Synthesis and Structure-Activity Relationships of 3,5-Disubstituted 4,5-Dihydro-6*H*-imidazo[1,5-*a*][1,4]benzodiazepin-6-ones at Diazepam-Sensitive and Diazepam-Insensitive Benzodiazepine Receptors

Subramaniam Ananthan,*,† Sarah D. Clayton,† Steven E. Ealick,‡ Garry Wong,§ Gary E. Evoniuk,§ and Phil Skolnick§

Organic Chemistry Department, Southern Research Institute, Birmingham, Alabama 35255, Section of Biochemistry, Molecular and Cell Biology, Cornell University, Ithaca, New York 14853, and Laboratory of Neuroscience, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland 20892

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A series of imidazobenzodiazepin-6-ones possessing varying substituents at the 3- and 5-positions were synthesized and evaluated for their affinities at diazepam-sensitive (DS) and diazepam-insensitive (DI) benzodiazepine receptors (BzR) in rat cortical and cerebellar membranes. Replacement of an ester substituent at the 3-position with a carbamate, acetylamino, formylamino, isothiocyanato, 2-oxazolinyl, 2-benzoxazolyl, or p-tolylsulfonyl groups lead to >100-fold reductions in affinity at both DS and DI BzR. Replacement of a methyl group on the nitrogen at the 5-position with propyl, allyl, or phenethyl groups also led to significant reductions in affinity at both BzR isoforms. However, incorporation of a benzyl group yields ligands (**11f,h,i** and **14a-c**) with moderate to high affinities at DS BzR, suggesting the presence of a hydrophobic pocket at the receptor site. Introduction of chlorine at the 7-position enhances ligand affinity at DS BzR while chlorine at the 8-position decreases affinity (IC_{50}: **11f**, 9.3 nM; **11h**, 2.4 nM; **11i**, 37.8 nM). In contrast, chlorine substitution at the 7- as well as the 8-position increases affinity at DI BzR (K_i: **11f**, 112 nM; **11h**, 20.2 nM; **11i**, 10.9 nM). Compound **11i** is among the few described high affinity DI-site ligands with a selectivity comparable to that of Ro 15-4513. Despite their in vitro affinities, compounds **11f**, **11h**, and **11i** exhibit low in vivo activities that may be attributable to unfavorable metabolic or pharmacokinetic properties.

Benzodiazepines possessing anxiolytic, anticonvulsant, and sedative-hypnotic properties are among the most prescribed drugs in medicine. It is now generally accepted that these compounds produce their pharmacological actions by binding to specific sites on the $GABA_A$ receptor complex. Various ligands that bind to the benzodiazepine receptor (BzR) allosterically modulate the ability of GABA to regulate chloride flux through the neuronal membrane in a positive, negative, or neutral manner.[1] Depending upon their intrinsic activity profiles, BzR ligands are classified as agonists (positive modulators possessing e.g. anxiolytic and anticonvulsant actions), inverse agonists (negative modulators possessing e.g. anxiogenic and proconvulsant properties), and antagonists (agents which block the actions of either agonists or inverse agonists). Pharmacological evaluations performed with a large number of compounds indicate that the intrinsic efficacies of BzR ligands span the entire continuum from full and partial agonists to full and partial inverse agonists.[1-3]

Among the 1,2-annelated 1,4-benzodiazepines, members of the 6-arylimidazobenzodiazepines **1** as well as the 6-oxoimidazobenzodiazepines **2-4** have been shown to possess a range of intrinsic efficacies (Chart I). While the 6*H*-imidazo[1,5-*a*][1,4]benzodiazepin-6-ones of the type **2**, in general, possess inverse agonist or antagonist profiles of activity, several derivatives of types **3** and **4** have been found to possess partial agonist properties.[4-6] Such partial agonist ligands are of current clinical interest because of the possibility that at anxiolytic and anticonvulsant doses they may produce less sedation, muscle relaxation, tolerance, and physical dependence than the full agonists such as diazepam.[7,8]

Among the imidazobenzodiazepinones, the azido compound **2b** (Ro 15-4513) has attracted considerable attention as a high affinity ligand for a unique subtype of receptor site predominantly localized in cerebellar granule cells. The cerebellar sites which are bound by imidazobenzodiazepinones such as **2a** and **2b** with high affinities (and "classical" 1,4-benzodiazepines with very low affinities) have been termed diazepam-insensitive (DI) BzR to differentiate them from other, diazepam-sensitive (DS) benzodiazepine receptors.[9] Recent molecular biological studies have indicated that the ligand binding properties of the DI site can be recreated by coexpression of $\alpha_4\beta_2\gamma_2$ or $\alpha_6\beta_2\gamma_2$ subunits of the $GABA_A$ receptors.[10,11] The high affinity of **2b** for the DI site, and the finding that this compound can antagonize some of the central effects of ethanol in rodents[12] has led to extensive investigations with **2b** for studying the interactions of ethanol with GABAergic pathways and of the functional role of the DI sites in the CNS.[13,14] A recent evaluation of an extended series of known imidazobenzodiazepinones has revealed that several compounds of this class possess moderate affinities and selectivities for the DI site.[15]

The imidazobenzodiazepinones are therefore attractive as targets for the development of ligands with desirable efficacy and selectivity profiles. In an effort to expand the available structure-activity relationship (SAR) correlations,[4-6] we initiated a program involving the synthesis and evaluation of imidazobenzodiazepinones possessing varying substituents at the 3- and 5-positions. The imidazobenzodiazepinones that have been investigated as BzR ligands possess an invariant methyl group on the nitrogen at the 5-position. Although the N-unsubstituted

† Southern Research Institute.
‡ Cornell University.
§ National Institute of Diabetes and Digestive and Kidney Diseases.

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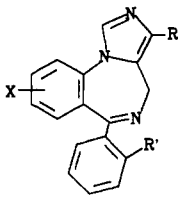
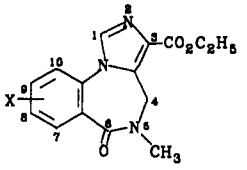
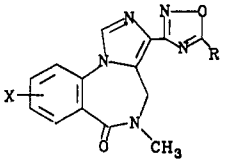
Chart I



1a R = H, R' = F, X = 6-Cl full agonist
1b R = $CONH_2$, R' = Cl, X = H partial agonist
1c R = $CO_2C(CH_3)_3$, R' = H, X = 7-Cl partial agonist



2a X = 6-F antagonist
2b X = 6-N_3 partial inverse agonist
2c X = 7-Cl partial inverse agonist
2d X = 6-Cl
2e X = H



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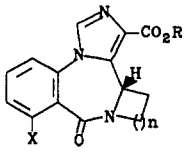

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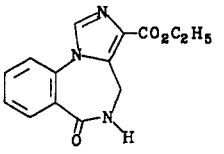
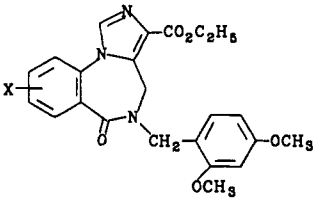
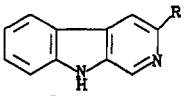


5 X = H, 7-Cl, 7-F, 6-F



6 X = H, 7-Cl, 6-F



7 R = $CO_2C_2H_5$
8 R = $NHCO_2CH_3$
9 R = $NHCO_2C_2H_5$
10 R = N=C=S

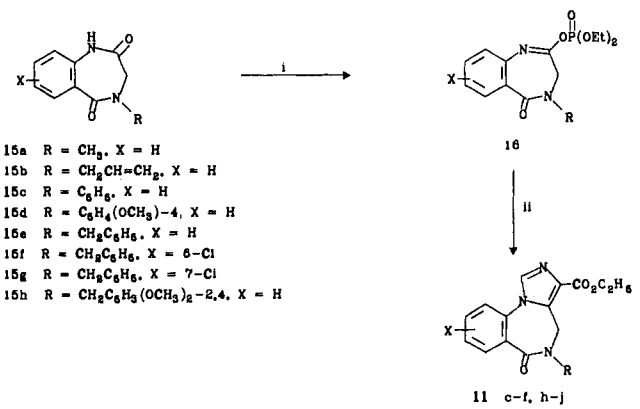
and the 5-(2,4-dimethoxybenzyl) compounds **5** and **6** (Chart I) have been prepared as intermediates leading to *N*-methyl analogues, their affinities for BzR have not been disclosed.[16-18] Several theoretical models have been proposed for the binding of various ligands to benzodiazepine receptors.[19] While some of these studies have included the imidazobenzodiazepinone group of ligands,[5,20-25] they do not provide any insights regarding the effect of N-substituents on affinity or activity.

Codding and Muir[25] have noted a remarkable structural similarity between the nonagonist imidazobenzodiazepinone-3-carboxylic esters such as **2** and β-carboline-3-carboxylic esters such as **7**. Moreover, in place of an ester group, other substituents such as Cl, NO_2, C≡N, and 3-alkyl-1,2,4-oxadiazol-5-yl groups are also tolerated well at the 3-position of these two templates.[6,26-29] Therefore it appears likely that, in the appropriate orientation, substituents at the 3-position of carbolines and imidazobenzodiazepinones may probe the same binding region. On the basis of this premise and the observation[30,31] that placement of a carbamate function at the 3-position of β-carboline provides ligands (**8**, **9**) with moderate affinities and useful intrinsic activities (e.g. an ability to antagonize the sedative effects of benzodiazepines), it was of interest to investigate a few imidazobenzodiazepinones carrying a carbamate function at the 3-position. Also included in the investigation were several other variants at the 3-position that could potentially function as bioisosteric replacements for the ester group. The synthesis and structure–affinity relationships of 5-substituted imidazobenzodiazepinone-3-carboxylic esters **11** and the 3,5-disubstituted imidazobenzodiazepinones **12–14** for binding at cortical BzR and cerebellar *DI* BzR are discussed.

Chemistry

Most of the imidazobenzodiazepine-3-carboxylic esters (**11c–f, h–j**) were prepared by the synthetic method shown

Scheme I [a]



15a R = CH_3, X = H
15b R = $CH_2CH=CH_2$, X = H
15c R = C_6H_5, X = H
15d R = $C_6H_4(OCH_3)$-4, X = H
15e R = $CH_2C_6H_5$, X = H
15f R = $CH_2C_6H_5$, X = 6-Cl
15g R = $CH_2C_6H_5$, X = 7-Cl
15h R = $CH_2C_6H_3(OCH_3)_2$-2,4, X = H

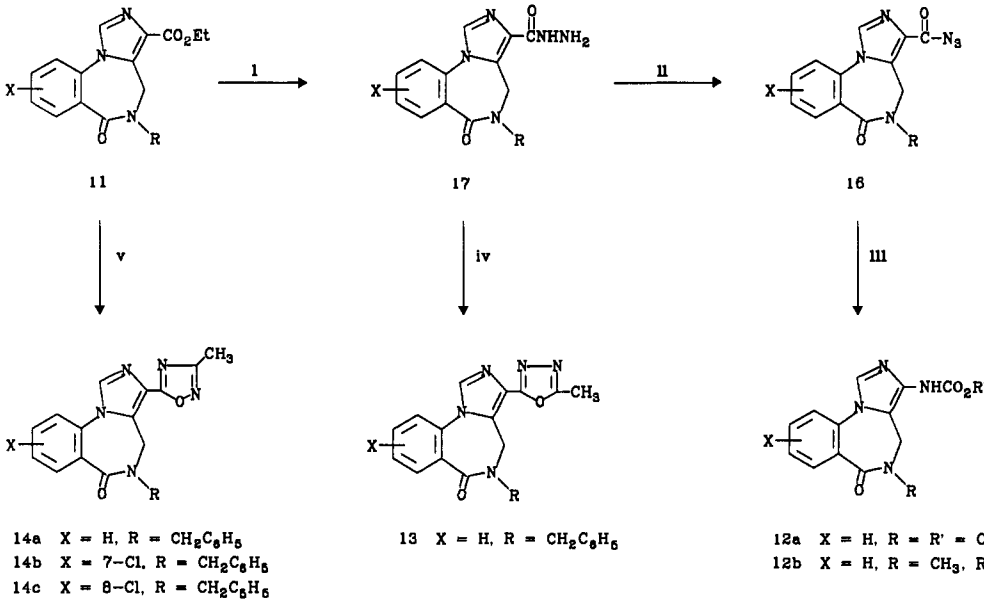
16

11 c–f, h–j

[a] (i) NaH, DMF, $(EtO)_2POCl$; (ii) $C{\equiv}NCH_2CO_2C_2H_5$, LiN[$CH(CH_3)_2$]$_2$, THF.

in Scheme I. In essence, the method involved the activation of the amide function of benzodiazepinedione **15** to an imino phosphate **16** and its cyclocondensation with the anion generated from ethyl isocyanoacetate. The required diazepinediones **15a,b,e,g,** and **h** were prepared by adaptation of known procedures[32,33] involving the condensation of isatoic anhydride or 5-chloroisatoic anhydride with ethyl *N*-methyl-, *N*-allyl-,[34] *N*-benzyl, or *N*-2,4-(dimethoxybenzyl)[35] glycinates. The (dimethoxybenzyl)glycinate was obtained by a slight modification of the reported method. The condensation of 2,4-dimethoxybenzaldehyde with ethyl glycinate hydrochloride was carried out in methanol in the presence of NaOAc in AcOH and the resulting aldimine was reduced in situ with $NaBH_3CN$. The 6-chlorodiazepinedione **15f** was obtained from 6-chloroanthranilic acid[36] by reaction with thionyl chloride followed by condensation of the resulting intermediate[37] with ethyl *N*-benzylglycinate. The *N*-aryldiazepinediones **15c** and **15d** were prepared as described in the literature by the conversion of 2-aminobenzanilide and 2-amino-

Scheme II [a]



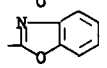
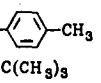
14a X = H, R = $CH_2C_6H_5$
14b X = 7-Cl, R = $CH_2C_6H_5$
14c X = 8-Cl, R = $CH_2C_6H_5$

13 X = H, R = $CH_2C_6H_5$

12a X = H, R = R' = CH_3
12b X = H, R = CH_3, R' = C_2H_5

[a] (i) $N_2H_4 \cdot H_2O$, EtOH; (ii) $NaNO_2$, AcOH, H_2O; (iii) R'OH, Δ; (iv) $CH_3C(=NH)OEt \cdot HCl$, Py, Δ; (v) $CH_3C(=NOH)NH_2$, NaH, THF, 4A molecular sieves.

Chart II

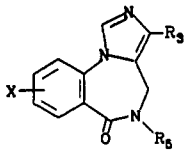
12c R = $NHCOCH_3$
12d R = NHCHO
12e R = N=C=S
12f R = 
12g R = 
12h R = 
19 R = $NHCO_2C(CH_3)_3$
20 R = CO_2H
21 R = $CONHCH_2CH_2OH$
22 R = $CONHCH_2CH_2Cl$

23 X = H
24 X = 7-Cl
25 X = 8-Cl

4'-methoxybenzanilide[38] to chloroacetyl derivatives ($ClCH_2COCl/Et_3N/CH_2Cl_2$) followed by intramolecular cyclization ($Et_3N/CH_3OCH_2CH_2OH$).[39] The N-unsubstituted imidazobenzodiazepine **11a** was accessible by the previously described procedure involving the acid-catalyzed removal of the 2,4-dimethoxybenzyl group from **11j**[16] or, by an alternative method involving the oxidative removal of the 4-methoxyphenyl group from **11e** using ceric ammonium nitrate in aqueous acetonitrile.[40] Alkylation of **11a** ($PhCH_2CH_2Br/NaH/DMF$) provided the phenethyl derivative **11g**. Catalytic hydrogenation of **11c** gave the *N*-propyl compound **11b**.

Target ligands of the general structure **12–14**, with the exception of **12h**, were prepared from the carboxylic esters **11** by functional group transformations (Scheme II). The carbamates **12a,b** were accessible by the Curtius rearrangement of the azide **18** in the presence of an alcohol. Cyclization of the hydrazide **17** (R = $PhCH_2$, X = H) with ethyl acetimidate yielded the 1,3,4-oxadiazole **13**. Condensation of the esters **11** with acetamidoxime provided the 1,2,4-oxadiazolyl compounds **14a–c**. The *t*-Boc derivative **19** (Chart II), prepared in a manner similar to that of **12a**, was utilized for the preparation of the amine derivatives **12c–e** by deprotection followed by acetylation (Ac_2O/Py), formylation (HCO_2H) or reaction with $CSCl_2$. The oxazoline compound **12f** was synthesized from the ester **2e** via the hydroxyethyl amide **21**. While treatment of the amide with thionyl chloride in isopropyl acetate at room temperature[41] returned the unreacted starting material, reaction in acetonitrile at reflux yielded the chloroethyl amide **22**. Cyclization of the amide **22** using NaH in DME[42] gave the desired oxazoline **12f**. Attempted condensation of the ester **2e** with *o*-aminophenol at elevated temperatures failed to yield the benzoxazole compound **12g**. The acid **20**, derived from the ester **2e**, could be successfully reacted with 2-aminophenol in the presence of P_2O_5 and hexamethyldisilazane in 1,2-dichlorobenzene at reflux[43] to yield the desired compound **12g**.

Table I. Physical Data and Binding Affinities at the Cortical Diazepam-Sensitive Benzodiazepine Receptors for 4,5-Dihydro-6*H*-imidazo[1,5-*a*][1,4]benzodiazepin-6-ones



compound	X	R_3	R_5	recryst solvent (% yield)	mp, °C	formula[a]	IC_{50},[b] nM
11a	H	$CO_2C_2H_5$	H	EtOH (50)	249–251[c]	$C_{14}H_{13}N_3O_3$	164 ± 42
11b	H	$CO_2C_2H_5$	n-C_3H_7	EtOAc/C_6H_{12} 3:2 (60)	86–88	$C_{17}H_{19}N_3O_3$	238 ± 25.6
11c	H	$CO_2C_2H_5$	$CH_2CH{=}CH_2$	EtOAc/C_6H_{12} 1:1 (40)	120–122	$C_{17}H_{17}N_3O_3$	157 ± 7.6
11d	H	$CO_2C_2H_5$	C_6H_5	EtOAc/C_6H_{12} 2:1 (45)	175–177	$C_{20}H_{17}N_3O_3$	>1000
11e	H	$CO_2C_2H_5$	$C_6H_4OCH_3$-4	EtOH (36)	178–180	$C_{21}H_{19}N_3O_4$	>1000
11f	H	$CO_2C_2H_5$	$CH_2C_6H_5$	EtOAc (49)	197–199	$C_{21}H_{19}N_3O_3$	9.3 ± 2.1
11g	H	$CO_2C_2H_5$	$CH_2CH_2C_6H_5$	EtOH/H_2O 2:1 (62)	135–137	$C_{22}H_{21}N_3O_3$	340 ± 127
11h	7-Cl	$CO_2C_2H_5$	$CH_2C_6H_5$	EtOAc (34)	186–188	$C_{21}H_{18}ClN_3O_3$	2.4 ± 0.1
11i	8-Cl	$CO_2C_2H_5$	$CH_2C_6H_5$	EtOAc/C_6H_{12} 2:1 (42)	202–204	$C_{21}H_{18}ClN_3O_3$	37.8 ± 4.6
11j	H	$CO_2C_2H_5$	$CH_2C_6H_3(OCH_3)_2$-2,4	EtOAc (51)	136–138[d]	$C_{23}H_{23}N_3O_5$	23.2 ± 11.0
12a	H	$NHCO_2CH_3$	CH_3	MeOH (79)	245–247	$C_{14}H_{14}N_4O_3$	>1000
12b	H	$NHCO_2C_2H_5$	CH_3	EtOH (90)	221–223 dec	$C_{15}H_{16}N_4O_3$	>1000
12c	H	$NHCOCH_3$	CH_3	EtOH (61)	255–257	$C_{14}H_{14}N_4O_2$	>1000
12d	H	NHCHO	CH_3	EtOH (70)	212–214 dec	$C_{13}H_{12}N_4O_2$	>1000
12e	H	N=C=S	CH_3	CH_2Cl_2/C_6H_{14} 1:2 (35)	150–151	$C_{13}H_{10}N_4OS$	739 ± 86
12f	H	4,5-dihydrooxazol-2-yl	CH_3	MeOH (53)	224–226 dec	$C_{15}H_{14}N_4O_2$	687 ± 304
12g	H	2-benzoxazolyl	CH_3	MeOH (35)	290–292	$C_{19}H_{14}N_4O_2 \cdot 0.2H_2O$	317 ± 135
12h	H	$SO_2C_6H_4(CH_3)$-4	CH_3	EtOH (46)	255–257 dec	$C_{19}H_{17}N_3O_3S$	>1000
13	H	5-methyl-1,3,4-oxadiazol-2-yl	$CH_2C_6H_5$	EtOAc (67)	204–206	$C_{21}H_{17}N_5O_2$	>1000
14a	H	3-methyl-1,2,4-oxadiazol-5-yl	$CH_2C_6H_5$	EtOH (64)	232–234	$C_{21}H_{17}N_5O_2$	34.3 ± 7.4
14b	7-Cl	3-methyl-1,2,4-oxadiazol-5-yl	$CH_2C_6H_5$	EtOH (79)	280–282 dec	$C_{21}H_{16}ClN_5O_2$	15.3 ± 5.0
14c	8-Cl	3-methyl-1,2,4-oxadiazol-5-yl	$CH_2C_6H_5$	EtOH (58)	230–232	$C_{21}H_{16}ClN_5O_2$	338 ± 152
2e[e]							3.0

[a] Elemental analyses for C,H,N were within ±0.4% of the calculated values. [b] Binding affinities in rat cortical membranes determined as described in the Experimental Section. Values are mean ± SEM values. [c] Lit.[16] mp 248–250 °C. [d] Lit.[16] mp 136–138 °C. [e] Data for compound 2e (ref 4) is included for comparison.

The sulfone **12h** was prepared by condensation of the imino phosphate derived from the dione **15a** (Scheme I) with the anion generated from (*p*-tolylsulfonyl)methyl isocyanide.

Pharmacology

The affinities of the synthesized compounds for the DS and DI BzR were determined with radioligand binding techniques. Relative affinities of the target compounds to the DS BzR were determined by testing each compound for its ability to displace [^{3}H]flunitrazepam from rat cortical membranes as described earlier.[44] The affinities of the compounds for the DI BzR were determined in rat cerebellar homogenates by using [^{3}H]Ro 15-4513 as the radioligand as described.[15] In brief, the displacement of this radioligand by Ro 15-1788 (10 μM) was defined as the binding of [^{3}H]Ro 15-4513 to the DI + DS sites. [^{3}H]Ro 15-4513 binding that is displaced by Ro 15-1788 (10 μM) and not by diazepam (10 μM) was defined as binding of the radioligand to the diazepam-insensitive sites. Data from competition experiments were analyzed using a mathematical modeling program to determine the concentration of compound required to inhibit 50% of the binding of the radioligand (IC_{50}). Dissociation constants (K_i) were calculated from IC_{50} values using the method of Cheng and Prusoff. The selectivity of the ligands for DI and DS BzR is expressed as a ratio of the K_i values at cerebellar DI and DS sites (DI/DS). A lower ratio corresponds to a greater selectivity of the ligands for the DI receptors. The "GABA-ratios" for high affinity ligands at the cortical receptors were obtained by the determination of the ratios of the IC_{50} values in the presence and absence of 100 μM of GABA.

Selected ligands with high affinities for the DS and DI BzR were tested in vivo in rodent models using previously described protocols.[45] The proconvulsant and anticonvulsant activities, as a measure of the inverse agonist and agonist nature of the ligands, were determined by evaluating the ability of the compound to increase or reduce the convulsions induced by 40 or 80 mg/kg of pentylenetetrazole (PTZ) in mice. The benzodiazepine antagonist effect of the ligands were determined by evaluation of the ability of the compound to block the anticonvulsant effects of diazepam (2.5 mg/kg, ip) in mice challenged with PTZ (80 mg/kg).

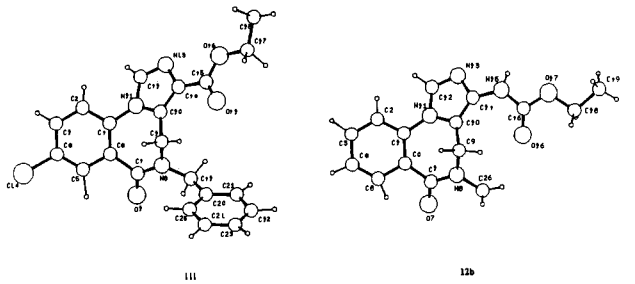
Results and Discussion

Structure–Affinity Relationships for Binding at Cortical (DS) BzR. An examination of the data presented in Table I for the 3-carboxylic esters **11a–j** indicates that N-substituents on the imidazobenzodiazepinone template have a profound influence on ligand affinity. The N-unsubstituted compound **11a**, for example, exhibits a nearly 50-fold reduction in affinity compared to the corresponding *N*-methyl compound **2e**. Placement of a higher alkyl group such as an *n*-propyl group (**11b**) also diminishes ligand affinity. A propenyl group appears to be better tolerated than the *N*-propyl group as the *N*-allyl compound **11c** has a marginally improved affinity in comparison to the *N*-propyl compound. Attachment of aryl groups on the nitrogen atom leads to compounds **11d** and **11e** devoid of affinity for the receptors. The *N*-phenethyl derivative **11g** also displays only moderate affinity for the BzR. In contrast, the *N*-benzyl compounds (**11f,h–j**) possess high affinities (2.4–37.8 nM). These results indicate that the receptor site interacting with the

N-substituent of the imidazobenzodiazepinones is sterically constrained since groups bulkier than a methyl group cause significant reductions in the affinities. However, the high affinities of the benzyl compounds suggest the presence of a hydrophobic pocket which can accept benzyl substitutents at the 5-position of imidazobenzodiazepinone ligands.

Replacement of the ester function at the 3-position of the imidazobenzodiazepinone with a carbamate group (**12a,b**) results in a dramatic loss in affinity. Replacement of the carbamate group with acetylamino or formylamino groups (compounds **12c, 12d**) also yields compounds with low affinity for the receptor. The isothiocyanato group is an amine-derived functional group that is structurally linear with no internal conformational flexibility. Earlier studies have revealed that the 3-isothiocyanato derivative of β-carboline (compound **10**) is a high affinity ligand (IC_{50} ~8 nM) with irreversible binding properties.[28] The 3-isothiocyanato derivative of imidazobenzodiazepinone **12e**, however, has only a marginal binding affinity. The moderate affinities of the 2-oxazolinyl and 2-benzoxazolyl compounds **12f** and **12g** show that these groups do not provide as favorable an interaction at the DS BzR as that provided by an ester function. The binding site also does not appear to tolerate the toluenesulfonyl group as indicated by the low affinity of compound **12h**. Although a number of heteroaromatic substituents have been placed at the 3-position of the 5-methylimidazobenzodiazepin-6-ones,[18] the 3-alkyl-1,2,4-oxadiazol-5-yl and 5-alkyl-1,2,4-oxadiazol-3-yl moieties appear to be the groups that can function as ester surrogates to provide ligands with high affinities. Conversion of the ester function in the *N*-benzyl derivatives to a 3-methyl-5-(1,2,4-oxadiazolyl) function (compounds **14a–c**), in general, reduces ligand affinity. Of the 5-methyl-1,3,4-oxadiazol-2-yl and 3-methyl-1,2,4-oxadiazol-5-yl groups, the former appears to be unfavorable for ligand binding as indicated by the relative affinities of compounds **13** and **14a**.[46]

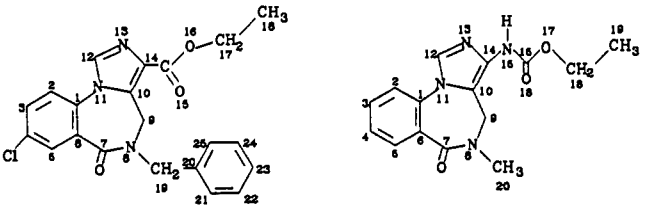
A comparison of the affinities of the *N*-benzyl esters (**11f,h,i**) and *N*-benzyl oxadiazoles (**14a–c**) with the reported affinities of related *N*-methyl compounds (**2c–e** and **23–25**) demonstrates some similarities between the two series. Among esters carrying *N*-benzyl substituents (**11f,h,i**), the introduction of Cl at the 7-position increases the affinity 4-fold while Cl at the 8-position decreases the affinity 4-fold. In the *N*-methyl ester series (**2c–e**), while the introduction of chlorine at the 7-position was without significant effect on affinity, chlorine at the 8-position reduced the affinity 2-fold. The reported IC_{50} values for the unsubstituted, 7-, and 8-chloro compounds **2e, 2c**, and **2d** are 3.0, 2.7, and 6.6 nM, respectively.[4] The enhancement of affinity by Cl at the 7-position in the *N*-benzyl 3-ester compounds is similar to that observed in the *N*-methyl 3-oxadiazolyl compounds exemplified by **3**. In this series of compounds, the affinity-enhancing effect of chlorine at the 7-position has been attributed to the stabilization of the diazepine ring in the conformation that is recognized by the receptor.[6] The effect of chlorine at the 7- or 8-position on the affinities of the 3-oxadiazolyl compounds is qualitatively similar to the effect observed in the ester compounds. The decrease in affinity caused by Cl at the 8-position is comparatively larger (10-fold) in the oxadiazole derivative **14c** than in the ester compound **11i**. The structure–affinity relationships among the *N*-benzyl oxadiazolyl compounds **14a–c** are similar to the



11i 12b

Figure 1. Single-crystal X-ray structures of **11i** and **12b**.

Table II. Selected Geometric Features in the X-ray Crystal Structures of **11i** and **12b**



11i 12b

compound 11i		compound 12b	
	Torsion Angles (deg)		
C18–C17–O16–C15	−161.4	C19–C18–O17–C16	−173.2
C17–O16–C15–O15	−2.3	C18–O17–C16–O16	3.2
O15–C15–C14–N13	177.1	C16–N15–C14–N13	−151.3
O15–C15–C14–C10	1.4	C16–N15–C14–C10	31.9
N11–C1–C6–C7	−8.5	N11–C1–C6–C7	−9.8
C1–C6–C7–N8	42.9	C1–C6–C7–N8	41.4
C6–C7–N8–C9	6.3	C6–C7–N8–C9	6.6
C7–N8–C19–C20	−124.8		
N8–C19–C20–C21	−148.5		
	Distances (Å)		
centroid[a]–N13	4.95	centroid[a]–N13	4.90
centroid–O15	6.65	centroid–N15	6.29
centroid–O16	7.26	centroid–O16	6.72
N13–O15	3.62	centroid–O17	8.29
		N13–O16	4.17

[a] Centroid of the annelated benzene ring.

SAR's for the *N*-methyl oxadiazolyl compounds **23–25**. The reported IC_{50} values for **23–25** are 51, 9.7, and 600 nM, respectively.[6] The close structure–affinity correlations between the *N*-benzyl and the *N*-methyl compounds suggest that the two groups of compounds may bind to the same receptor site in analogous orientations.

The solid state structures of the active compound **11i** and the inactive carbamate **12b** as determined by single crystal X-ray diffraction analyses are shown in Figure 1. Selected details of the geometric features of the two are presented in Table II. The conformation of the imidazobenzodiazepinone portion of **11i** is nearly identical to that found in the crystal structures of the ester **2a**[25,47] and the oxadiazole **3** (R = $CHMe_2$, X = 7-Cl).[6] The conformation of the ester group in **11i**, however, significantly differs from that found in the crystal structure of **2a**. While the carbonyl group in **11i**, as shown in Figure 1, adopts a conformation in which the carbonyl oxygen is trans to the imidazole nitrogen, the ester carbonyl group of **2a** favors the opposite cis conformation in the crystalline state. Energy calculations using molecular mechanics (MM2) as implemented in the molecular modeling program MacroModel[48] (Version 3.0) for conformers of the esters **2a** and **11f** show that *s-trans* conformers are, in general, more stable than the *s-cis* conformers. However, since the energy

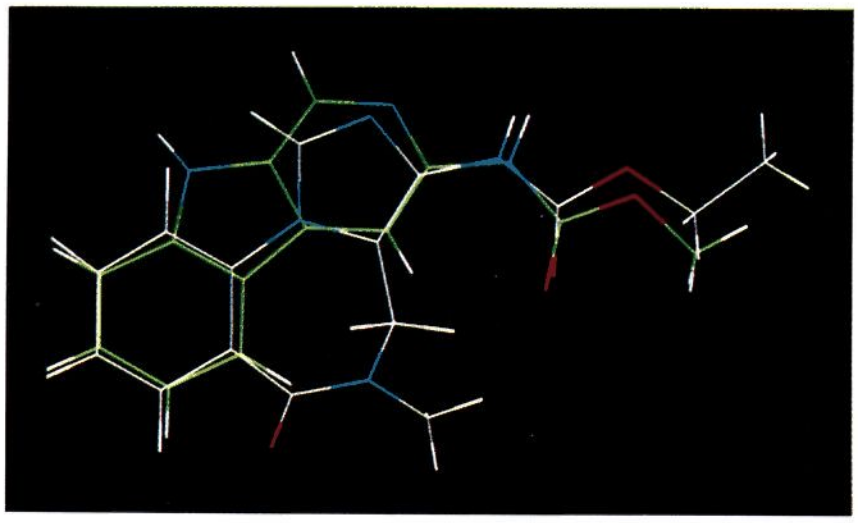


Figure 2. A rigid superimposition of the crystal structures of the carboline carbamate 8 (green) and imidazobenzodiazepinone carbamate **12b** (gray).

difference between the cis and trans conformers are relatively small (ΔE = <5 kcal/mol) it is difficult to draw any conclusions regarding the solution conformation that is preferentially recognized by the receptor.[49] The conformation of the imidazobenzodiazepinone portion in the crystal structure of the carbamate **12b** is essentially similar to that present in **11i**. Moreover, the conformational features of the carbamate side chain in **12b** are very similar to that found for the carbamate side chain in the crystal structure of the carboline carbamate 8.[50] In both molecules the side chain adopts an extended conformation with the carbamate NH cis and carbonyl oxygen trans, respectively, to the ring nitrogen. The carbamate side chain in **12b** deviates from the plane of the imidazole ring as indicated by the torsion angles −151.3° and 31.9° for C(16)–N(15)–C(14)–N(13) and C(16)–N(15)–C(14)–C(10), respectively. This deviation is similar to the displacement of the carbamate substituent from the mean plane of the carboline ring in 8, the corresponding torsion angles in 8 being −158.2° and 24.3°. A rigid superimposition of the crystal structures of the carboline carbamate 8 and the imidazobenzodiazepinone carbamate **12b**, as shown in Figure 2, provides an indication of the structural similarities between the two molecules.[51]

Structure–Affinity Relationships for Binding at the DI BzR. All the compounds synthesized were evaluated for their affinities at the DI BzR. Ligands with low affinities (IC_{50} >1000 nM) for the cortical receptors were also found to display low affinities for the cerebellar DI receptors. Presented in Table III are the affinities of selected ligands at the cerebellar sites. The data for compounds **2b** (Ro 15-4513), and **2c–e**[15] are included in the table for comparison. The benzene ring unsubstituted compound **11f** exhibits moderate affinity for DI BzR. The 7- and 8-chloro compounds **11h** and **11i**, however, exhibit high affinities. The placement of chlorine at the 7-position enhances affinity while chlorine at the 8-position reduces affinity at DS BzR. In contrast, at the 7- as well as at the 8-position a chlorine substituent enhances affinity at DI BzR. Indeed, the 8-chloro analogue **11i** has a higher affinity for the DI site than the 7-chloro analogue. This differential modulation of the ligand affinity at DS and DI BzR is also reflected in the selectivity of these ligands, with the 8-chloro compound being more selective than the 7-chloro analogue. The selectivity observed for the 8-chloro compound **11i** (DI/DS ratio = 0.8) is nearly equal to that of **2b** (DI/DS ratio = 0.6). Although the oxadiazolyl compounds **14a–c** have much lower affinities at DI BzR

Table III. Affinity Data for Selected Imidazobenzodiazepinone Ligands at the Diazepam-Sensitive (DS) and the Diazepam-Insensitive (DI) Benzodiazepine Receptors in Rat Cerebellar Membranes

compound	affinity at cerebellar DS site Ki,[a] nM	affinity at cerebellar DI site Ki,[a] nM	DI/DS
11f	1.5 ± 0.1	112 ± 8.1	75
11h	0.4 ± 0.1	20.2 ± 0.9	51
11i	13.7 ± 1.3	10.9 ± 1.4	0.8
11j	5.4 ± 1.6	127 ± 32	24
13	1209 ± 118	>10000[b]	–
14a	907 ± 111	>10000[b]	–
14b	7.5 ± 1.6	761 ± 184	101
14c	88.4 ± 5.7	115 ± 7.3	1.3
2b (Ro15–4513)	5.3 ± 1.2	3.1 ± 0.1	0.6
2c	0.2 ± 0.0	20 ± 2.4	100
2d	5.4 ± 0.9	16.9 ± 1.1	3.1
2e	1.3 ± 0.1	214 ± 26	165

[a] Binding affinities in rat cerebellar membranes determined as described in the Experimental Section. Values are mean ± SEM. [b] IC_{50} values. Data for compounds **2b**, **2c**, and **2e** (ref 15) and **2d** (unpublished data) are included for comparison.

than their corresponding esters **11f,h,i**, a similar structure–affinity and structure–selectivity relationship is discernible with regard to the effect of chlorine at the 7- and 8-positions. A comparison of the *N*-benzyl (**11f,h,i**) and *N*-methyl compounds (**2e,2c**, and **2d**) indicates that the former possess enhanced selectivity for the DI receptors compared to the latter. Thus, the *N*-benzyl compounds **11h** and **11i** rank among the very few high affinity ligands for the DI site reported to date. Moreover, the high affinity and moderate selectivity of **11i** for the DI site indicate that the azido function present in **2b** is not an essential structural requirement for selective binding to the DI site, and that it might be possible to design DI-selective ligands by placement of bulky, lipophilic functions at the 8-position of the imidazobenzodiazepinone template.

In Vitro and in Vivo Efficacies. The "GABA-shift" ratios of BzR ligands are, in general, believed to be a useful predictor of the intrinsic activity.[52] While antagonist ligands exhibit GABA-shift values of ~1, agonist and inverse agonist ligands display GABA-shift values that are >1 and <1, respectively.[1-4] As a measure of intrinsic efficacy, GABA-shift ratios were determined for selected high affinity ligands. The GABA-shift values determined for compounds **11f**, **11h**, and **11i** were 1.15 ± .03, 1.12 ± .02, and 1.04 ± .03, respectively. Based on previous findings,[1-4] these GABA-shift values suggest that the compounds could function as partial agonists or antagonists. Nonetheless, in vivo studies indicated that **11f** and **11h** have some proconvulsant activity. Thus, at the highest dose tested (40 mg/kg) **11f** produced convulsions in 5/7 mice while compound **11h** induced convulsions in 7/10 mice. The 8-chloro ester compound **11i**, however, was inactive as proconvulsant or anticonvulsant at 40 mg/kg. At this dose level it decreased the anticonvulsant effects of diazepam by 50%, indicating that the compound may possess some antagonist properties. The two oxadiazolyl compounds **14a** and **14b** were inactive at 40 mg/kg in all the three paradigms tested. Given the high affinities of these ligands in vitro, the modest in vivo activities described here indicate that poor bioavailability may limit or confound the determination of the efficacies of these ligands in vivo. However, additional studies are needed to confirm this possibility.

Model for Binding of Imidazobenzodiazepinones to Cortical (DS) BzR. On the basis of common structural

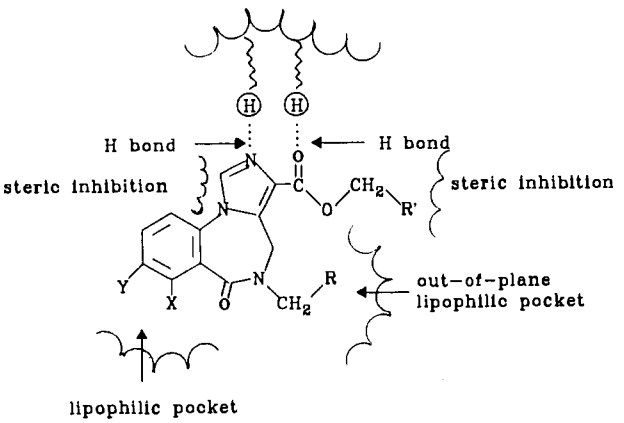


Figure 3. A model for the interaction of imidazobenzodiazepinone carboxylic esters at the benzodiazepine receptor antagonist site.

features of BzR ligands, Codding and Muir[25] proposed a model for the binding of antagonist imidazobenzodiazepinones such as **2a**, with primary interactions involving the aromatic ring, the ester carbonyl oxygen, and the hydrophobic ester chain. Watjen and co-workers[6] have described the interaction of 3-oxadiazolyl derivatives of the type **3** using a similar model. They have suggested that the binding of the partial agonist oxadiazoles to the receptor site may involve the imidazole nitrogen at the 2-position as the hydrogen acceptor as opposed to the carbonyl oxygen in the antagonist esters. According to Fryer,[5] the interaction of imidazobenzodiazepinones of the type **2** involves hydrogen bonding interactions at the imidazole nitrogen, designated π_1, as well as the ester carbonyl oxygen π_2 at the receptor site, the presence of the π_2 in the ligand being a common feature of the antagonist imidazobenzodiazepine ligands. On the basis of this model, and considering the GABA-shift and limited in vivo data, the interactions of the imidazobenzodiazepinones can be depicted as shown in Figure 3. As might be expected, modeling of **11f** as well as the crystal structure of **11i** indicates that the aromatic ring of the benzyl group is likely to occupy a region that is not coplanar with the benzodiazepine ring and the site that is occupied by the benzyl substituent is therefore depicted as an out-of-plane lipophilic pocket. The low affinities of the compounds possessing carbamate, acylamino, sulfonyl, oxazolinyl, and benzoxazolyl functions (**12a–h**) clearly indicate that favorable hydrogen bonding and steric interactions in regions surrounding the π_1 and π_2 proton-accepting sites are important for high affinity binding of the imidazobenzodiazepinone group of ligands to the DS BzR.

The results described herein establish for the first time that the benzodiazepine receptors can accommodate a hydrophobic substituent such as a benzyl group at the 5-position of the imidazobenzodiazepinone template and that the structural requirements for the binding of imidazobenzodiazepinone group of ligands at DS and DI BzR are different. Moreover, the observed differential SAR's for binding at DS and DI BzR indicates that the affinities of the ligands can be selectively modulated by the placement of suitable substituents at the 3-, 5-, 7-, and 8-positions of the imidazobenzodiazepinone framework.

Experimental Section

Melting points were determined in open capillary tubes with a Mel-Temp melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Nicolet NT 300NB spectrometer operating at 300.635 MHz. Chemical shifts are expressed in parts per million downfield from tetramethylsilane. Mass spectra were recorded on a Varian MAT 311A double-focusing mass spectrometer in the fast atom bombardment (FAB) mode. UV spectra were determined with a Perkin-Elmer Model Lambda 9 spectrometer. Infrared spectra were recorded on a Nicolet FT IR spectrometer, Model 10DX. Elemental analyses were performed by Atlantic Microlab, Inc. (Atlanta, GA) or the Molecular Spectroscopy Section of Southern Research Institute. Analytical results indicated by elemental symbols were within ±0.4% of the theoretical values. All reactions involving air- and moisture-sensitive reagents were performed under a positive pressure of argon or nitrogen. Unless noted otherwise, organic extracts were dried over anhydrous Na_2SO_4 and concentrated on a rotary evaporator under reduced pressure. TLC was performed on Analtech precoated (250 μM) silica gel (GF) plates. Flash column chromatography was performed using 230–400 mesh silica gel from E. Merck.

Benzodiazepine-2,5-diones (15a–d). 4-Methyl,[33] 4-allyl,[31] and 4-aryl[39] benzodiazepinediones **15a–d** were prepared by the literature procedures.

3,4-Dihydro-4-benzyl-1*H*-1,4-benzodiazepine-2,5-dione (15e). A mixture of isatoic anhydride (32.63 g, 0.2 mol), ethyl *N*-benzylglycinate (38.65 g, 0.2 mol), and powdered glass (1.0 g) was stirred and heated in an oil bath at 115 °C for 4 h. After cooling, the mixture was dissolved in $CHCl_3$ (300 mL) and filtered, and the filtrate was washed successively with 200 mL of water, 10% aqueous hydrogen chloride, water, saturated aqueous sodium bicarbonate, and water. The organic layer was dried and filtered, and the filtrate was evaporated to dryness under reduced pressure. Recrystallization of the crude product from EtOH yielded 15.84 g (30%) of **15e**: mp 175–176 °C (lit.[53] mp 172–173 °C); TLC, 1:1 cyclohexane–ethyl acetate, R_f 0.38; MS *m/z* 267 $(M + 1)^+$; ^{1}H NMR ($CDCl_3$) 3.82 (2 H, s, H-3), 4.88 (2 H, s, $CH_2C_6H_5$), 6.97 (1 H, dd, $J_{8,9}$ = 8.0, $J_{7,9}$ = 1.0 Hz, H-9), 7.22–7.40 (6 H, m, $CH_2C_6H_5$, H-7), 7.48 (1 H, td, $J_{7,8}$ = 7.4 Hz, $J_{6,8}$ = 1.6 Hz, H-8), 8.04 (1 H, dd, $J_{6,7}$ = 7.9 Hz, H-6), 8.58 (1 H, br s, NH). Anal. ($C_{16}H_{14}N_2O_2$) C, H, N.

6-Chloro-3,4-dihydro-4-benzyl-1*H*-1,4-benzodiazepine-2,5-dione (15f). Thionyl chloride (24.5 mL) was added to a stirred suspension of 2-amino-6-chlorobenzoic acid (8.0 g, 46.6 mmol) in benzene (160 mL) and the mixture was refluxed for 2 h. The mixture was evaporated to dryness under reduced pressure, and the residue was treated with benzene (80 mL) and evaporated to dryness again. The process was repeated one more time. The residue was treated with ethyl *N*-benzylglycinate (10.826 g, 56.0 mmol) in pyridine (40 mL) and the mixture was refluxed for 6 h. Volatile components were removed under reduced pressure and the residue was dissolved in $CHCl_3$ (300 mL). The usual workup as described for **15e** and recrystallization of the product from EtOAc gave 3.34 g (24%) of **15f**: mp 188–190 °C; TLC, EtOAc, R_f 0.80; MS *m/z* 301 $(M + 1)^+$; ^{1}H NMR ($CDCl_3$) δ 3.63 (1 H, dd, *J* = 14.5, 1.5 Hz, H-3), 3.96 (1 H, d, *J* = 14.5 Hz, H-3), 4.42 (1 H, d, *J* = 15 Hz, $CH_2C_6H_5$), 5.32 (1 H, d, *J* = 15 Hz, $CH_2C_6H_5$), 6.89 (1 H, m, H-4′), 7.26–7.42 (7 H, m, aryl H), 8.28 (1 H, br s, NH). Anal. ($C_{16}H_{13}ClN_2O_2$) C, H, N.

7-Chloro-3,4-dihydro-4-benzyl-1*H*-1,4-benzodiazepine-2,5-dione (15g) was prepared from 5-chloroisatoic anhydride and ethyl *N*-benzylglycinate by a procedure similar to that described for **15e**. Crystallization from EtOAc–cyclohexane 1:2 gave 3.66 g (14.5%) of **15g**: mp 184–186 °C; TLC, 1:1 cyclohexane–ethyl acetate, R_f 0.50; MS *m/z* 301 $(M + H)^+$; ^{1}H NMR ($CDCl_3$) δ 3.80 (2 H, s, H-3), 4.85 (2 H, s, $CH_2C_6H_5$), 6.91 (1 H, d, $J_{8,9}$ = 8.6 Hz, H-9), 7.27–7.40 (5 H, m, C_6H_5), 7.44 (1 H, dd, $J_{6,8}$ = 2.4 Hz, H-8), 8.02 (1 H, d, H-6), 8.23 (1 H, br s, NH). Anal. ($C_{16}H_{13}ClN_2O_2$) C, H, N.

3,4-Dihydro-4-(2,4-dimethoxybenzyl)-1*H*-1,4-benzodiazepine-2,5-dione (15h). A mixture of ethyl glycinate hydrochloride (9.78 g, 0.07 mol) and anhydrous sodium acetate (5.75 g, 0.07 mol) in AcOH (98 mL) was stirred at room temperature for 5 min and treated with 2,4-dimethoxybenzaldehyde (11.65 g, 0.07 mol), and the mixture was stirred for 30 min. The mixture was cooled in ice bath and was treated with sodium cyanoborohydride (8.76 g, 0.139 mol) in portions. After allowing the mixture to stir at room temperature overnight, it was treated with water (25 mL), stirred for 30 min, and concentrated under reduced pressure.

The residue was cooled, made basic with aqueous 6 N sodium hydroxide, extracted with $CHCl_3$ (3 × 200 mL), washed with water (300 mL), and dried, and the solvent was removed under reduced pressure. The residue was chromatogrpahed over a column of silica using 3:1 cyclohexane–ethyl acetate as the eluent to obtain 13.48 g (76%) of ethyl *N*-(2,4-dimethoxybenzyl)glycinate as an oil: TLC, 1:1 cyclohexane–ethyl acetate, R_f 0.54; MS *m/z* 254 (M + 1)$^+$; ^{1}H NMR ($CDCl_3$) δ 1.26 (3 H, t, CH_2CH_3), 1.79 (1 H, br s, NH), 3.28 (2 H, s, H-3), 3.76 (2 H, s, $C_6H_5CH_2$), 3.80, 3.82 (6 H, 2 s, OCH_3), 4.16 (2 H, q, CH_2CH_3), 6.39–6.49 (2 H, m, H-3,5), 7.12 (1 H, d, H-6). The product was used as obtained in the next step.

The (dimethoxybenzyl)glycinate (12.92 g, 0.051 mol) was condensed with isatoic anhydride (8.32 g, 0.051 mol) in a manner similar to that described for the preparation of **15e**. Recrystallization of the crude product from EtOAc yielded 3.5 g (21%) of **15h** as colorless crystals: mp 150–151 °C (lit.[16] mp 151–152.5 °C); TLC, R_f 0.68; MS *m/z* 327 (M + 1)$^+$; ^{1}H NMR ($CDCl_3$) δ 3.80, 3.84 (6 H, 2 s, 2′,4′-(OCH_3), 3.90 (2 H, s, H-3), 4.80 [2 H, s, $CH_2C_6H_3$-$(OCH_3)_2$], 6.43–6.47 (2 H, m, H-3′,5′), 6.92 (1 H, dd, $J_{8,9}$ = 8.0, $J_{7,9}$ = 1.1 Hz, H-9), 7.22–7.34 (2 H, m, H-7, H-6′), 7.45 (1 H, td, $J_{7,8}$ = 7.4, $J_{6,8}$ = 1.6 Hz, H-8), 7.99 (1 H, dd, $J_{6,7}$ = 7.9 Hz, H-6), 8.04 (1 H, br s, NH). Anal. ($C_{18}H_{18}N_2O_4$) C, H, N.

General Procedure for the Preparation of Ethyl Oxoimidazobenzodiazepine-3-carboxylates. Ethyl 5,6-Dihydro-5-benzyl-6-oxo-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3-carboxylate (11f). A stirred solution of ethyl isocyanoacetate (0.848 g, 7.5 mmol) in THF (12 mL) was cooled to −78 °C in a dry ice–acetone bath. To the solution was added dropwise a solution of lithium diisopropylamide (1.5 M solution in THF, 5.0 mL, 7.5 mmol) and the resulting mixture was stirred at −78 °C for 1 h. Meanwhile sodium hydride (60% dispersion in mineral oil; 0.23 g, 5.68 mmol) was added in portions to a stirred solution of the dione **15e** (1.322 g, 5.0 mmol) in DMF (12 mL) under a N_2 atmosphere, and the mixture was stirred at ambient temperature for 30 min and then cooled to −20 °C. Diethyl chlorophosphate (0.98 g, 5.68 mmol) was added to the DMF solution, and the mixture was stirred at −20 to −10 °C for 30 min. This mixture was transferred via a cannula to the solution of the isocyanoacetate anion in THF at −78 °C. The resulting mixture was stirred at −78 °C for 2 h. After allowing the mixture to warm to −30 °C, acetic acid (0.45 g, 7.5 mmol) was added dropwise. Volatile components were removed under reduced pressure, and the residue was dissolved in $CHCl_3$ (100 mL), washed with water (100 mL), dried, and concentrated under reduced pressure. The residue was purified by chromatography over a column of silica. Elution with $CHCl_3$ and recrystallization from EtOAc gave **11f** as colorless crystals: 0.885 g (49%); mp 197–199 °C; TLC, 40:1 $CHCl_3$–MeOH, R_f 0.38; MS *m/z* 362 (M + 1)$^+$; UV (EtOH) λ_{max} 243 nm (ε 17030), 285 (sh); IR (KBr) 1699, 1646, 1495, 1376, 756 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.42 (3 H, t, CH_3), 4.19 (1 H, d, J = 16 Hz, H-4_{eq}), 4.40 (2 H, q, CH_2CH_3) 4.45 (1 H, d, J = 15 Hz, $CH_2C_6H_5$), 5.18 (1 H, d, J = 15 Hz, $CH_2C_6H_5$), 5.24 (1 H, d, J = 16 Hz, H-4_{ax}), 7.28–7.40 (5 H, m, aryl H), 7.43 (1 H, dd, $J_{9,10}$ = 7.8, $J_{8,10}$ = 1.0 Hz, H-10), 7.56 (1 H, td, $J_{7,8}$ = 7.8, $J_{8,9}$ = 7.7 Hz, H-8), 7.65 (1 H, td, $J_{7,9}$ = 1.5 Hz, H-9), 7.90 (1 H, s, H-1), 8.16 (1 H, d, H-7). Anal. ($C_{21}H_{19}N_3O_3$) C, H, N.

The following compounds were similarly prepared: **Ethyl 5,6-Dihydro-5-allyl-6-oxo-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3-carboxylate (11c).** This compound was obtained from the dione **15b** in 40% yield: mp 120–122 °C; TLC, EtOAc, R_f 0.30; MS *m/z* 312 (M + 1)$^+$; ^{1}H NMR ($CDCl_3$) δ 1.46 (3 H, t, CH_3), 3.95, 4.55 (2 H, 2 br d, $CH_2CH{=}CH_2$), 4.25 (1 H, d, J = 16 Hz, H-4_{eq}), 4.43 (2 H, q, CH_2CH_3), 5.22–5.38 (3 H, m, $CH{=}CH_2$ and H-4_{ax}), 5.84 (1 H, m, $CH{=}CH_2$), 7.43 (1 H, dd, $J_{9,10}$ = 7.9, $J_{8,10}$ = 1.2 Hz, H-10), 7.55 (1 H, td, $J_{7,8}$ = 7.8, $J_{8,9}$ = 7.5 Hz, H-8), 7.66 (1 H, td, $J_{7,9}$ = 1.7 Hz, H-9), 7.92 (1 H, s, H-1), 8.10 (1 H, dd, H-7). Anal. ($C_{17}H_{17}N_3O_3$) C, H, N.

Ethyl 5,6-Dihydro-5-phenyl-6-oxo-4*H*-imidazo[1,5-*a*][1,4]-benzodiazepine-3-carboxylate (11d). This compound was obtained from the dione **15c** in 45% yield: mp 175–177 °C; TLC, EtOAc, R_f 0.39; MS *m/z* 348 (M + 1)$^+$; ^{1}H NMR ($CDCl_3$) δ 1.24 (3 H, t, CH_3), 4.30 (2 H, q, CH_2CH_3), 4.73 (1 H, d, J = 16 Hz, H-4_{eq}), 5.61 (1 H, d, J = 16 Hz, H-4_{ax}), 7.28–7.48 (5 H, m, aryl H), 7.49 (1 H, dd, $J_{9,10}$ = 7.8, $J_{8,10}$ = 1.2 Hz, H-10), 7.58 (1 H, td, $J_{7,8}$ = 7.8, $J_{8,9}$ = 7.7 Hz, H-8), 7.70 (1 H, td, $J_{7,9}$ = 1.6 Hz, H-9), 8.00 (1 H, s, H-1), 8.18 (1 H, dd, H-7). Anal. ($C_{20}H_{17}N_3O_3$) C, H, N.

Ethyl 5,6-Dihydro-5-(4-methoxyphenyl)-6-oxo-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3-carboxylate (11e). This compound was obtained from the dione **15d** in 36% yield: mp 178–180 °C; TLC, EtOAc, R_f 0.29; MS *m/z* 378 (M + 1)$^+$; ^{1}H NMR ($CDCl_3$) δ 1.26 (3 H, t, CH_3), 3.82 (3 H, s, OCH_3), 4.32 (2 H, q, CH_2CH_3), 4.70 (1 H, d, J = 15 Hz, H-4_{eq}) 5.56 (1 H, d, J = 15 Hz, H-4_{ax}), 6.92 (2 H, dd, H-3′,5′), 7.20 (2 H, dd, H-1′,6′), 7.48 (1 H, dd, $J_{9,10}$ = 7.9, $J_{8,10}$ = 1.2 Hz, H-10), 7.58 (1 H, td, $J_{7,8}$ = 7.8, $J_{8,9}$ = 7.5 Hz, H-8), 7.69 (1 H, td, $J_{7,9}$ = 1.6 Hz, H-9), 7.98 (1 H, s, H-1), 8.16 (1 H, dd, H-7). Anal. ($C_{21}H_{19}N_3O_4$) C, H, N.

Ethyl 7-Chloro-5,6-dihydro-5-benzyl-6-oxo-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3-carboxylate (11h). This compound was obtained from the dione **15f** in 34% yield: mp 186–188 °C; TLC, EtOAc, R_f 0.44; MS *m/z* 396 (M + 1)$^+$; ^{1}H NMR ($CDCl_3$) δ 1.41 (3 H, t, CH_3), 4.16 (1 H, d, J = 16 Hz, $NCH_2C_6H_5$), 4.28 (1 H, d, J = 16 Hz, H-4_{eq}), 4.39 (2 H, q, CH_2CH_3), 5.18 (1 H, d, J = 16 Hz, $NCH_2C_6H_5$), 5.29 (1 H, d, J = 16 Hz, H-4_{ax}), 7.24–7.42 (6 H, m, H-8 and H-1′-5′) 7.52 (1 H, t, $J_{9,10}$ = 8.1, $J_{8,9}$ = 8.0 Hz, H-9), 7.60 (1 H, dd, $J_{8,10}$ = 1.2 Hz, H-10), 7.91 (1 H, s, H-1). Anal. ($C_{21}H_{18}ClN_3O_3$) C, H, N.

Ethyl 8-Chloro-5,6-dihydro-5-benzyl-6-oxo-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3-carboxylate (11i). This compound was obtained from the dione **15g** in 42% yield: mp 202–204 °C; TLC, EtOAc, R_f 0.48; MS *m/z* 396 (M + 1)$^+$; ^{1}H NMR ($CDCl_3$) δ 1.41 (3 H, t, CH_3), 4.16 (1 H, br d, J = 15 Hz, H-4_{eq}), 4.37 (2 H, q, CH_2CH_3), 4.42 (1 H, br d, J = 16 Hz, $NCH_2C_6H_5$), 5.22 (2 H, br m, H-4_{ax} and $NCH_2C_6H_5$), 7.26–7.40 (6 H, m, H-10 and H-1′-5′) 7.61 (1 H, dd, $J_{9,10}$ = 8.6, $J_{7,9}$ = 2.4 Hz, H-9), 7.88 (1 H, s, H-1), 8.15 (1 H, d, H-7). Anal. ($C_{21}H_{18}ClN_3O_3$) C, H, N.

Ethyl 5,6-Dihydro-5-(2,4-dimethoxybenzyl)-6-oxo-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3-carboxylate (11j). This compound was obtained from the dione **15h** in 51% yield: mp 136–138 °C (lit.[16] mp 136–138 °C); TLC, EtOAc, R_f 0.26; MS *m/z* 422 (M + 1)$^+$; ^{1}H NMR ($CDCl_3$) δ 1.39 (3 H, t, CH_2CH_3), 3.78, 3.80 (6 H, 2 s, OCH_3), 4.19 (1 H, d, J = 16 Hz, H-4_{eq}), 4.32 (2 H, q, CH_2CH_3), 4.70 (1 H, d, J = 15 Hz, $NCH_2C_6H_5$), 4.84 (1 H, d, J = 15 Hz, $NCH_2C_6H_5$), 5.36 (1 H, d, J = 16 Hz, H-4_{ax}), 6.4–6.8 (2 H, m, H-3′,5′), 7.21 (1 H, d, J = 7.8 Hz, H-6′) 7.40 (1 H, dd, $J_{9,10}$ = 7.9, $J_{8,10}$ = 1.2 Hz, H-10), 7.52 (1 H, td, $J_{7,8}$ = 7.8, $J_{8,9}$ = 7.5 Hz, H-8), 7.63 (1 H, td, $J_{7,9}$ = 1.5 Hz, H-9), 7.89 (1 H, s, H-1), 8.11 (1 H, dd, H-7). Anal. ($C_{23}H_{23}N_3O_5$) C, H, N.

3-[(4-Methylphenyl)sulfonyl]-4,5-dihydro-5-methyl-6*H*-imidazo[1,5-*a*][1,4]benzodiazepin-6-one (12h). This compound was obtained from the dione **15a** according to the procedure described for the preparation of **11f** using tosylmethyl isocyanide in place of ethyl isocyanoacetate: yield 46%; mp 255–257 °C dec; TLC, 20:1 $CHCl_3$–MeOH, R_f 0.58; MS *m/z* 368 (M + 1)$^+$; ^{1}H NMR ($CDCl_3$) δ 2.44 (3 H, s, CH_3), 3.30 (3 H, s, NCH_3), 4.37 (1 H, d, J = 16 Hz, H-4_{eq}), 5.25 (1 H, d, J = 16 Hz, H-4_{ax}), 7.32–7.4 (3 H, m, H-10,3′,5′), 7.56 (1 H, td, $J_{7,8}$ = 7.8, $J_{8,9}$ = 7.4, $J_{8,10}$ = 1.3 Hz, H-8) 7.64 (1 H, td, $J_{9,10}$ = 8.0, $J_{7,9}$ = 1.6 Hz, H-9), 7.86 (1 H, s, H-1), 7.96 (2 H, d, J = 8.3 Hz, H-2′,6′), 8.07 (1 H, dd, H-7). Anal. ($C_{19}H_{17}N_3O_3S$) C, H, N.

Ethyl 5,6-Dihydro-6-oxo-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3-carboxylate (11a). A stirred suspension of **11e** (0.189 g, 0.5 mmol) in CH_3CN (10 mL) was cooled to 0 °C and treated with a solution of ceric ammonium nitrate (0.823 g, 1.5 mmol) in water (10 mL). The mixture was stirred at 0–5 °C for 1 h and then at room temperature for 5 h. A solution of ceric ammonium nitrate (0.823 g, 1.5 mmol) in water (5 mL) was added and the mixture was stirred at room temperature overnight. The reaction mixture was diluted with water (50 mL) and extracted with EtOAc (3 × 50 mL). The organic extract was washed with 10% sodium sulfite (3 × 60 mL), 5% sodium bicarbonate (75 mL), and water (75 mL). The organic layer was dried and filtered and the solvent was removed under reduced pressure. Recrystallization of the residue from EtOH yielded **11a** as colorless crystals, 0.068 g (50%): mp 249–251 °C (lit.[16] mp 248–250 °C); TLC, EtOAc, R_f 0.31; MS *m/z* 272 (M + 1)$^+$; ^{1}H NMR ($CDCl_3$) δ 1.43 (3 H, t, CH_3), 4.42 (2 H, q, CH_2CH_3), 4.60–4.88 (2 H, br hump, H-4), 6.70 (1 H, br t, NH), 7.47 (1 H, dd, $J_{9,10}$ = 7.9, $J_{8,10}$ = 1.2 Hz, H-10), 7.57 (1 H, td, $J_{7,8}$ = 7.8, $J_{8,9}$ = 7.5 Hz, H-8), 7.69

(1 H, td, $J_{7,9}$ = 1.6 Hz, H-9), 7.90 (1 H, s, H-1), 8.12 (1 H, dd, H-7). Anal. ($C_{14}H_{13}N_3O_3$) C, H, N.

Ethyl 5-Propyl-5,6-dihydro-6-oxo-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3-carboxylate (11b). A solution of **11c** (0.417 g, 1.34 mmol) in EtOH (20 mL) was hydrogenated at atmospheric pressure over 5% Pd/C (40 mg). After the theoretical amount of hydrogen was absorbed (2 h), the catalyst was removed by filtration, the filtrate was evaporated to dryness, and the residue was chromatographed over a column of silica. Elution with EtOAc and crystallization from EtOAc–cyclohexane 3:2 yielded 0.252 g (60%) of **11b** as a colorless solid: mp 86–88 °C; TLC, EtOAc, R_f 0.30; MS m/z 314 $(M + 1)^+$; ^1H NMR ($CDCl_3$) δ 0.91 (3 H, t, $CH_2CH_2CH_3$), 1.45 (3 H, t, OCH_2CH_3), 1.70 (2 H, m, $CH_2CH_2CH_3$), 3.61 (2 H, m, $CH_2CH_2CH_3$), 4.30 (1 H, d, J = 16 Hz, H-4_{eq}), 4.44 (2 H, m, OCH_2CH_3), 5.25 (1 H, d, J = 16 Hz, H-4_{ax}), 7.43 (1 H, dd, $J_{9,10}$ = 7.7, $J_{8,10}$ = 1.2 Hz, H-10), 7.54 (1 H, td, $J_{8,9}$ = 7.7, $J_{7,8}$ = 7.6 Hz, H-8), 7.64 (1 H, td, $J_{7,9}$ = 1.6 Hz, H-9), 7.90 (1 H, s, H-1), 8.09 (1 H, dd, H-7); ^1H NMR (DMSO-d_6 at 100 °C) δ 0.80 (3 H, t, $CH_2CH_2CH_3$), 1.34 (3 H, t, OCH_2CH_3), 1.60 (2 H, sextet, $CH_2CH_2CH_3$), 3.52 (2 H, t, $CH_2CH_2CH_3$), 4.43 (2 H, q, OCH_2CH_3), 4.71 (2 H, br s, H-4), 7.55 (1 H, m, H-8), 7.70 (2 H, m, H-9,10) 7.93 (1 H, dd, J = 8.0, 1.4 Hz, H-7), 8.27 (1 H, s, H-1). Anal. ($C_{17}H_{19}N_3O_3$) C, H, N.

Ethyl 5,6-Dihydro-5-(2-phenylethyl)-6-oxo-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3-carboxylate (11g). To a suspension of sodium hydride (0.14 g, 3.54 mmol) in DMF (11 mL) was added **11a** (0.3 g, 1.11 mmol). The mixture was stirred at ambient temperature for 10 min, treated with 2-(bromoethyl)-benzene (0.944 g, 5.1 mmol) and stirred at room temperature for 5 h. The reaction mixture was diluted with water (125 mL), neutralized with drops of AcOH, and extracted with $CHCl_3$ (3 × 100 mL). The organic layer was washed with water (150 mL) and dried and volatile components were removed under reduced pressure. The crude product was applied on a column of silica. Elution with hexane–EtOAc 9:1 and recrystallization from EtOH–H_2O 2:1 gave the product **11g** as colorless crystals: 0.258 g (62%), mp 135–137 °C; TLC, EtOAc, R_f 0.44; MS m/z 376 $(M + 1)^+$; UV (EtOH) λ_{max} 244 nm (ϵ 20 940), 285 (sh); IR (KBr) 1700, 1636, 1498, 1375, 1191, 764, 705 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.45 (3 H, t, CH_3), 2.96 (2 H, m, $CH_2C_6H_5$), 3.88 (2 H, m, NCH_2CH_2), 4.22 (1 H, d, J = 16 Hz, H-4_{eq}), 4.45 (2 H, q, CH_2CH_3), 5.17 (1 H, d, J = 16 Hz, H-4_{ax}), 7.22–7.32 (5 H, m, aryl H), 7.41 (1 H, dd, $J_{9,10}$ = 8.0, $J_{8,10}$ = 1.2 Hz, H-10), 7.54 (1 H, td, $J_{7,8}$ = 7.8, $J_{8,9}$ = 7.5 Hz, H-8), 7.64 (1 H, td, $J_{7,9}$ = 1.6 Hz, H-9), 7.78 (1 H, s, H-1), 8.08 (1 H, dd, H-7). Anal. ($C_{22}H_{21}N_3O_3$) C, H, N.

3-[(Methoxycarbonyl)amino]-4,5-dihydro-5-methyl-6*H*-imidazo[1,5-*a*][1,4]benzodiazepin-6-one (12a). A solution of 0.385 g (1.36 mmol) of the azide **18** (X = H, R = CH_3)[27] in MeOH (10 mL) was heated under reflux until the disappearance of the starting material was complete. The reaction mixture was allowed to cool to room temperature and the solid obtained was collected by filtration, dried, and crystallized from MeOH to yield **12a** as colorless crystals; 0.31 g (79%), mp 245–247 °C; TLC, 10:1 $CHCl_3$–MeOH, R_f 0.6; MS m/z 287 $(M + 1)^+$; IR (KBr) 3185, 1721, 1648, 1629, 1492, 1289, 1066, 754 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.12 (3 H, s, NCH_3), 3.64 (3 H, s, OCH_3), 4.38 (2 H, br s, H-4), 7.51 (1 H, td, $J_{7,8}$ = 7.8, $J_{8,9}$ = 7.4, $J_{8,10}$ = 1.6 Hz, H-8), 7.68 (2 H, m, H-9,10), 7.86 (1 H, dd, $J_{7,9}$ = 1.5 Hz, H-7), 8.14 (1 H, s, H-1). Anal. ($C_{14}H_{14}N_4O_3$) C, H, N.

3-[(Ethoxycarbonyl)amino]-4,5-dihydro-5-methyl-6*H*-imidazo[1,5-*a*][1,4]benzodiazepin-6-one (12b). This compound was prepared in a manner similar to that described above for **12a** using EtOH. Crystallization from EtOH afforded **12b** as colorless crystals in 90% yield: mp 221–223 °C dec; TLC, 20:1 $CHCl_3$–MeOH, R_f 0.27; MS m/z 301 $(M + 1)^+$; ^1H NMR (DMSO-d_6) δ 1.24 (3 H, t, CH_2CH_3), 3.11 (3 H, s, NCH_3), 4.10 (2 H, q, CH_2CH_3), 4.36 (2 H, br s, H-4), 7.51 (1 H, td, $J_{8,9}$ = 8.0, $J_{7,8}$ = 6.8, $J_{8,10}$ = 1.6 Hz, H-8), 7.68 (2 H, m, H-9,10), 7.87 (1 H, dd, $J_{7,9}$ = 1.5 Hz, H-7), 8.13 (1 H, s, H-1), 9.20 (1 H, br s, NH). Anal. ($C_{15}H_{16}N_4O_3$) C, H, N.

3-[(*tert*-Butoxycarbonyl)amino]-4,5-dihydro-5-methyl-6*H*-imidazo[1,5-*a*][1,4]benzodiazepin-6-one (19). This compound was prepared in a manner similar to that described above for **12a** by using *t*-BuOH. Crystallization from EtOH afforded **19** as colorless crystals in 60% yield: mp 213–215 °C dec; TLC, 20:1 $CHCl_3$–MeOH, R_f 0.37; MS m/z 329 $(M + 1)^+$; ^1H NMR (DMSO-d_6) δ 1.46 [9 H, s, $C(CH_3)_3$], 3.12 (3 H, s, NCH_3), 4.34 (2 H, br s, H-4), 7.50 (1 H, m, H-8), 7.66 (2 H, m, H-9,10), 7.87 (1 H, dd, H-7), 8.11 (1 H, s, H-1), 8.90 (1 H, br s, NH). Anal. ($C_{17}H_{20}N_4O_3$) C, H, N.

3-(Acetylamino)-4,5-dihydro-5-methyl-6*H*-imidazo[1,5-*a*][1,4]benzodiazepin-6-one (12c). A stirred suspension of **19** (0.5 g, 1.52 mmol) in dioxane (5 mL) was treated with a 4.0 M solution of hydrogen chloride in dioxane (5 mL), and the mixture was stirred at ambient temperature for 4 h. Volatile components were removed under reduced pressure, the residue was dissolved in pyridine (5 mL) and treated with acetic anhydride (2 mL), and the mixture was stirred at room temperature overnight. The reaction mixture was then concentrated under reduced pressure and the residue obtained on trituration with water (10 mL) was collected, dried, and crystallized from EtOH to give **12c** as shiny crystals: yield 61%; mp 255–257 °C; TLC, 20:1 $CHCl_3$–MeOH, R_f 0.71; MS m/z 271 $(M + 1)^+$; ^1H NMR ($CDCl_3$) δ 2.27 (3 H, s, $COCH_3$) 3.30 (3 H, s, NCH_3), 4.37 (1 H, d, H-4_{eq}), 5.17 (1 H, d, H-4_{ax}), 7.41 (1 H, m, H-10), 7.55 (2 H, m, H-8,9), 8.09 (1 H, m, H-7), 8.18 (1 H, br s, H-1), 9.38 (1 H, br hump, NH). Anal. ($C_{14}H_{14}N_4O_2$) C, H, N.

3-(Formylamino)-4,5-dihydro-5-methyl-6*H*-imidazo[1,5-*a*][1,4]benzodiazepin-6-one (12d). A stirred suspension of **19** (0.125 g, 0.381 mmol) in 88% aqueous formic acid (6.5 mL) was heated under reflux for 6 h, volatile components were removed under reduced pressure, and the residue was crystallized from EtOH to provide **12d** in 70% yield: mp 212–214 °C dec; TLC, 20:1 $CHCl_3$–MeOH, R_f 0.36; MS m/z 257 $(M + 1)^+$; ^1H NMR ($CDCl_3$) δ 3.28 (3 H, s, NCH_3), 4.40 (1 H, d, H-4_{eq}), 5.14 (1 H, d, H-4_{ax}), 7.36 (1 H, dd, H-10), 7.50 (1 H, td, H-8), 7.61 (1 H, td, H-9), 7.74 (1 H, s, H-1), 8.06 (1 H, dd, H-7), 8.28–8.62 (2 H, m, CHO, NH). Anal. ($C_{13}H_{12}N_4O_2$) C, H, N.

3-(Isothiocyanato)-4,5-dihydro-5-methyl-6*H*-imidazo[1,5-*a*][1,4]benzodiazepin-6-one (12e). A stirred suspension of **19** (1.267 g, 3.86 mmol) in EtOAc (55 mL) was cooled in ice bath and hydrogen chloride was bubbled in for 15 min. After allowing the mixture to stir for an additional 15 min, volatile components were removed under reduced pressure and the residue was suspended in $CHCl_3$ (28 mL). A saturated solution of sodium bicarbonate (28 mL) was added, and the mixture was treated with thiophosgene (0.50 g, 4.25 mmol) and stirred at room temperature for 20 min. The layers were separated, the aqueous layer was extracted with $CHCl_3$ (50 mL), the combined organic extracts were washed with water (100 mL) and dried, and the solvent was removed under reduced pressure. Recrystallization of the residue from CH_2Cl_2–hexane 1:2 gave **12e** in 35% yield: mp 150–151 °C; TLC, EtOAc, R_f 0.70; MS m/z 271 $(M + 1)^+$; ^1H NMR ($CDCl_3$) δ 3.16 (3 H, s, NCH_3), 4.34 (2 H, br s, H-4), 7.38 (1 H, dd, $J_{9,10}$ = 7.9, $J_{8,10}$ = 1.2 Hz, H-10), 7.52 (1 H, td, $J_{7,8}$ = 7.7, $J_{8,9}$ = 7.6 Hz, H-8), 7.63 (1 H, td, $J_{7,9}$ = 1.6 Hz, H-9), 7.73 (1 H, s, H-1), 8.05 (1 H, dd, H-7). Anal. ($C_{13}H_{10}N_4OS$) C, H, N.

3-(4,5-Dihydro-2-oxazolyl)-4,5-dihydro-5-methyl-6*H*-imidazo[1,5-*a*][1,4]benzodiazepin-6-one (12f). A mixture of the ester **2e**[16] (0.285 g, 1.0 mmol) and ethanolamine (1.0 mL) was heated under reflux at 170 °C for 2 h, poured on ice–water mixture (25 mL), and stirred. The solid obtained was collected by filtration, dried, and crystallized from EtOAc to obtain 0.17 g (57%) of **21**: mp 180–182 °C; TLC, 20:1 $CHCl_3$–MeOH, R_f 0.26; MS m/z 301 $(M + 1)^+$; ^1H NMR ($CDCl_3$) δ 2.81 (1 H, t, CH_2OH), 3.27 (3 H, s, NCH_3), 3.62 (2 H, br m, $NHCH_2CH_2$), 3.85 (2 H, q, CH_2CH_2OH), 4.36 (1 H, br hump, H-4), 5.36 (1 H, br hump, H-4), 7.40 (1 H, dd, H-10), 7.49–7.59 (2 H, m, H-8, NH), 7.64 (1 H, td, H-9), 7.81 (1 H, s, H-1), 8.08 (1 H, dd, H-7). Anal. ($C_{15}H_{16}N_4O_3$) C, H, N.

To a stirred solution of **21** (0.16 g, 0.53 mmol) in warm acetonitrile (32 mL) was added thionyl chloride (0.5 mL), and the mixture was refluxed for 2 h with protection from moisture. After allowing the mixture to stand at room temperature overnight, volatile components were removed under reduced pressure and the residue was chromatographed over a column of silica. Elution with $CHCl_3$ gave 0.127 g (75%) of **22** as a dark brown oil which solidified on standing: TLC, 100:1 $CHCl_3$–MeOH, R_f 0.17; MS m/z 319 $(M + 1)^+$; ^1H NMR ($CDCl_3$) δ 3.27 (3 H, s, NCH_3), 3.4–4.8 (6 H, br m, H-4, CH_2CH_2Cl) 7.38–7.72 (4 H, m, H-8,9,10, NH), 7.82 (1 H, s, H-1), 8.05 (1 H, m, H-7). The product was used as such in the next step.

A 60% dispersion of sodium hydride (0.020 g, 0.5 mmol) was washed free of mineral oil, suspended in 1,2-dimethoxyethane (2 mL), and cooled in ice bath. To the stirred suspension was added a solution of **22** (0.12 g, 0.38 mmol) in 1,2-dimethoxyethane (3 mL). After stirring in the cold bath for 3 h, the reaction mixture was allowed to warm up to room temperature and stir overnight. The solvent was removed under reduced pressure and the residue was treated with water (5 mL). The solid obtained was collected by filtration. The aqueous layer was evaporated under reduced pressure, the residue was extracted with $CHCl_3$ (3 × 50 mL) and dried, and the solvent was removed to obtain an additional quantity of the product. The crude products were combined and crystallized from MeOH to provide 0.056 g (53%) of **12f**: mp 224–226 °C dec; TLC, 20:1 $CHCl_3$–MeOH, R_f 0.34; MS m/z 283 $(M + 1)^+$; ^1H NMR ($CDCl_3$) δ 3.25 (3 H, s, NCH_3), 4.08 (2 H, t, NCH_2CH_2), 4.36 (1 H, br s, H-4_{eq}), 4.45 (2 H, t, OCH_2CH_2), 5.18 (1 H, br s, H-4_{ax}), 7.43 (1 H, dd, $J_{9,10}$ = 8.0, $J_{8,10}$ = 1.2 Hz, H-10), 7.52 (1 H, td, $J_{7,8}$ = 7.8, $J_{8,9}$ 7.5 Hz, H-8), 7.63 (1 H, td, $J_{7,9}$ = 1.5 Hz, H-9), 7.90 (1 H, s, H-1), 8.07 (1 H, dd, H-7). Anal. ($C_{15}H_{14}N_4O_2$) C, H, N.

3-(2-Benzoxazolyl)-4,5-dihydro-5-methyl-6*H*-imidazo[1,5-*a*][1,4]benzodiazepin-6-one (12g). A mixture of phosphorus pentoxide (1.50 g, 10.6 mmol) and HMDS (2.90 g, 18.0 mmol) in 1,2-dichlorobenzene (7.5 mL) was refluxed for 5 min with protection from moisture. The mixture was cooled to room temperature and the acid **20**[27] (0.64 g, 2.5 mmol) and 2-aminophenol (0.330 g, 3.0 mmol) were added. The reaction mixture was refluxed for 4 h, cooled, and diluted with dichloromethane (100 mL). The organic layer was washed with 1 N aqueous sodium hydroxide (30 mL). The aqueous layer was extracted with dichloromethane (3 × 30 mL), the combined organic extracts were washed with brine (100 mL), dried and filtered, and the filtrate was evaporated to dryness under reduced pressure. The residue thus obtained was crystallized from MeOH to yield 0.288 g (35%) of **12g**: mp 290–292 °C; TLC, EtOAc, R_f 0.50; MS m/z 331 $(M + 1)^+$; ^1H NMR (DMSO-d_6) δ 3.36 (3 H, s, NCH_3), 4.56 (1 H, br hump, H-4), 5.30 (1 H, br hump, H-4), 7.42 (2 H, m, benzoxazolyl H), 7.60 (1 H, m, H-8), 7.73–7.85 (4 H, m, H-9,10, benzoxazolyl H), 7.94 (1 H, dd, H-7), 8.58 (1 H, s, H-1). Anal. ($C_{19}H_{14}N_4O_2 \cdot 0.2H_2O$) C, H, N.

3-(5-Methyl-1,3,4-oxadiazol-2-yl)-4,5-dihydro-5-benzyl-6*H*-imidazo[1,5-*a*][1,4]benzodiazepin-6-one (13). A mixture of **11f** (0.50 g, 1.38 mmol) and hydrazine hydrate (1.5 mL) in EtOH (8 mL) was refluxed for 2 h and cooled and the solid obtained was collected by filtration. Crystallization from EtOH yielded (0.435 g, 90%) of the hydrazide **17** (R = $CH_2C_6H_5$, X = H) as a colorless solid: mp 245–247 °C; TLC, 9:1 $CHCl_3$–MeOH, R_f 0.48; MS m/z 348 $(M + 1)^+$; ^1H NMR (DMSO-d_6) δ 4.30, 5.16 (4 H, br m, H-4, $CH_2C_6H_5$), 4.42 (2 H, d, $NHNH_2$), 7.25–7.42 (5 H, m, $CH_2C_6H_5$), 7.58 (1 H, m, H-8), 7.70–7.80 (2 H, m, H-9,10), 7.99 (1 H, dd, H-7), 8.35 (1 H, s, H-1), 9.31 (1 H, br s, $NHNH_2$). Anal. ($C_{19}H_{17}N_5O_2$) C, H, N.

A mixture of the hydrazide (0.425 g, 1.22 mmol) and ethyl acetimidate hydrochloride (0.302 g, 2.44 mmol) in pyridine (6 mL) was heated under reflux at 130 °C for 4 h. Volatile components were removed under reduced pressure and the residue was partitioned between water (100 mL) and EtOAc (100 mL). The organic layer was washed with 1 N aqueous HCl, 5% sodium bicarbonate, and water. The organic extract was dried and the solvent was removed under reduced pressure. The crude product thus obtained was purified by chromatography over silica. Elution with $CHCl_3$–MeOH 99:1 and crystallization from EtOAc gave 0.304 g (67%) of **13** as colorless solid: mp 204–206 °C; TLC, 40:1 $CHCl_3$–MeOH, R_f 0.50; MS m/z 372 $(M + 1)^+$; ^1H NMR (DMSO-d_6) δ 2.56 (3 H, s, CH_3), 4.57 (1 H, br d, H-4), 4.76 (2 H, d, $CH_2C_6H_5$), 4.95 (1 H, br d, H-4), 7.12–7.22 (5 H, m, $CH_2C_6H_5$), 7.62 (1 H, m, H-8), 7.77 (2 H, m, H-9,10), 8.02 (1 H, dd, H-7), 8.50 (1 H, s, H-1). Anal. ($C_{21}H_{17}N_5O_2$) C, H, N.

3-(3-Methyl-1,2,4-oxadiazol-5-yl)-4,5-dihydro-5-benzyl-6*H*-imidazo[1,5-*a*][1,4]benzodiazepin-6-one (14a). Sodium hydride (0.16 g, 60% dispersion in mineral oil, 4.0 mmol) was added in portions to a stirred mixture of acetamidoxime (0.294 g, 4.0 mmol) and powdered 4A molecular sieves in THF (5 mL). After stirring the mixture at room temperature for an additional 30 min, a suspension of **11f** (0.723 g, 2.0 mmol) in THF (7.5 mL) was added and the mixture was refluxed for 1 h. After allowing it to cool to room temperature, acetic acid (0.24 g, 4.0 mmol) was added dropwise and the mixture was then filtered through a pad of Celite. The residue was washed with dichloromethane (3 × 75 mL). The organic extracts were combined, washed with water (100 mL), and dried. The solvents were removed under reduced pressure and the residue was crystallized from EtOH to obtain 0.475 g (64%) of **14a** as a colorless crystalline solid: mp 232–234 °C; TLC, 40:1 $CHCl_3$–MeOH, R_f 0.45; MS m/z 372 $(M + 1)^+$; ^1H NMR (DMSO-d_6) δ 2.38 (3 H, s, CH_3), 4.54 (1 H, d, H-4), 4.76 (2 H, d, $CH_2C_6H_5$), 5.08 (1 H, d, H-4), 7.10–7.27 (5 H, m, $CH_2C_6H_5$), 7.64 (2 H, m, H-8,9), 7.79 (1 H, dd, H-10), 8.03 (1 H, dd, H-7), 8.54 (1 H, s, H-1). Anal. ($C_{21}H_{17}N_5O_2$) C, H, N.

7-Chloro-3-(3-methyl-1,2,4-oxadiazol-5-yl)-4,5-dihydro-5-benzyl-6*H*-imidazo[1,5-*a*][1,4]benzodiazepin-6-one (14b) was prepared from **11h** (0.37 g, 0.94 mmol) and acetamidoxime (0.14 g, 1.88 mmol) using the procedure described for the synthesis of **14a**. Crystallization of the crude product from EtOH gave 0.30 g (79%) of **14b** as a colorless crystalline solid: mp 280–282 °C dec; TLC, 40:1 $CHCl_3$–MeOH, R_f 0.48; MS m/z 406 $(M + 1)^+$; ^1H NMR (DMSO-d_6) δ 2.40 (3 H, s, CH_3), 4.60 (1 H, d, J = 16.3 Hz, H-4), 4.62 (1 H, d, J = 14.7 Hz, $CH_2C_6H_5$), 4.78 (1 H, d, J = 14.7 Hz, $CH_2C_6H_5$), 5.02 (1 H, d, J = 16.3 Hz, H-4), 7.12–7.25 (5 H, m, $CH_2C_6H_5$), 7.68–7.79 (3 H, m, H-8,9,10), 8.59 (1 H, s, H-1). Anal. ($C_{21}H_{16}ClN_5O_2$) C, H, N.

8-Chloro-3-(3-methyl-1,2,4-oxadiazol-5-yl)-4,5-dihydro-5-benzyl-6*H*-imidazo[1,5-*a*][1,4]benzodiazepin-6-one (14c) was prepared from **11i** (0.54 g, 1.36 mmol) and acetamidoxime (0.20 g, 2.72 mmol) using the procedure described for **14a**. Crystallization of the crude product from EtOH gave 0.32 g (58%) of **14c** as colorless crystals: mp 230–232 °C; TLC, 40:1 $CHCl_3$–MeOH, R_f 0.56; MS m/z 406 $(M + 1)^+$; ^1H NMR (DMSO-d_6) δ 2.38 (3 H, s, CH_3), 4.59 (1 H, br d, H-4), 4.75 (2 H, s, $CH_2C_6H_5$), 5.06 (1 H, br d, H-4), 7.10–7.24 (5 H, m, $CH_2C_6H_5$), 7.80–7.92 (2 H, m, H-9,10), 8.00 (1 H, d, H-7), 8.53 (1 H, s, H-1). Anal. ($C_{21}H_{16}ClN_5O_2$) C, H, N.

Biological Methods. Radioligand Binding Assays. Ligand binding to cortical BzR: Drug effects on radioligand binding to cortical BzR were examined in washed membranes prepared from rat cerebral cortex. Adult (150–175 g) male Sprague-Dawley rats (Taconic Farms, Germantown, NY) were killed by decapitation. The brains were removed and placed in ice-cold Tris-citrate buffer (pH 7.4). Cerebral cortices were dissected and disrupted in 100 volumes of buffer with a Polytron (setting 6–7, 15 s). The tissues were then centrifuged at 20000*g* (4 °C) for 20 min. The supernatants were discarded and the suspension–centrifugation repeated two more times. Following the last centrifugation, the tissues were resuspended in 50 volumes of buffer and frozen on solid CO_2. The tissues were stored at −70 °C until used. [^3H]-Flunitrazepam (DuPont-NEN, Boston, MA) binding was determined in a total volume of 1 mL consisting of the following: buffer, 0.6–0.7 mL; NaCl (2.5 M), 0.1 mL; tissue suspension (~100 μg), 0.1 mL; radioligand (sp act. 90 Ci/mmol; final concentration, ~1 nM), 0.1 mL; test compound, 0.1 mL. Reactions were initiated with radioligand and terminated after 2 h (4 °C) by filtration (Whatman GF/B filters) under vacuum (Brandel M-24R) with two 5-mL washes of ice-cold buffer. The radioactivity retained on the filters was measured in a Beckman LS 5801 liquid scintillation counter. Nonspecific binding was determined using Ro 15-1788 (10 μM) and represented <10% of the total binding. Six to eight concentrations of inhibitor were routinely used to estimate potency. IC_{50} values were estimated by fitting data to a sigmoid curve (GraphPad Inplot). Values represent X ± SEM of three determinations unless otherwise specified. Stock solutions of 1–5 mM in ethanol or methanol were diluted in buffer to yield the desired concentrations. For the evaluation of the isothiocyanato compound **12e**, the tissue was prepared essentially as described above using 10 mM potassium phosphate (pH 7.4) as the washing buffer. The compound was made up to 2 mM in DMSO as a stock solution. The binding and washing conditions were the same as described above except Tris–citrate was replaced by 10 mM potassium phosphate (pH 7.4).

Ligand binding to cerebellar "diazepam-sensitive" (DS) and "diazepam-insensitive" (DI) BzR: Drug effects on radioligand binding to DS and DI BzR were examined in washed membranes prepared from rat cerebellum as described.[26] In brief, cerebella were disrupted in 60 volumes of 50 mM Tris–citrate buffer (pH

7.8). Homogenates were centrifuged at 20000*g* for 20 min (4 °C), resuspended in 60 volumes of buffer, and recentrifuged. This "washing" procedure was repeated a total of five times. [^{3}H]Ro 15-4513 (DuPont-NEN, Boston, MA) binding was performed in a total volume of 0.5 mL consisting of the following: 0.05 mL of tissue (~100 μg protein), 0.05 mL [^{3}H]Ro 15-4513 (sp act. 29 Ci/mmol; final concentration ~2 nM), 0.05 mL drug solution (final concentrations 0.1 nM–1 μM), 0.05 mL 2 M NaCl, and 0.6 mL Tris–citrate buffer (pH 7.8) to volume. Incubations (0–4 °C) were initiated by the addition of tissue and terminated after 60 min by rapid filtration with two 5-mL washes of ice-cold Tris–citrate buffer through Whatman GF/B filters using a Brandel M-48R filtering manifold (Brandel Instruments, Gaithersburg, MD). Nonspecific binding was determined with Ro 15-1788 (10 μM) and typically represented <10% of total binding. ^{3}[H]Ro 15-4513 binding to DI receptors was defined as follows: [^{3}H]Ro 15-4513 binding displaced by Ro 15-1788 (10 μM) was defined as DS + DI binding, typically 90–95% of [^{3}H]Ro 15-4513 binding with the remainder defined as nonspecific binding. [^{3}H]Ro 15-4513 binding displaced by Ro 15-1788 (10 μM) that was not displaced by diazepam (10 μM) was defined as DI binding. This value typically represented 30–40% of total binding. Substraction of [^{3}H]Ro 15-4513 binding to DI from DS + DI defined DS binding. Stock solutions of 1–2 mM in ethanol were used as described above. At least six concentrations of inhibitor were used. IC_{50} values were estimated as described above and converted to K_i values by the Cheng Prusoff method. Assays were in duplicate, and the values presented are the mean ± SEM of three experiments unless otherwise specified.

Biological Evaluations in Vivo. Adult (25–30 g) male NIH/S mice were used in these experiments. Mice were injected intraperitoneally with the indicated doses of compounds (0.1 mL) suspended in 10% diluted Emulphor (diluted Emulphor/saline, 1:9) or an equal volume of vehicle. Emulphor is a vegetable oil derivative kindly donated by GAF (Wayne, NJ). Fifteen minutes later, the animals were injected (0.1 mL, ip) with pentylenetetrazole (40 or 80 mg/kg) to assess pro- and anticonvulsant activities, respectively. To assess the BzR antagonist potential of test compounds, the indicated doses or an equal volume of vehicle were injected (0.1 mL) followed 10 min later by diazepam (2.5 mg/kg, ip). Five minutes later, mice were challenged with pentylenetetrazole (80 mg/kg). Animals were observed for the presence of clonic/tonic seizures for an additional 15 min. In vehicle-pretreated mice, 40 and 80 mg/kg of pentylenetetrazole produced clonic/tonic seizures in ≪10% and 100% of mice, respectively. The dose of diazepam employed in these studies protected >95% of the mice against pentylenetetrazole-induced seizures.

X-ray Crystallography. Single Crystal X-ray Analysis of 11i and 12b. Crystals of **11i** suitable for single crystal X-ray diffraction studies were grown from ethyl acetate. The crystal selected for data collection was platelike with approximate dimensions of 0.65 × 0.45 × 0.07 mm. The crystals belong to the triclinic space group $P\bar{1}$ with a = 6.609 (4) Å, b = 10.333 (3) Å, c = 14.218 (3) Å, α = 104.27 (3)°, β = 92.06 (3)°, γ = 98.54 (3)°, V = 928.0 Å^3, Z = 2 and D_{calc} = 1.366 g/cm^3. X-ray intensities were measured on a Siemens diffractometer using graphite monochromatized Cu Kα radiation (λ = 1.5418 Å) and ω–2θ scans. Corrections were made for Lorentz and polarization effects but not for absorption (μ = 20.5 cm^{-1}). A total of 2711 independent intensities were measured with $2\theta < 116°$. A total of 890 reflections had net intensities less than two times their estimated standard deviation and were omitted from all further calculations.

The structure was determined by direct methods using the computer program MULTAN80.[54] All hydrogen atom positions were located using difference Fourier maps. The structure was refined using full matrix least-squares analysis in which all non-hydrogen atoms were given anisotropic thermal parameters and all hydrogen atoms were given fixed thermal parameters calculated as 1.5 times the equivalent isotropic thermal parameter of the atom to which the hydrogen atom was attached. The final R factor for 1821 observations and 321 variables was 0.070 and the goodness-of-fit was 2.31. All crystallographic calculations were carried out using the Enraf-Nonius Structure Determination Package.[55] A computer-generated model of **11i** is shown in Figure 1. Positional parameters and thermal parameters have been deposited as supplementary material.

Crystals of **12b** suitable for single crystal X-ray analysis were grown by slow evaporation from ethanol. The crystal selected for data collection was a diamond shape plate with approximate dimensions of 0.25 × 0.25 × 0.02 mm. The crystals belong to the triclinic space group $P\bar{1}$ with a = 11.304 (3) Å, b = 9.015 (2) Å, c = 8.522 (2) Å, α = 118.28 (1)°, β = 77.35 (1)°, γ = 112.86 (1)°, V = 704.1 Å^3, Z = 2 and D_{calc} = 1.416 g/cm^3. X-ray intensities were measured on an Enraf-Nonius CAD-4 diffractometer using graphite monochromatized Cu Kα radiation (λ = 1.5418 Å) and ω–2θ scans. Corrections were made for Lorentz and polarization effects but not for absorption (μ = 8.0 cm^{-1}). A total of 3034 independent intensities were measured with $2\theta < 150°$. The data were particularly weak because of the small crystal volume and 1000 observations with $I < 2\sigma(I)$ were omitted from all further calculations.

The structure was determined by direct methods using the computer program MULTAN80.[54] All hydrogen atom positions were located using difference Fourier maps. The structure was refined using full matrix least-squares analysis in which all non-hydrogen atoms were given anisotropic thermal parameters and all hydrogen atoms were given fixed thermal parameters calculated as 1.5 times the equivalent isotropic thermal parameter of the atom to which the hydrogen atom was attached. The final R factor for 2034 observations and 249 variables was 0.088 and the goodness-of-fit was 2.74. All crystallographic calculations were carried out using the Enraf-Nonius Structure Determination Package.[55] A computer-generated model of **12b** is shown in Figure 1. Tables of positional and thermal parameters have been deposited as supplementary material.

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Supplementary Material Available: Tables of atomic positional and thermal parameters, anisotropic thermal parameters for non-hydrogen atoms, bond distances and bond angles for **11i** and **12b**, and elemental analysis data for imidazobenzodiazepinones and intermediates prepared for this study (16 pages). Ordering information is given on any current masthead page.

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