with hexanes, and dried under vacuum to give 830 mg (75%) of the carboxylic acid **11** as a light yellow solid. Mp: 179−184 °C (dec). ^{1}H NMR (400 MHz, $CDCl_3$): δ 14.11 (s, 1H), 12.22 (d, 1H, J = 12.8 Hz), 7.77 (d, 1H, J = 13.4 Hz), 7.53−7.38 (m, 4H), 7.34 (d, 2H, J = 8.7 Hz), 6.97 (d, 2H, J = 8.7 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.47, 170.14, 156.62, 136.45, 136.42, 132.47, 131.56, 130.72, 130.28, 130.15, 129.01, 127.29, 119.56, 101.54 ppm. Anal. ($C_{16}H_{11}Cl_2NO_3$) C, H, N.

2-Chloro-α-[(dimethylamino)methylene]-*N*-ethyl-β-oxobenzenepropanamide (18a). General procedure for the direct conversion of acyl Meldrum's acid **12** to β-ketoamides **17** and conversion to enaminones **18**.

2-Chloro-*N*-ethyl-β-oxobenzenepropanamide (17a). A suspension of **12** (23.5 g, 83.2 mmol) in 800 mL of toluene was stirred at room temperature for 30 min. The mixture was filtered and the toluene solution was treated with a 2 M solution of ethylamine in THF (24 mL, 48 mmol) added dropwise via addition funnel. The resulting precipitate was collected and washed with toluene (50 mL) and hexanes (2 × 50 mL). A suspension of the salt (18.54 g, 56.58 mmol) in 250 mL of benzene was heated at reflux for 5 h. Once at room temperature, the reaction was concentrated in vacuo to give the crude β-ketoamide as an oil. Chromatography with 1:1 hexanes/EtOAc afforded **17a** as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$; mixture of keto and enol forms): δ 14.19 (enol OH; s, 1H), 7.56 (d, 1H, J = 7.6 Hz), 7.44−7.29 (m, 3H), 6.91 (br s, 1H), 5.42 (br s, 1H), 5.36 (enol =CH; s, 1H), 3.93 (keto CH_2; s, 2H), 3.43−3.31 (m, 2H), 1.21 (enol CH_3; t, 3H, J = 7.3 Hz), 1.17 (keto CH_3; t, 3H, J = 7.3 Hz). Anal. ($C_{11}H_{12}ClNO_2$) C, H, N.

2-Chloro-α-[(dimethylamino)methylene]-*N*-ethyl-β-oxobenzenepropanamide (18a). A solution of **17a** (5.63 g, 25.0 mmol) in 60 mL of CH_2Cl_2 was treated with DMFDMA (4.0 mL, 3.6 g, 30 mmol) and stirred at room temperature overnight. The reaction was concentrated to dryness and then subjected to column chromatography. Elution with 3% and 4% MeOH/CH_2Cl_2 afforded 3.37 g of the crude product as an oil. Trituration with hexanes afforded 2.97 g (42%) of **18a** as a yellow solid. Mp: 97.5−100 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23 (br s, 1H), 7.41−7.39 (m, 1H), 7.34−7.27 (m, 3H), 7.15 (br s, 1H), 3.37 (pentet, 1H, J = 6.7 Hz), 3.08 (br s, 6H), 1.18 (t, 3H, J = 6.7 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.18, 165.55, 161.18, 140.60, 131.03, 129.86, 129.80, 128.45, 126.71, 105.96, 45.00 (br), 34.16, 14.72 ppm. Anal. ($C_{14}H_{17}ClN_2O_2$) C, H, N.

2-Chloro-β-oxo-*N*-propylbenzenepropanamide (17d) was isolated as a colorless oil after chromatography with 1% MeOH/CH_2Cl_2. ^{1}H NMR (400 MHz, $CDCl_3$; 2.3:1 mixture of keto and enol forms): δ 14.21 (enol OH; s, 1H), 7.56 (keto ArH; d, 1H, J = 7.9 Hz), 7.44−7.29 (m, 3H), 6.96 (keto NH; br s, 1H), 5.47 (enol NH; br s, 1H), 5.29 (enol =CH; s, 1H), (3.93 (keto CH_2; s, 2H), 3.31 (enol CH_2CH_3; q, 3H, J = 6.7 Hz), 3.27 (keto CH_2CH_3; q, 3H, J = 7.0 Hz), 1.59 (enol CH_2CH_3, hextet, 2H, J = 7.3 Hz), 1.56 (keto CH_2CH_3, hextet, 2H, J = 7.3 Hz), 0.96 (enol CH_3; t, 3H, J = 7.3 Hz), 0.94 (keto CH_3; t, 3H, J = 7.3 Hz). Anal. ($C_{12}H_{14}ClNO_2$) C, H, N.

2-Chloro-α-[(dimethylamino)methylene]-β-oxo-*N*-propylbenzenepropanamide (18d) was isolated as a light yellow solid after chromatography with 2.5% MeOH/CH_2Cl_2 and trituration with hexanes. Mp: 85−90 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.29 (br s, 1H), 7.39 (d, 1H, J = 7.0 Hz), 7.34−7.27 (m, 3H), 7.14 (br s, 1H), 3.31 (q, 2H, J = 6.6 Hz), 3.07 (br s, 6H), 1.58 (hextet, 2H, J = 7.0 Hz), 0.96 (t, 3H, J = 7.3 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.17, 165.55, 161.23, 140.52, 130.95, 129.83, 129.76, 128.42, 126.66, 105.88, 45.00 (br), 41.11, 22.75, 11.43 ppm. Anal. ($C_{15}H_{19}ClN_2O_2$) C, H, N.

2-Chloro-*N*-methyl-β-oxobenzenepropanamide (17c) was isolated as a light yellow oil in 82% yield after chromatography with 1:1 hexanes/EtOAc. ^{1}H NMR (400 MHz, $CDCl_3$; 2.6:1 mixture of keto and enol forms): δ 14.20 (enol OH; br s, 1H), 7.59−7.29 (m, 4H), 7.00 (keto NH; br s, 1H), 5.50 (enol NH; br s, 1H), 5.38 (enol =CH; s, 1H), 3.95 (keto CH_2, s, 2H), 2.91 (enol Me; d, 3H, J = 4.6 Hz), 2.86 (keto Me; d, 3H, J = 4.9 Hz). Anal. ($C_{10}H_{10}ClNO_2$) C, H, N.

2-Chloro-α-[(dimethylamino)methylene]-*N*-methyl-β-oxobenzenepropanamide (18c) was isolated as a light yellow oil that solidified on standing. Mp: 84−88 °C, after chromatography with 5% MeOH/CH_2Cl_2. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.34 (br s, 1H), 7.11 (br s, 1H), 3.07 (s, 6H), 2.90 (d, 3H, J = 4.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) 191.21, 166.12, 161.50, 140.37, 130.84, 129.79, 129.72, 128.34, 126.64, 105.57, 47.30 (br), 42.30 (br), 25.84 ppm. Anal. ($C_{13}H_{15}ClN_2O_2$) C, H, N.

2-Chloro-*N*-isopropyl-β-oxobenzenepropanamide (17e) was isolated as a white solid (65% yield) after chromatography with 3:1 hexanes/EtOAc. Mp: 85−86 °C. ^{1}H NMR (400 MHz, $CDCl_3$; mixture of keto and enol forms, keto form given): δ 7.56 (d, 1H, J = 7.3 Hz), 7.44−7.30 (m, 3H), 6.72 (br s, 1H), 3.91 (s, 2H), 1.18 (d, 6H, J = 6.4 Hz). Anal. ($C_{12}H_{14}ClNO_2$) C, H, N.

2-Chloro-α-[(dimethylamino)methylene]-*N*-isopropyl-β-oxobenzenepropanamide (18e). The crude reaction was concentrated to dryness and partitioned between EtOAc and water. The EtOAc layer was washed with a dilute aqueous $NaHCO_3$ solution and brine. After drying (Na_2SO_4), the mixture was filtered and concentrated to a light yellow foam. Trituration with hexanes gave a light yellow solid which was further purified by RPHPLC, affording the product as a white solid. Mp: 96−97 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 (dd, 1H, J = 7.6, 0.9 Hz), (7.31−7.24 (m, 3H), 7.18 (br s, 1H), 4.07 (m, 1H), 3.05 (br s, 6H), 1.14 (d, 6H, J = 5.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) 190.90, 164.87, 160.65, 140.42, 130.84,

129.83, 129.71, 128.23, 126.66, 105.89, 47.79 (br), 41.93 (br), 41.07, 22.56 ppm. Anal. ($C_{15}H_{19}ClN_2O_2$) C, H, N.

2-Chloro-*N*-cyclopropyl-β-oxobenzenepropanamide (17g) was isolated as an off-white solid after chromatography with 2:1 hexanes/EtOAc. Mp: 54.5−59 °C. ^{1}H NMR (400 MHz, $CDCl_3$; 4:1 mixture of keto and enol forms, keto form given): δ 7.44−7.29 (m, 4H), 7.03 (br s, 1H), 3.91 (s, 2H), 2.81−2.73 (m, 1H), 0.86−0.77 (m, 2H), 0.61−0.53 (m, 2H). Anal. ($C_{12}H_{12}ClNO_2$) C, H, N.

2-Chloro-*N*-cyclopropyl-α-[(dimethylamino)methylene]-β-oxobenzenepropanamide (18g). A solution of **17g** (234 mg, 0.984 mmol) and DMFDMA (0.5 mL, 3.75 mmol) in 3 mL of CH_2Cl_2 was stirred at room temperature for 4 d. The resulting yellow solution was then concentrated in vacuo and the residue was purified by RPHPLC and recrystallized from CH_2Cl_2/hexanes to give a white solid. Mp: 121−122 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.43 (br s, 1H), 7.38 (d, 1H, *J* = 7.6 Hz), 7.33−7.24 (m, 3H), 7.15 (br s, 1H), 3.08 (br s, 6H), 2.80 (m, 1H), 0.75 (br s, 2H), 0.50 (br s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) 191.05, 166.91, 161.25, 140.34, 130.75, 129.80, 129.66, 128.22, 126.62, 47.67 (br), 42.53 (br), 22.26, 6.31 ppm. Anal. ($C_{15}H_{17}ClN_2O_2$) C, H, N.

2-Chloro-*N*-(1,1-dimethylethyl)-β-oxobenzenepropanamide (17k) was isolated as a white solid. Mp: 109−110 °C after chromatography (100% CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$; mixture of keto and enol forms, NMR of keto form given): δ 7.56 (d, 1H, *J* = 7.3 Hz), 7.43−7.30 (m, 3H), 6.66 (br s, 1H), 3.85 (s, 2H), 1.36 (s, 9H). Anal. ($C_{13}H_{16}ClNO_2$) C, H, N.

2-Chloro-α-[(dimethylamino)methylene]-*N*-(1,1-dimethylethyl)-β-oxobenzenepropanamide (18k). A solution of **17k** (879 mg, 3.46 mmol) in 5 mL of CH_2Cl_2 was treated with 1.0 mL (7.5 mmol) of DMFDMA. After stirring at room temperature for 3 d, the reaction was concentrated to dryness and the residue was partitioned between EtOAc and water. The EtOAc layer was separated, washed with a brine solution, dried ($MgSO_4$), filtered, and concentrated. The oil that formed was purified by flash chromatography (silica gel; 3 and 5% MeOH/CH_2Cl_2) and RPHPLC. The resulting oil (200 mg; 20% yield) was carried on without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (d, 1H, *J* = 7.3 Hz), 7.31−7.26 (m, 3H), 3.06 (br s, 6H), 1.31 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) 190.62, 165.25, 159.97 (br), 140.72, 130.84, 129.78, 129.63, 128.25, 126.69, 50.70, 47.71 (br), 41.63 (br), 28.58 ppm. Anal. ($C_{16}H_{21}ClN_2O_2 \cdot {}^1/_3H_2O$) C, H, N.

2-Chloro-α-[[(4-chlorophenyl)amino]methylene]-*N*-(1-methylpropyl)-β-oxobenzenepropanamide (**16f**). The following is a general method for the conversion of acid **11** to amides **16**. To a solution of the carboxylic acid **11** (250 mg, 0.74 mmol) in CH_2Cl_2 (15 mL) was added $SOCl_2$ (0.5 mL). The resulting solution was stirred at room temperature for 16 h. The reaction was evaporated to dryness, dissolved in toluene, and then reconcentrated to give the crude acid chloride. A solution of the acid chloride in CH_2Cl_2 (15 mL) was added dropwise into a solution of sec-butylamine (100 mg, 1.37 mmol) in CH_2Cl_2 (3 mL) and stirred at room temperature for 5 h. The reaction was then evaporated to dryness and the residue was purified by chromatography over silica gel, eluting with 7/3 hexanes/EtOAc to give 240 mg (83%) of the amide **16f** as an off-white solid. Mp: 104−105 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.99 (d, 1H, *J* = 11.9 Hz), 9.46 (d, 1H, *J* = 7.9 Hz), 7.64 (d, 1H, *J* = 12.5 Hz), 7.47 (dd, 1H, *J* = 7.6, 1.4 Hz), 7.40 (dt, 1H, *J* = 7.0, 2.0 Hz), 7.36 (dt, 1H, *J* = 7.0, 1.4 Hz), 7.32 (dd, 1H, *J* = 7.0, 2.0 Hz), 7.26 (d, 2H, *J* = 8.8 Hz), 6.83 (d, 2H, *J* = 8.8 Hz), 4.04 (heptet, 1H, *J* = 6.7 Hz), 1.60 (m, 2H), 1.27 (d, 3H, *J* = 6.7 Hz), 1.61 (m, 2H), 1.00 (t, 3H, *J* = 7.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.98, 167.96, 155.83, 139.34, 137.74, 130.80, 130.66, 130.44, 130.00, 129.88, 128.79, 126.88, 118.58, 104.47, 46.17, 29.57, 20.27, 10.30 ppm. Anal. ($C_{20}H_{20}Cl_2N_2O_2$) C, H, N.

2-Chloro-α-[[(4-chlorophenyl)amino]methylene]-*N*-(1-ethylpropyl)-β-oxobenzenepropanamide (**16j**). Mp: 111−112 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.99 (d, 1H, *J* = 12.2 Hz), 9.43 (d, 1H, *J* = 8.5 Hz), 7.65 (d, 1H, *J* = 12.5 Hz), 7.43 (d, 1H, *J* = 7.3 Hz), 7.41 (dt, 1H, *J* = 7.0, 1.8 Hz), 7.36 (t, 1H, *J* = 7.9 Hz), 7.33 (dd, 1H, *J* = 7.3, 2.3 Hz), 6.83 (d, 2H, *J* = 8.8 Hz), 3.93 (hextet, 1H, *J* = 7.6 Hz), 1.62 (m, 4H), 0.99 (t, 6H, *J* = 7.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.13, 168.33, 155.84, 139.19, 137.60, 130.72, 130.62, 130.52, 130.04, 129.89, 128.75, 126.95, 118.58, 104.27, 51.58, 27.25, 10.37 ppm. Anal. ($C_{21}H_{22}Cl_2N_2O_2$) C, H, N.

2-Chloro-α-[[(4-chlorophenyl)amino]methylene]-*N*-(1,2-dimethylpropyl)-β-oxobenzenepropanamide (**16l**). Mp: 110 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.99 (d, 1H, *J* = 12.5 Hz), 9.57 (d, 1H, *J* = 8.5 Hz), 7.65 (d, 1H, *J* = 12.2 Hz), 7.36 (t, 1H, *J* = 7.9 Hz), 7.26 (d, 2H, *J* = 7.6 Hz), 6.83 (d, 2H, *J* = 8.5 Hz), 4.01 (hextet, 1H, *J* = 7.0 Hz), 1.86 (octet, 1H, *J* = 6.7 Hz), 1.22 (d, 3H, *J* = 6.7 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.12, 167.91, 155.83, 139.14, 137.57, 130.69, 130.62, 130.51, 130.02, 129.88, 128.75, 126.94, 118.55, 104.28, 49.61, 32.88, 18.60, 18.55, 17.51 ppm. Anal. ($C_{21}H_{22}Cl_2N_2O_2$) C, H, N.

2-Chloro-β-oxobenzenepropionic Acid (19). TFA (10 mL) was added slowly to a solution of 1,1-dimethylethyl 2-chloro-β-oxobenzenepropionate (**13**, 7.23 g, 28.4 mmol) in CH_2Cl_2 (70 mL) at room temperature with stirring. The resulting purple solution was stirred at room temperature for 5 h. The yellow solution that formed was evaporated to dryness, the residual solid was triturated with hexanes (50 mL) and filtered, and the solid was washed with hexanes (10 mL) and dried under vacuum to give 4.5 g (80%) of the carboxylic acid as an off-white powder. Mp: 101 °C (dec). The ^{1}H NMR ($CDCl_3$) indicated that it was a mixture of keto and enol forms. It was used for the next reaction without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ (1.1:1 mixture of keto and enol forms) 12.14 (s, 1H, enol OH), 10.18 (br s, 1H), 7.66−7.31 (m, 4H), 5.61 (s, 1H, enol =CH), 4.13 (s, 2H, keto CH_2). Anal. ($C_9H_7ClO_3$) C, H.

2-Chloro-*N*-cyclobutyl-β-oxobenzenepropanamide (17h). A solution of the carboxylic acid **19** (1.99 g, 10.0 mmol) obtained above and DCC (2.1 g, 11 mmol) in CH_2Cl_2 (30 mL) was stirred at room temperature for 1.5 h and a solution of cyclobutylamine (710 mg, 10.0 mmol) in CH_2Cl_2 (10 mL) was added. After stirring for 5 h, the resulting mixture was filtered to remove a white solid and the filtrate was evaporated to dryness. Purification by chromatography over silica gel (7/3 hexanes/EtOAc) gave 1.99 g (80%) of the cyclobutyl amide as a white sold. It was used for the next reaction without further purification. Mp: 82−83 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (1:1 mixture of keto and enol forms) 14.17 (br s, 1H, enol OH), 7.59−7.28 (m, 4H), 7.07 (br s, 1H), 5.58 (br s, 1H), 5.34 (s, 1H, enol =CH), 4.49 (hextet, 1H, *J* = 8.1 Hz), 4.42 (hextet, 1H, *J* = 8.1 Hz), 3.90 (s, 2H, keto CH_2), 2.42−2.31 (m, 2H), 1.98−1.88 (m, 2H), 1.78−1.69 (m, 2H). Anal. ($C_{13}H_{14}ClNO_2$) C, H, N.

2-Chloro-*N*-cyclobutyl-α-[(dimethylamino)methylene]-β-oxobenzenepropanamide (18h). A solution of 2-chloro-*N*-cyclobutyl-β-oxobenzenepropanamide (1.88 g, 7.52 mmol) obtained above and DMFDMA (1.0 g, 8.3 mmol) in toluene (25 mL) was stirred at 80−85 °C for 15 h and evaporated to dryness. The residue was purified by chromatography over silica gel (20/1 CH_2Cl_2/MeOH) to give 1.75 g (95%) of the enaminone as an off-white foam that gave a solid after trituration with hexanes. Mp: 112−113 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.60 (br s, 1H), 7.39 (d, 1H, *J* = 7.6 Hz), 7.34−7.26 (m, 3H), 7.21 (br s, 1H), 4.43 (m, 1H), 3.06 (br s, 6H), 2.34 (m, 2H), 1.94 (m, 2H), 1.72 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.10, 164.68, 161.19, 140.66, 131.02, 129.85, 129.78, 128.44, 126.69, 105.70, 44.85, 44.80 (br), 31.06, 15.37 ppm. Anal. ($C_{16}H_{19}ClN_2O_2$) C, H, N.

2-Chloro-α-[[(4-chlorophenyl)amino]methylene]-*N*-cyclobutyl-β-oxobenzenepropanamide (**16h**). A solution of 2-chloro-*N*-cyclobutyl-α-[(dimethylamino)methylene]-β-oxobenzenepropanamide (175 mg, 0.57 mmol) and 4-chloroaniline (73 mg, 0.57 mmol) in toluene (6 mL) was stirred at 75−80 °C for 5 h and evaporated to dryness. The residue was purified by chromatography over silica gel (7/3 hexanes/EtOAc) to give 175 mg (79%) of the product as a white powder. Mp: 161−162 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.95 (d, 1H, *J* = 12.3 Hz), 9.72 (d, 1H, *J* = 7.0 Hz), 7.64 (d, 1H, *J* = 12.5 Hz), 7.47 (d, 1H, *J* = 7.5 Hz), 7.41 (dt, 1H, *J* = 7.3, 1.8 Hz), 7.37 (t, 1H, *J* = 7.2 Hz), 7.31 (dd, 1H, *J* = 7.5, 1.8 Hz), 6.82 (d, 2H, *J* = 8.6 Hz), 4.49 (h, 1H, *J* = 8.1 Hz), 2.41 (m, 2H), 2.09 (m, 2H), 1.80 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ

192.90, 167.62, 155.88, 139.21, 137.60, 130.75, 130.72, 130.46, 129.99, 129.86, 128.73, 126.90, 118.58, 104.18, 44.34, 30.99, 15.54 ppm. Anal. ($C_{20}H_{18}Cl_2N_2O_2$) C, H, N.

2-Chloro-α-[[(4-chlorophenyl)amino]methylene]-*N*-ethyl-*β*-oxobenzenepropanamide (16a). Mp: 150.5−151.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.99 (d, 1H, J = 12.5 Hz), 9.54 (br t, 1H), 7.65 (d, 1H, J = 12.5 Hz), 7.47 (dd, 1H, J = 7.8, 1.5 Hz), 7.41 (dt, 1H, J = 7.3, 1.8 Hz), 7.36 (dt, 1H, J = 7.3, 1.5 Hz), 7.31 (dd, 1H, J = 7.3, 2.1 Hz), 7.26 (d, 2H, J = 8.9 Hz), 6.83 (d, 2H, J = 8.8 Hz), 3.45 (br m, 2H), 1.29 (t, 3H, J = 7.3 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.01, 168.49, 155.85, 139.24, 137.66, 130.79, 130.75, 130.48, 130.04, 129.92, 128.76, 129.93, 118.61, 104.34, 33.68, 14.73 ppm. Anal. ($C_{18}H_{16}Cl_2N_2O_2$) C, H, N.

2-Chloro-α-[[(4-chlorophenyl)amino]methylene]-*β*-oxobenzenepropanamide (16b). Mp: 186.5−187.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.75 (d, 1H, J = 12.8 Hz), 9.28 (br s, 1H), 7.61 (d, 1H, J = 12.8 Hz), 7.48 (dd, 1H, J = 7.6, 1.2 Hz), 7.42 (dt, 1H, J = 7.0, 1.8 Hz), 7.38 (dt, 1H, J = 7.2, 1.4 Hz), 7.33 (dd, 1H, J = 7.2, 2.0 Hz), 7.28 (d, 2H, J = 8.9 Hz), 6.79 (d, 2H, J = 8.8 Hz), 5.59 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.67, 170.61, 156.28, 139.17, 137.51, 131.02, 130.71, 130.56, 130.03, 129.90, 128.74, 126.98, 118.86, 104.02 ppm. Anal. ($C_{16}H_{12}Cl_2N_2O_2$) C, H, N.

2-Chloro-α-[[(4-chlorophenyl)amino]methylene]-*N*-methyl-*β*-oxobenzenepropanamide (16c). Mp: 169.5−170.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.98 (d, 1H, J = 12.2 Hz), 9.49 (br s, 1H), 7.65 (d, 1H, J = 12.5 Hz), 7.47 (dd, 1H, J = 7.9, 1.2 Hz), 7.41 (dt, 1H, J = 7.3, 1.8 Hz), 7.37 (dt, 1H, J = 7.6, 1.2 Hz), 7.31 (dd, 1H, J = 7.3, 1.8 Hz), 7.26 (d, 2H, J = 8.8 Hz), 6.83 (d, 2H, J = 8.8 Hz), 2.98 (d, 3H, J = 4.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.00, 169.26, 155.78, 139.22, 137.66, 130.81, 130.52, 130.06, 129.95, 128.75, 126.96, 118.63, 104.43, 25.34 ppm. Anal. ($C_{17}H_{14}Cl_2N_2O_2$) C, H, N.

2-Chloro-α-[[(4-chlorophenyl)amino]methylene]-*β*-oxo-*N*-propylbenzenepropanamide (16d). Mp: 119−120 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.99 (d, 1H, J = 12.2 Hz), 9.60 (br s, 1H), 7.65 (d, 1H, J = 12.5 Hz), 7.47 (dd, 1H, J = 7.9, 1.2 Hz), 7.41 (dt, 1H, J = 7.2, 2.0 Hz), 7.37 (dt, 1H, J = 7.2, 1.4 Hz), 7.32 (dd, 1H, J = 7.3, 1.8 Hz), 7.26 (d, 2H, J = 8.5 Hz), 6.83 (d, 2H, J = 8.8 Hz), 3.38 (br s, 2H), 1.68 (hextet, 2H, J = 7.3 Hz), 1.03 (t, 3H, J = 7.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.04, 168.64, 155.86, 139.36, 137.76, 130.86, 130.78, 130.50, 130.07, 129.96, 118.64, 104.50, 40.66, 22.79, 11.57 ppm. Anal. ($C_{19}H_{18}Cl_2N_2O_2$) C, H, N.

2-Chloro-α-[[(4-chlorophenyl)amino]methylene]-*N*-isopropyl-*β*-oxobenzenepropanamide (16e). Mp: 130.5−131.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.01 (d, 1H, J = 12.2 Hz), 9.46 (d, 1H, J = 7.0 Hz), 7.47 (dd, 1H, J = 7.6, 1.2 Hz), 7.41 (dt, 1H, J = 7.3, 2.0 Hz), 7.36 (dt, 1H, J = 7.3, 1.2 Hz), 7.31 (dd, 1H, J = 7.3, 2.1 Hz), 7.25 (d, 2H, J = 8.8 Hz), 7.64 (d, 1H, J = 12.5 Hz), 6.83 (d, 2H, J = 8.5 Hz), 4.20 (octet, 1H, J = 6.8 Hz), 1.30 (d, 6H, J = 6.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.97, 167.77, 155.89, 139.32, 137.73, 130.80, 130.70, 130.47, 130.03, 129.91, 128.79, 126.92, 118.61, 104.43, 40.89, 22.74 ppm. Anal. ($C_{19}H_{18}Cl_2N_2O_2$) C, H, N.

2-Chloro-α-[[(4-chlorophenyl)amino]methylene]-*N*-cyclopropyl-*β*-oxobenzenepropanamide (16g). Mp: 158−159 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.99 (d, 1H, J = 12.5 Hz), 9.58 (br s, 1H), 7.64 (d, 1H, J = 12.5 Hz), 7.47 (d, 1H, J = 7.9 Hz), 7.42 (dt, 1H, J = 7.7, 1.4 Hz), 7.36 (t, 1H, J = 7.3 Hz), 7.29 (d, 1H, J = 7.2 Hz), 7.27 (d, 2H, J = 8.8 Hz), 6.83 (d, 2H, J = 8.8 Hz), 2.86 (hextet, 1H, J = 3.7 Hz), 0.87 (m, 2H), 0.68 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.84, 170.14, 155.68, 139.05, 137.50, 130.75, 130.67, 130.47, 129.97, 129.87, 128.65, 126.88, 118.51, 104.11, 21.97, 6.28 ppm. Anal. ($C_{19}H_{16}Cl_2N_2O_2$) C, H, N.

2-Chloro-α-[[(4-chlorophenyl)amino]methylene]-*N*-cyclopentyl-*β*-oxobenzenepropanamide (16i). Mp: 165−166 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.00 (d, 1H, J = 12.2 Hz), 9.58 (d, 1H, J = 6.4 Hz), 7.63 (d, 1H, J = 12.2 Hz), 7.47 (dd, 1H, J = 7.9, 1.2 Hz), 7.41 (dt, 1H, J = 7.0, 2.0 Hz), 7.36 (dt, 1H, J = 7.2, 1.4 Hz), 7.30 (dd, 1H, J = 7.2, 2.0 Hz), 6.83 (d, 2H, J = 8.8 Hz), 4.32 (hextet, 1H, J = 6.6 Hz), 2.06 (m, 2H), 1.78 (m, 2H), 1.64 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.92, 168.10, 155.76, 139.28, 137.70, 130.77, 130.66, 130.44, 129.99, 129.87, 128.77, 126.88, 118.56, 104.44, 50.67, 33.17, 23.84 ppm. Anal. ($C_{21}H_{20}Cl_2N_2O_2$) C, H, N.

2-Chloro-α-[[(4-chlorophenyl)amino]methylene]-*N*-(1,1-dimethylethyl)-*β*-oxobenzenepropanamide (16k). Mp: 177−177.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.98 (d, 1H, J = 12.2 Hz), 9.56 (s, 1H), 7.62 (d, 1H, J = 12.2 Hz), 7.46 (d, 1H, J = 7.6 Hz), 7.40 (dd, 1H, J = 1.5 Hz), 7.35 (t, 1H, J = 6.7 Hz), (dd, 1H, J = 7.0, 2.0 Hz), 7.25 (d, 2H, J = 8.5 Hz), 6.84 (d, 2H, J = 8.8 Hz), 1.49 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.11, 168.04, 156.11, 139.49, 137.87, 130.81, 130.65, 130.42, 130.02, 129.88, 128.80, 126.91, 118.72, 105.22, 50.96, 29.03 ppm. Anal. ($C_{20}H_{20}Cl_2N_2O_2$) C, H, N.

2-Chloro-α-[[(4-ethynylphenyl)amino]methylene]-*β*-oxo-*N*-propylbenzenepropanamide (20). A solution of 2-chloro-α-[(dimethylamino)methylene]-*β*-oxo-*N*-propylbenzenepropanamide (104 mg, 0.35 mmol) and 41 mg (0.35 mmol) of 4-ethynylaniline in 2 mL of toluene was stirred at room temperature for 4 d. The reaction was diluted with 10 mL of EtOAc; extracted with a 1 M aqueous HCl solution (3 × 10 mL), saturated aqueous $NaHCO_3$, and NaCl solutions; dried (Na_2SO_4); filtered; and concentrated. The residue was triturated with 3 mL of MeOH to give 74 mg (58%) of the product as a light yellow solid. Mp: 175−176.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.03 (d, 1H, J = 12.5 Hz), 9.59 (s, 1H), 7.70 (d, 1H, J = 12.5 Hz), 7.48 (dd, 1H, J = 7.9, 1.2 Hz), 7.47−7.40 (m, 1H), 7.37 (dt, 1H, J = 7.3, 1.2 Hz), 7.41 (d, 2H, J = 8.5 Hz), 7.32 (dd, 1H, J = 7.3, 1.8 Hz), 6.84 (d, 2H, J = 8.5 Hz), 3.39 (br s, 2H), 3.08 (s, 1H), 1.68 (hextet, 2H, J = 7.3 Hz), 1.03 (t, 3H, J = 7.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.19, 168.58, 155.40, 139.31, 139.18, 133.76, 130.89, 130.55, 130.11, 128.82, 126.97, 119.09, 117.08, 104.74, 82.75, 40.68, 22.79, 11.59 ppm. Anal. ($C_{21}H_{19}ClN_2O_2$) C, H, N.

[^{35}S]TBPS Binding Assay. The cortex from male Sprague−Dawley rats (weighing 160−200 g) was removed immediately after euthanization and dissected over ice. A P_2 homogenate was prepared for binding assay as previously described.[10] The tissue was homogenized in 0.32 M sucrose (J.T. Baker Chemical Co., Phillipsburg, NJ) with a Teflon-coated pestle, followed by centrifugation at 1000*g* for 10 min. The supernatant was collected and centrifuged at 9000*g* for 20 min. The resultant P_2 pellet was resuspended in ice-cold 50 mM sodium potassium phosphate (J.T. Baker) buffer (pH 7.4) containing 200 mM NaCl (J.T. Baker) and used immediately in binding assays. A 2 nM concentration of [^{35}S]-TBPS (86 Ci/mmol) was incubated with 100 μL of tissue homogenate (10% w/v) in the presence or absence of 5 μM GABA and 5 μL aliquots of test drug dissolved in dimethyl sulfoxide (≤10 μL of solvent used in all assays). At the concentration (≤1%) used, dimethyl sulfoxide had no effect on specific [^{35}S]TBPS binding. All assays were brought to a final volume of 1 mL with 50 mM sodium potassium phosphate buffer (pH 7.4) containing 200 mM NaCl. Nonspecific binding was defined as binding in the presence of 2 μM TBPS and accounted for ∼30% of the total binding. Assays were terminated after a 90 min steady-state incubation at 25 °C by rapid filtration through glass fiber filters (no. 32; Schleicher & Schuell, Keene, NH). Filter-bound radioactivity was quantified by liquid scintillation spectrophotometry (LSC). The data were evaluated by nonlinear regression (GraphPad, Inc., San Diego, CA) to obtain IC_{50} (concentration at which half-maximal inhibition of radioligand occurs) values and I_{max} values (maximal inhibition).

[^{3}H]Flunitrazepam Binding Assay. The [^{3}H]flunitrazepam binding assay was carried using the conditions and tissue preparation described for the [^{35}S]TBPS assay, with the exception that 1 μM GABA was used instead of 5 μM GABA. [^{3}H]Flunitrazepam (0.2 nM, 75 Ci/mmol) was used to label BZ-sites. Nonspecific binding was defined as binding in the presence of 1 μM clonazepam. Values are means and SEMs of three independent experiments.

[^{3}H]Muscimol Binding Assay. The cortex from male Sprague−Dawley rats (weighing 160−200 g) was removed immediately after euthanization and dissected over ice. The tissue was homogenized in 15 vol of 0.32 M sucrose followed by centrifugation at 1000*g*

for 10 min. The supernatant was transferred to a 38 mL polycarbonate tube (Beckman Instruments, Palo Alto CA) and centrifuged at 20000*g* for 20 min. The membrane pellet was resuspended in 10 vol of distilled water and centrifuged at 8000*g* for 20 min. The resulting pellet was washed with distilled water once and with Na^+-free assay buffer (40 mM KH_2PO_4, 100 mM KCl, pH 7.4). The pellet was resuspended in 35 mL of Na^+-free assay buffer, incubated at 37 °C for 30 min, and then centrifuged at 31000*g* for 20 min. The final pellet was resuspended in 10 vol of Na^+-free assay buffer. The protein concentration was about 1 mg/mL by BCA reagent protein assay. Aliquots of membrane suspension (100 μL) were incubated in Na^+-free assay buffer with 5 nM [^{3}H]muscimol (25 Ci/mmol) and 5 μL of DMSO or drug dissolved in DMSO. The final volume of the incubation medium was 1 mL. Nonspecific binding was defined as binding in the presence of 1 mM GABA. After the membranes were added, the tubes were briefly vortexed and incubated at 4 °C in the dark. The incubation was terminated after 60 min by rapid filtration through glass filters followed by three washes with ice-cold assay buffer. Filter-bound radioactivity was quantified by LSC after overnight extraction. The data were evaluated as described for the [^{35}S]TBPS assay.

Locomotor Activity Paradigm. Nonhabituated male non-Swiss albino (NSA) mice were injected with test compounds dissolved in 100% PEG 400 immediately before being placed in an E63-12 Tru Scan activity chamber (Colbourn Instruments, Allentown, PA). Activity was monitored by horizontal beam breaks initiated by the test animal and recorded every 5 min. Habituated male NSA mice were exposed for 30 min to the activity chamber for three consecutive days. On the fourth day, habituated male NSA mice were injected with the test compound in PEG 400 or PEG 400 and immediately placed into the activity chamber. Activity in habituated mice was recorded every 5 min for 1 h. Activity for habituated and nonhabituated animals was defined as the total distance traveled (cm). All animals were tested between 9 a.m. and 2 p.m.

LRR Method. Male NSA mice were dosed with test compounds at 50 mg/kg ip or po in PEG 400. After injection animals were placed on their backs. Animals that righted themselves within 1 min were considered not to have lost their righting reflex. Those that remained on their backs for more than 1 min were considered to have lost their righting reflex.

Rotarod Test. The CNS depressant potential of compounds was evaluated in the rotarod test as previously described.[9] A dose that causes behavioral toxicity in half the animals (toxic dose; TD_{50}) was calculated on the basis of each dose−response function by the method of Litchfield and Wilcoxon.[29]

Light−Dark Paradigm. Male NSA mice (25−30 g) were used. The apparatus consisted of an open-topped box divided into small and large area by a partition that has a hole at floor level. The small compartment was painted black and the large compartment white. The white compartment was illuminated with light and the black compartment with red light. The time spent in the light compartment was recorded during a 3 min test session. Vehicle or test compounds were administered 30 min prior to the test.

Anticonvulsant Assay. Adult male NSA mice (25−30 g) were used. Time to peak anticonvulsant effect was determined against pentylenetetrazole (PTZ) induced seizures. Mice were injected (ip) with various doses of drug dissolved in PEG 400 or PEG 400 at the time of peak effect before administration (sc) of a CD_{97} dose of PTZ (85 mg/kg) or vehicle (0.9% saline 5 μL/g body weight). Immediately after the injection mice are observed for a period of 45−60 min. Six animals were used per dose of test drug. The number of animals with tonic/clonic convulsions was recorded.

Electrophysiology. Preparation, maintenance, and microinjection of *Xenopus* oocytes were performed as reported previously.[25] Individual oocytes were microinjected with ∼1−5 ng of cRNA encoding human α_1, β_2, and γ_{2L} $GABA_A$ receptor subunits. Membrane current responses were measured at a holding potential of −70 mV using conventional two-electrode voltage clamp techniques, 3−11 days following injection. All drugs were dissolved in DMSO and diluted with frog Ringer ((in mM) NaCl, 115; KCl, 2; $CaCl_2$, 1.8; HEPES, 5; pH adjusted to 7.4 with NaOH; final DMSO concentration <1%) and applied to oocytes via a linear array rapid perfusion system.[25] Modulatory effects of compounds were assayed on control responses that were 10% of the maximum GABA response (EC_{10}) in an individual oocyte. Modulation was measured as a percentage of I_{max}. Numerical data values listed refer to value ±SEM.

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

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