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DEVELOPMENT OF SELECTIVE LIGANDS FOR BENZODIAZEPINE RECEPTOR SUBTYPES BY MANIPULATING THE SUBSTITUENTS AT POSITIONS 3- AND 7- OF OPTICALLY ACTIVE BzR LIGANDS

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Abstract. Two series of analogs of the optically active α5 subtype selective imidazobenzodiazepine **20** have been prepared. The framework constrained analogs were synthesized by variation of the C (3) ethyl ester function **20** to either t-butyl **7** or 2, 2, 2-trifluoroethyl **14**. In both cases receptor binding was decreased; as well as α5 selectivity. In the second series the 7-acetylenyl function in **14** was varied over the range vinyl, 2-furyl, 2-thienyl and 2-phenyl. Again receptor binding was maintained in most cases; however, α5 selectivity was not increased. The significance of this in regard to occupation of lipophilic regions L_{Di} *vs* L_2 in the pharmacophore/receptor model of the BzR is discussed.

The type A γ-aminobutyric acid ($GABA_A$) receptors are heteroligomeric membrane-bound protein complexes that are composed of several subunits. The inhibitory effects of GABA mediated by these receptors can be modulated by a number of pharmacological agents that selectively bind to allosteric sites on these ion channels.[1-4] $GABA_A$ receptors are pentameric assemblies of proteins derived from a family of subunits (6α, 3β, 3γ, 1δ, 1π, 1θ, 1ε and 3ρ)[4,5] which form the chloride ion channel. The most common form of native $GABA_A$ receptors contains α, β, and γ subunits in a 2:2:1 stoichiometry [4-6] and it has been shown that recombinant receptors which contain these subunits most closely mimic the biological, electrophysiological and pharmacological

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properties of native $GABA_A$ receptors which contain a benzodiazepine recognition site ($GABA_A$/Bz receptors). The benzodiazepine binding site is located at the interface between the α and γ subunits.[7] While it is clear the γ subunit is also required for benzodiazepine binding,[4,6] the fact that most native $GABA_A$ receptors contain a γ2 subunit results in the α subunit as the key determinant of benzodiazepine binding and efficacy.[4, 6]

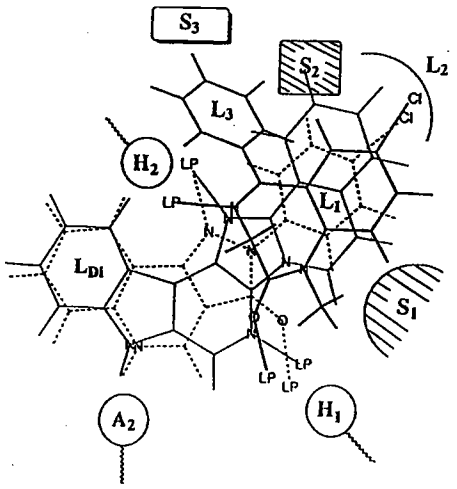


Figure 1. The pyrazolo[3,4-c]quinolin-3-one ligand CGS-9896 (dotted line), diazepam (thick line), and diindoles (thin line) fitted to a schematic representation of the inclusive pharmacophore model for the BzR. The descriptors H_1 and H_2 designate hydrogen bond donator sites on the receptor protein while A_2 represents a hydrogen bond acceptor site necessary for potent inverse agonist activity *in vivo*. L_1, L_2, L_3 and L_{Di} are four lipophilic regions in the binding pharmacophore. Agonist activity requires interaction with H_1, H_2, L_1, L_2, and /or L_3. Receptor descriptors S_1, S_2, and S_3 are regions of negative steric repulsion. Lp=lone pair of electrons.

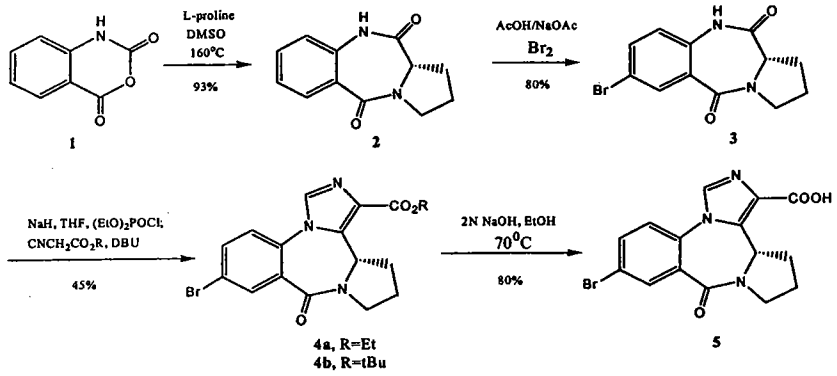
$GABA_A$ receptors which contain the α5 subunit are of minor abundance (5%) in the whole brain, but are significantly expressed in the hippocampus, where they comprise 15-20% of the diazepam-sensitive $GABA_A$ receptor population and are predominantly coassembled with β3 and γ2 subunits.[6,8] This has been confirmed by *in situ* hybridization and immunohistochemical studies indicating that the hippocampus is relatively enriched in α5

containing $GABA_A$ receptors compared to other brain areas.[9,10] Interest in the $GABA_A$/Bz α5 subtype has been stimulated recently by data concerning α5 "knock in"[38] and α5 "knock out" mice,[11,12] which showed that hippocampal α5 $GABA_A$ receptors play a critical role in associative learning and memory.[11,12] In addition, an α5 subtype selective inverse agonist was shown by Bailey et al.[13] to be important in the acquisition of fear conditioning and provided further evidence for the involvement of hippocampal $GABA_A$/ BZ receptors in learning and anxiety.[13] This was later supported by the work of DeLorey et al with α5 selective inverse agonists.[14]

In order to understand the conformational requirements for each receptor subtype and to facilitate the design of high affinity subtype selective ligands, the modification of optically active (S)-enantiomers of imidazobenzodiazepines at positions C (3) and C(7) was carried out. Previous research in this area indicated that the (S)-enantiomers of ligands are much more potent *in vitro* than their corresponding (R)-isomers.[15] These ligands were then evaluated *in vitro* on six major recombinant human $GABA_A$/Bz receptor subtypes; the so-called diazepam-sensitive (DS; α1, α2, α3 and α5-containing) and diazepam-insensitive (DI; α4- and α6-containing) $GABA_A$/Bz receptors, the latter of which have very low affinity for " classical" benzodiazepines, such as diazepam. This is due to the replacement of an α subunit histidine residue critical for the binding to α1, α2, α3 and α5-containing receptors by an arginine. The validity of this approach with recombinant receptors in regard to α5 receptor isoforms was recently confirmed on hippocampal "wild type" membranes.[15-17] The binding affinities of these ligands provided evidence which indicated the conformational preference for $GABA_A$/Bz receptor ligands was highly conserved at these six recombinant receptor subsites. The configurational preference for the (S)-enantiomers in both series suggested that pharmacophoric descriptors H_1, H_2 and L_1 are the same in these six binding subtypes which was in agreement with previous modeling studies.[18-23] In addition, substituents at both the 3- and 7-positions of these framework-constrained imidazobenzodiazepines are important in regard to subtype selectivity. The conformational topography of these individual BzR binding subsites appears to be similar and this suggests a major difference among BzR subtypes arises from the size of lipophilic pockets designated L_2, L_3 and L_{Di} in the pharmacophore/receptor model.[23] According to the

most recent Comparative Molecular Field Analysis (CoMFA), an increase in lipophilic interaction in the L_2 region should enhance the α5 selectivity of a ligand; however, lipophilic interactions at the L_{Di} region should lead to a decrease in α5 selectivity, by enhancing the affinity at α1 containing receptor subtypes. Based on these observations, it was felt the size and lipophilicity of substituents at positions –3 or –7 of these imidazobenzodiazepines may play a role in interactions and could lead to subtype selectivity.[23] Hence, a series of 3-t-butyl and 2,2,2-trifluoro ethyl esters were prepared and evaluated pharmacologically *in vitro* on $GABA_A$/Bz receptor subtypes.

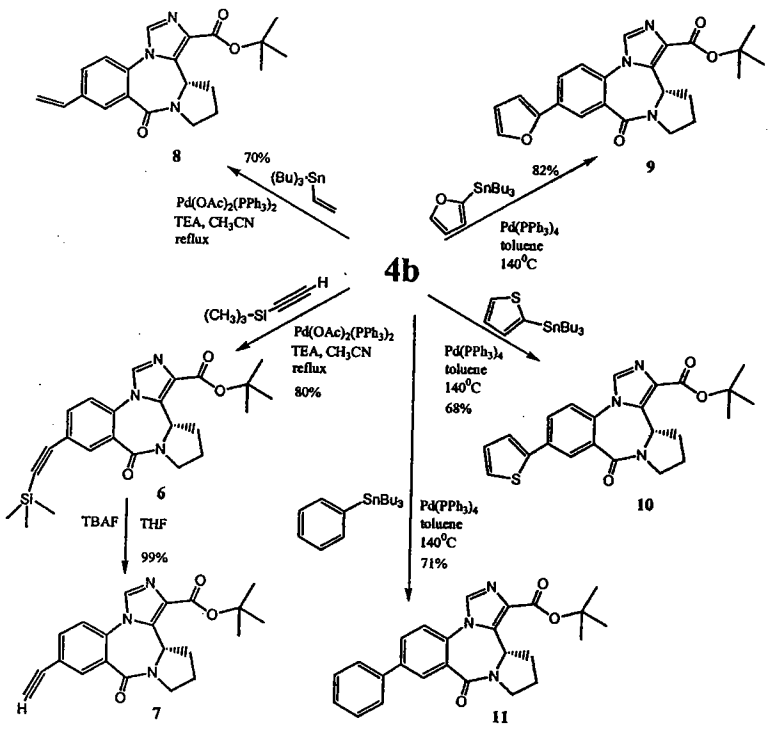
Scheme 1



Chemistry

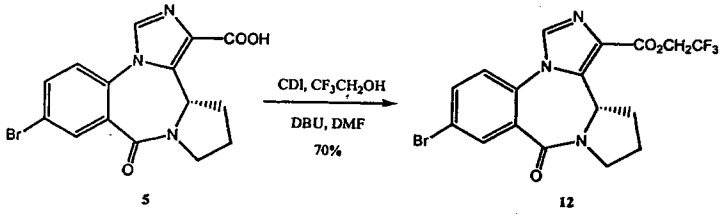
The synthesis of the optically active pyrroloimidazobenzodiazepines is depicted in Schemes 1-4. When a mixture of isatoic anhydride **1** and optically active (L) -proline was heated in DMSO, the corresponding enantiomerically pure benzodiazepine **2** was obtained. The bromination of **2** was carried out with bromine in AcOH/NaOAc to provide the 8-bromo analogs represented by **3**. Conversion of **3** into the optically pure 7-bromopyrroloimidazobenzodiazepines **4a** and **4b** were accomplished, following the elegant work of Fryer and colleagues.[24] The saponification of **4a** provided the key carboxylic acid intermediate **5**.

Scheme 2



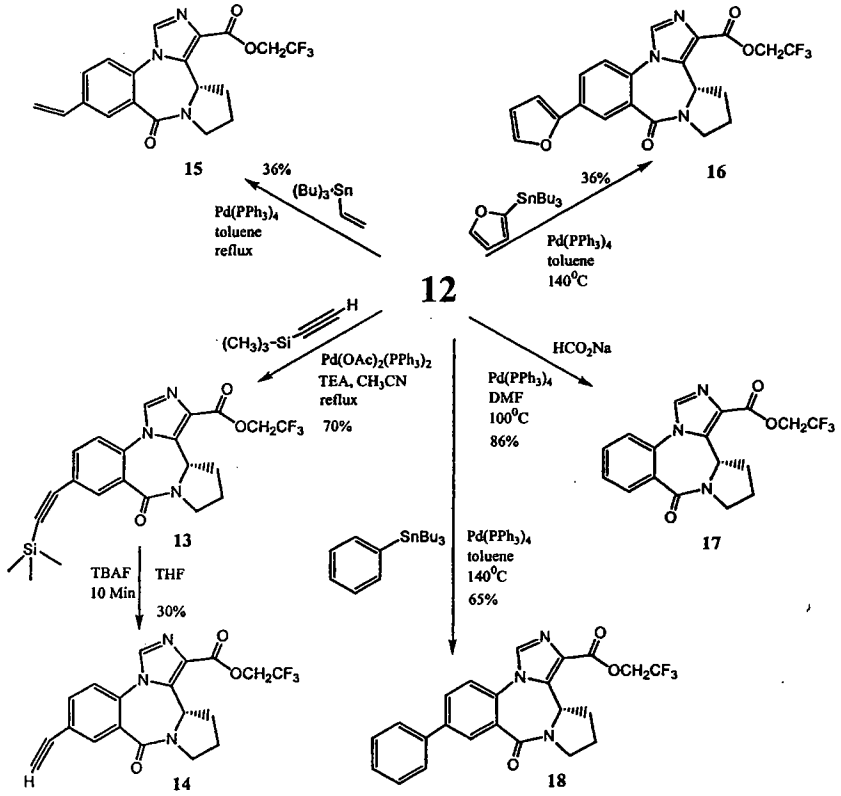
As depicted in Scheme **2**, the 8-bromoanalog **4b** was converted into the trimethylsilyl-acetyleno congener **6** *via* a Heck – type coupling reaction with a Pd catalyst.[25] The trimethylsilylacetyleno group was removed under standard conditions to provide the

Scheme 3



target 7-acetylenopyrroloimidazobenzodiazepine **7** in optically active form. Treatment of bromides represented by **4b** (individually) with the appropriate tributyl(vinyl)tin, 2-(tributylstannyl)furan,2-(tributylstannyl)thiophene and tributyl-phenyltin reagents in the presence of tetrakis-(triphenylphosphine)-palladium(0) in dry toluene[26,27] provided the desired analogs **8**, **9**, **10**, and **11**.

Scheme 4



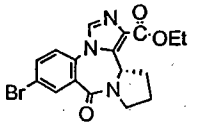
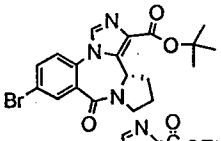
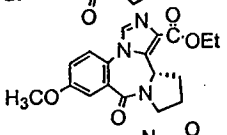
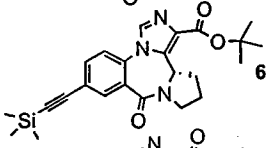
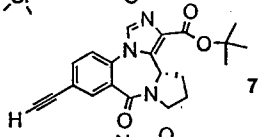
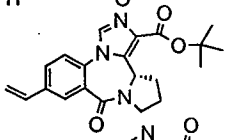
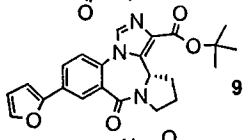
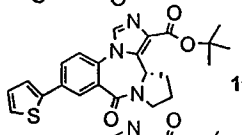
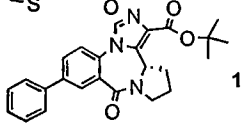
The 2, 2, 2-trifluroro ethyl esters **13-18** were prepared from the corresponding bromide **12**, which was available on large scale by the CDI-mediated reaction of 2,2,2-trifluroethanol with acid **5** (Scheme 3).[28] All of the 7-substituated analogs **13-18** in Scheme 4 were

prepared by a palladium mediated process with the reagents outlined in the Scheme (see Experimental Section for details).

Results and Discussion

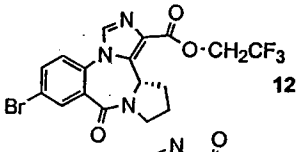
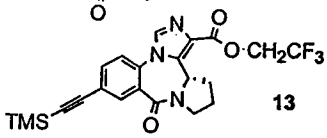
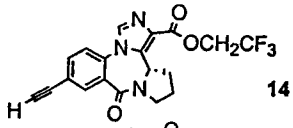
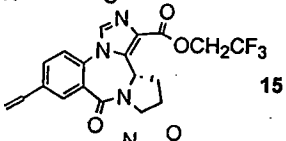
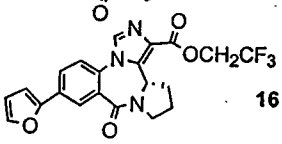
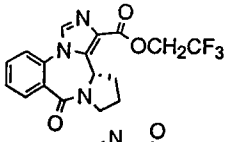
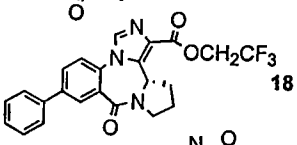
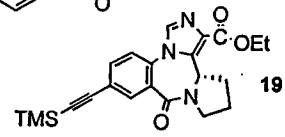
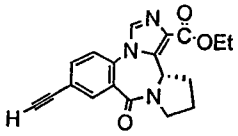
The conformational recognition of the two general classes of $GABA_A$/Bz subtypes has been studied with chiral benzodiazepines by Fryer et al.[15,29] Analysis of these results revealed that diazepam sensitive (DS) and diazepam insensitive (DI) receptor subtypes from brain synaptosmal membranes exhibited a preference for the (S)-enantiomers of benzodiazepines.[29] This was supported by the earlier work of Haefely on 1,4 benzodiazepines.[30] Analysis of the trends also from a previous study[15] indicated the (S)-enantiomers of imidazobenzodiazpine ligands were more potent *in vitro* at $GABA_A$ subtypes than their corresponding (R)-isomers. Consequently, a series of alkyl esters at C(3) in the (S) series were prepared and evaluated pharmacologically. Illustrated in Table 1 are the in vivo binding affinities of ligands **4a-20** on recombinant human $GABA_A$/Bz receptor subtypes. The α5 selectivity of control ligands **4a, 4c, 19** and **20** had earlier been demonstrated,[15,28] moreover, the lead compounds for this study had exhibited K_i values for α5 subtypes of **4a** (1 nM), **19**, (4 nM) and **20** (1.3 nM), respectively. For these reasons in the present study, a series of analogs of **20** were prepared by variation of the substituents at positions C(3) and C(7). Outlined in Table 1 is the *in vitro* binding affinity of the C(3) substituted t-butyl and 2, 2, 2-trifluoro ethyl esters generated by replacement of the ethyl ester functions in **20** by these two alkyl ester groups. In addition, variation of the substituents at C (7) from vinyl to phenyl was also executed in both the t-butyl and 2, 2, 2-trifluoroethyl ester series (see Scheme 3, Scheme 4 and Table 1 for details).

Table 1. In vitro affinities of novel imidazobenzodiazepines at αxβ3γ2 $GABA_A$/BzR receptor subtypes. [a] Values reported are in nM.

Compound	α1	α2	α3	α4	α5	α6	α1 /α5
 4a	49	29	15	NA	1	46	49
 4b	150	123	49	29	4.0	72	37.5
 MSD 4c	48.5	27.4	24.5	NA	0.45	83	108
 6	>333	>333	>333	175	103	>333	—
 7	>333	>333	>333	213	40	308	—
 8	50	35	26	26	2.4	58	20.8
 9	1.8	16.2	15.6	11.6	1.7	46	1.1
 10	16	120	123	119	12	>333	1.3
 11	28	129	59	114	13	>333	2.2

[a] K_i values represent the mean of two determinations which differed by less than 10%. Data were generated using Ltk$^-$ cell membranes expressing human αxβ3γ2 receptors. 1.8 nM [^{3}H]Ro 15-1788 and 8 nM [^{3}H] Ro15 -4513 (for cells expressing α4β3γ2 and α6β3γ2) were used as radioligands.

Table 1 (cont.). In vitro affinities of novel imidazobenzodiazepines at αxβ3γ2 $GABA_A$/BzR receptor subtypes. [a] Values reported are in nM.

Compound	α1	α2	α3	α4	α5	α6	α1 /α5
 **12**	>333	>333	245	291	57	>333	—
 **13**	>333	>333	>333	>333	137	>333	—
 **14**	299	172	169	345	8.3	320	36.0
 **15**	94	55	65	175	6.9	292	13.6
 **16**	7.1	55	52	51	10	251	0.71
 **17**	34	34	13	>333	4.3	>333	7.9
 **18**	141	>333	>333	>333	>333	>333	—
 **19**	200	124	79	NA	4	340	50
 **20**	59	44	27	NA	1.3	126	45

As illustrated in Table 2, most of the trifluoroalkyl esters (C3) (see the affinities for **12, 13,** and **14** as compared to the parents **4a, 19,** and **20**) displayed weaker binding affinities at all receptor subtypes than the corresponding ethyl or t-butyl esters.[28] The weak binding affinities for the fluoroalkyl esters is presumably a consequence of the compromised interaction of this ligand at H_2 between the carbonyl oxygen atom on the fluoroalkyl ester and the hydrogen bond donating group at the receptor site. Since the trifluoromethyl moiety is a strong electron-withdrawing group, the electron density on the carbonyl oxygen atom of the trifluoroalkyl ester group was decreased, thereby compromising the electron-donating ability of the carbonyl oxygen to form a strong hydrogen bond with H_2. It must be pointed out, however, that trifluoromethyl groups are more polar and larger than ethyl functions[28,31] and this may play some role in the loss of affinity. Additional work in this area is necessary to determine this effect on ligand affinity. It is possible the L_{Di} region is very large and the ligands prepared to date are not bulky enough to affect this region of the pharmacophore in a selective fashion. The t-butyl esters **4b, 6** and **7** also displayed weaker affinities at all $GABA_A$/Bz receptor subtypes, however, the trends toward $\alpha5$ selectivity were maintained[15,23] in both ester series. Since it was known that occupation of the region L_{Di} in $GABA_A$/Bz subtypes promoted affinity at $\alpha1$ subtypes,[20-23] the bulkier ester functions in both the 2, 2, 2-trifluoro methyl series and the t-butyl series have presumably, enhanced the interaction at $\alpha1$ subtypes at the expense of the $\alpha5$ selectivity. This indicates that smaller 3-alkyl esters such as methyl may be important in regard to maintenance of $\alpha5$ selectivity in this series of framework constrained 3, 7-disubstituted imidazobendiazpines. Further work in this area is underway at present.

Substituents of varying lipophilicity or size were introduced into position C(7) of the imidazobenzodiazepine nucleus in both the t-butyl and 2, 2, 2-trifluoro ethyl series. It was known that groups at this position interacted with lipophilic pocket L_2 and exerted a profound effect on $\alpha5$ receptor subtype selectivity.[16,32] The thiophene and furan ring are usually considered as bioisosteres for the phenyl ring(flat aromatic ring). The furan ring is smaller than the phenyl ring and considered as an electron rich π aromatic system while the thienyl group is more similar to phenyl.[33] The size of these aromatic rings follows the order phenyl $\cong$ thienyl > furyl and the lipophilic pocket L_2 of the receptor should accept the

thiophene or furan ring readily based on steric considerations. It had been reported by Crippen[34] in a different series that replacement of the 5-phenyl ring of diazepam with a thiophene ring would reduce steric interactions and enhance the binding affinity at BzR.[33] The *in vitro* results obtained here are consistent with the previous report [α5, **9**(1.7nM); α5, **10**(12nM) and α5, **11**(13nM)]. Furthermore, the polarity of the function which interacted with L_2 seems to play an important role, as expected.[15,20-23,35-37] The polarity of the phenyl, thienyl, and furyl rings follows the order phenyl < thiophene < furan. Increasing the lipohilicity increased the affinity. These results further demonstrate that this region of the receptor binding site is lipophilic in nature.[20-23] In the t-butyl ester series 8- vinyl, acetyleno, 2-furyl and phenyl substitutents were well tolerated, presumably by interaction in L_2. In the 2, 2, 2-trifluoro ethyl ester series, substitutents at position 8 from vinyl to 2-furyl were well tolerated; however, binding affinity decreased dramatically in the case of the 7-phenyl analog **18**.

Conclusion

The synthesis and *in vitro* affinities of a series of analogs of the optically active α5 selective (S) isomer, ethyl (S)-11,12,13,13a-tetrahydro-7-acetylenyl-9-oxo-9*H*-imidazo-[1,5-a]pyrrolo [2,1-c][1,4] benzodiazepine-1-carboxylate **20**, were described. The substitutents at C(3) and/or C(7) were varied over a range of size and/or lipophilicity. These imidazobenzodiazepines were then evaluated in vitro on recombinant human $GABA_A$/Bz receptor subtypes. It was clear that the increase in the size of the ester function [compare affinities for ethyl esters **4a**, **19** and **20** to the t-butyl series **4b**, **6** and **7** or the 2, 2, 2 – trifluoroethyl analogs **12**, **13** and **14** (Table 1)] has resulted in a decrease in α5 subtype selectivity, presumably, by enhancing the affinity of the ester function in region L_{Di}[20-23 28] to the α1 subtype at the expense of affinity at the α5 subtype. This is in agreement with previous work in other series[15,22,23] in which this phenomenon was observed. This implies that C(3) alkyl esters, the size of methyl, as mentioned previously, may result in enhanced α5 subtype selectivity. Although acetyleno substituted α5 selective inverse agonist **20** (1.3 nM)[28,31] bound more potently to this receptor subtype, it is now clear region L_2 will tolerate vinyl (**8**, 2.4 nM), 2-furyl (**9**, 1.7 nM), 2-thienyl (**10**, 12 nM) and phenyl (**11**, 13 nM)

substituents at position –7 in the t-butyl series. However, when ligands become to large, affinity at all subtypes decreased, as expected [compare the affinities of the active vinyl (**15**) and 2-furyl (**16**) analogs to the inactive 7-substituted phenyl ligand (**18**)]. Apparently, the combination of the larger groups at C (3) and C (7) in 2, 2, 2- trifluroethyl ester **18**, as compared to the t-butyl analog **11** was simply too great to permit potent receptor affinity for ligand **18**. It is clear that pocket L_2 in the α5 pharmacophore/receptor subtype can more readily accept planar large lipophilic groups than can the α1 subtype in agreement with previous work.[20-23] Further work is in progress to alter the lipophilicity, size and chirality of substituents in lipophilic pockets L_{Di} and L_2 in the pharmacophore/receptor model in order to better understand the differences between there two subtypes (α1 and α5) in search of more α5-subtype selective ligands. This is one means in which to determine which physiological function(s) are subserved by α5 $GABA_A$/Bz receptor subtypes, a critical component of memory and learning.[3,13,14,38,39]

Experimental Section

Binding Assays

In brief, the affinity of compounds for human recombinant $GABA_A$receptors containing β3, γ2 plus either α1-α6 subunits was measured by competition binding experiments using 1.8 nM [^{3}H]Ro 15-1788 (70-87 Ci/mmol, Perkin Elmer Life Sciences) for α1-, α2-, α3- and α5-containing receptors or 8 nM [^{3}H]Ro 15-4513 (20-40 Ci/mmol, Perkin Elmer Life Sciences) for α4- and α6-containing receptors. Cells were harvested into phosphate-buffered saline, centrifuged at 3,000 g and stored at –70°C until required. On the day of the assay, pellets were thawed and re-suspended in sufficient volume of 50 mM Tris/HCl (pH 7.4 at 4°C) to give total binding of approximately 1500-2000 dpm. Non-specific binding was defined in the presence of 10 μM (final concentration) flunitrazepam for the α1, α2, α3 and α5 subtypes and 10 μM Ro 15-4513 for the α4 and α6 subtypes. Test compounds were dissolved in DMSO at a concentration of 10 mM and diluted in assay buffer to give an appropriate concentration range in the assay, such that the final DMSO concentration in

the assay was always less than 1%. Total assay volume was 500 μL and assays were carried out in 96-well plates and started by the addition of 100 μL of re-suspended cell membranes. Following incubation for 1 hour at 4°C, assays were terminated by filtration through GF/B filters, washed with 10 mL ice cold buffer, dried and then counted using a liquid scintillation counter. The percentage inhibition of [^{3}H]Ro 15-1788 or [^{3}H]Ro 15-4513 binding, the IC_{50} and the K_i values were calculated using the Activity Base software package (ID Business Solutions, Guildford, UK) according to the Cheng-Prusoff equation: $K_i = IC_{50} / 1 + ([L] / K_D)$, where [L] and K_D = concentration and affinity of radioligand, assuming K_D values of 0.92, 1.05, 0.58 and 0.45 nM for [^{3}H]Ro 15-1788 binding to α1-, α2-, α3- and α5-containing receptors, respectively and 5.0 and 6.5 nM for [^{3}H]Ro 15-4513 binding to α4- and α6-containing receptors, respectively.

The chemistry employed for the synthesis of the imidazobenzodiazepines **4a, 4c, 19** and **20** has been previously reported.[15,28]

tert-Butyl (S)-11,12,13,13a-tetrahydro-7-bromo-9-oxo-9*H*-imidazo[1,5-a]pyrrolo[2,1-c][1,4]benzodiazepine-1-carboxylate 4b.

The synthesis of **4b** was carried out analogous to the literature precedure.[40] Briefly, a solution of bromide **3** (2 g, 6.8 mmol) in dry DMF (14 mL) and THF (21 mL) was cooled in an ice-water bath, and sodium hydride (327 mg, 60% in mineral oil, 8.2 mmol) was added in one portion. After stirring for 20 min, diethyl phosphorochloridate (1.76 g, 10.2 mmol)) was added dropwise, and the solution was allowed to stir for 30 min with cooling from an ice bath. A solution of tert-butyl isocyanoacetate (1.15 g, 8.16 mmol) and sodium hydride (380 mg, 60% in mineral oil, 9.52 mmol) in THF (10 mL), which had been stirred for 15 min with cooling (ice bath), was slowly added through a cannula. After stirring for another 30 min with cooling, the reaction mixture was allowed to stir at rt overnight. Acetic acid was added to quench the reaction, and it was then poured into ice water and extracted with EtOAc. The combined extracts were washed with water, brine and dried (Na_2SO_4). The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography [silica gel, EtOAc/hexane (1:1)] to provide **4b** as white solid (0.51

g, 27%). **4b**: mp 234-240°C; IR (KBr) 2915, 1709, 1639, 1440, 1254, 1150 cm^{-1}; ^1H NMR (DMSO) δ 1.54 (s, 9H), 2.05 (m, 2H), 2.18 (m, 1H), 3.10 (d, 1H, J= 12.3 Hz), 3.41 (m, 1H,), 3.48 (m, 1H), 4.89 (d, 1H, J=1.73 Hz), 7.75 (d, 1H, J = 7.3 Hz), 7.95 (d, 1H, J = 6.15), 8.01 (s, 1H), 8.22 (s, 1H). MS (EI) m/e (relative intensity) 418 (M^+ +1, 8), 417 (M^+, 8), 361 (96), 345 (86), 317 (100) 289 (35), Anal. Calcd. for $C_{19}H_{20}BrN_3O_3$: C, 55.56; H, 4.82; N,10.05. Found: C, 55.21; H, 4.71; N, 10.14.

tert-Butyl (S)-11,12,13,13a-tetrahydro-7-[(trimethylsily)-ethynyl]-9-oxo-9*H*-imidazo[1,5-a]pyrrolo[2,1-c][1,4]benzodiazepine-1-carboxylate 6.

A solution of benzodiazepine **4b** (418 mg, 1.0 mmol) in TEA (25 mL) and CH_3CN (20 mL) was degassed by passing pure dry nitrogen through the solution for 20 min. The mixture was heated to 70 °C under nitrogen after which bis(triphenylphosphine)-palladium(II) acetate (749.08 mg, 0.1 mmol, 10 mol %) and (trimethylsilyl)acetylene (196 mg, 2.0 mmol) were added at once. The mixture was heated to reflux under nitrogen. After 20 h, the mixture was allowed to cool to rt and the precipitate which resulted was removed by vacuum filtration. The filtrate was concentrated under reduced pressure and the residue was treated with a saturated aq solution of $NaHCO_3$ (30 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined extracts were washed with brine and dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue was purified by gradient column chromotography (silica gel, EtOAc/hexane) to provide a white solid. (350 mg, 80%). **6**: mp 215-218°C; IR (KBr) 2961, 2356, 1713, 2091,1643, 1495, 1439, 1366 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.25 (s, 9H), 1.53 (s, 9H), 2.03 (m, 2H), 2.18 (m, 1 H), 2.50 (d, 1H, J =1.59), 3.44 (m, 1H), 3.59 (m, 1H), 4.86 (d, 1H, J= 1.56 Hz), 7.50(d, 1H, J= 8.64 Hz), 7.68 (d, 1H, J=8.37 Hz), 7.90 (S,1H), 8.21 (s, 1H); MS (EI) m/e (relative intensity) 435 (M^+, 9), 420 (17), 379 (100), 361 (53), 333 (94). Anal. Calcd. for $C_{24}H_{29}N_3O_3$ Si•1/3 H_2O: C, 65.28; H, 6.77; N, 9.51. Found: C, 65.62; H, 7.02; N, 9.72.

tert-Butyl (S)-11,12,13,13a-tetrahydro-7-acetylenyl-9-oxo-9*H*-imidazo[1,5-a]pyrrolo[2,1-c][1,4]benzodiazepine-1-carboxylate 7.

A solution of 6 (395 mg, 1.09 mmol), in THF (15 mL) was treated with $Bu_4NF•H_2O$ (0.39 g, 1.5 mmol). The mixture which resulted was allowed to stir for 10 min at rt after which

the mixture was added to H_2O (10 mL) and extracted with EtOAc (3x30 mL). The combined organic extracts were washed with brine (25 mL) and dried (Na_2SO_4). After removal of the solvent under reduced pressure, the residue was purified by a wash column (silica gel, EtOAc) to furnish **7** as a white solid (0.33 g, 99%). **7**: mp >250°C (dec.); IR (KBr) 3159, 3107, 2092, 1721, 1606 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.64 (s, 9H), 2.25(m, 3H), 3.25 (s, 1H), 3.60 (m, 2H), 3.85 (m, 1H), 4.75 (d, 1H, J = 6.87 Hz), 7.53 (d, 1H, J=8.22 Hz), 7.75 (d, 1H, J = 1.44 Hz), 8.09 (s, 1H), 8.25 (s, 1H); MS (EI) m/e (relative intensity) 363 (M^+, 6), 307 (94), 289 (56), 261 (100), 251 (9) 233 (19), 221 (11). Anal. Calcd. for $C_{21}H_{21}N_3O_3 \bullet 1/2\ H_2O$: C, 67.72; H, 5.95; N, 11.28. Found: C, 67.43; H, 5.73; N, 11.16.

tert-Butyl (S)-11,12,13,13a-tetrahydro-7-vinyl-9-oxo-9*H*-imidazo[1,5-a]pyrrolo[2,1-c][1,4]benzodiazepine-1-carboxylate 8.

A solution of benzodiazepine **4b** (278 mg, 0.67 mmol) in toluene (15 mL) was degassed by passing pure dry nitrogen through the solution for 20 min. The mixture was heated to 140 °C under nitrogen after which tetrakis(triphenylphosphine)palladium(0) (77 mg, 0.067 mmol, 10 mol %) and tributyl(vinyl)tin (637 mg, 2.01mmol) were added at once. The mixture was heated to reflux under nitrogen. After 26 h, the mixture was allowed to cool to rt and the precipitate which resulted was removed by vacuum filtration. The filtrate was concentrated under reduced pressure and the residue was treated with a saturated aq solution of $NaHCO_3$ (30 mL) and extracted with CH_2Cl_2 (3 x 25 mL). The combined extracts were washed with brine and dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue was purified by gradient column chromotography (silica gel, EtOAc/hexane to EtOAc) to provide a white solid. (170 mg, 70%). **8**: mp 208-212°C; IR (KBr) 2977, 1713, 1636, 1495, 1442, 1367, 1255 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.16 (s, 9H), 2.25 (m, 3H), 3.55 (m, 2H), 3.82 (m, 1H,), 4.76 (d, 1H, J = 6.83 Hz), 5.45 (d, 1H, J = 10.9 Hz), 5.92 (d, 1H, J = 17.6 Hz), 6.70 (m, 1H), 7.39(d, 1H, J= 8.29 Hz), 8.09 (s, 1H), 8.20 (s,1H); MS (EI) m/e (relative intensity) 365 (M^+, 5), 309 (61), 291 (34), 277 (100), 263 (64) 235 (11). Anal. Calcd. for $C_{21}H_{23}N_3O_3$: C, 69.02; H, 6.34; N, 11.50. Found: C, 69.32; H, 6.33; N, 10.62.

tert-Butyl (S)-11,12,13,13a-tetrahydro-7-(2-furyl)-9-oxo-9*H*-imidazo[1,5-a]pyrrolo[2,1-c][1,4]benzodiazepine-1-carboxylate 9.

A solution of benzodiazepine **4b** (278 mg, 0.67 mmol) in toluene (15 mL) was degassed by passing pure dry nitrogen through the solution for 20 min. The mixture was heated to 140 °C under nitrogen after which tetrakis(triphenylphosphine)palladium(0) (77 mg, 0.067 mmol, 10 mol %) and 2-(tributylstannyl) furan (718 mg, 2.01 mol) were added at once. The mixture was heated to reflux under nitrogen. After 12 h, the mixture was allowed to cool to rt and the precipitate which resulted was removed by vacuum filtration. The filtrate was concentrated under reduced pressure and the residue was treated with a saturated aq solution of $NaHCO_3$ (30 mL) and extracted with CH_2Cl_2 (3 x 25 mL). The combined extracts were washed with brine and dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue was purified by gradient column chromatography (silica gel, EtOAc/hexane to EtOAc) to provide a white solid. (220 mg, 82%). **9**: mp 195-198°C; IR (KBr) 3490, 2977, 1711, 1636, 1152, 730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.71 (s, 9H), 2.35 (m, 3H), 3.65 (m, 2H), 3.83 (m, 1H), 4.81(d, 1H, J = 6.78 Hz), 6.53 (dd, 1H, J = 1.8 Hz and 3.4 Hz), 6.83 (d, 1H, J = 3.36 Hz), 7.44 (d, 1H, J = 8.4 Hz), 7.54 (d, 1H, J= 1.25 Hz), 7.91 (dd, 1 H, J = 2.07 Hz and 8.4 Hz), 8 .01 (s, 1H), 8.43 (s, 1 H); MS (EI) m/e (relative intensity) 405 (M^+, 9.4), 349 (33.7), 331 (47), 304 (85), 303 (100) 301(53), 275 (11.9). Anal. Calcd. for $C_{23}H_{23}N_3O_4$•1/3 H_2O: C, 67.14; H, 5.79; N, 10.21. Found: C, 67.40; H, 5.75; N, 10.03.

tert-Butyl (S)-11,12,13,13a-tetrahydro-7-(2-thienyl)-9-oxo-9*H*-imidazo[1,5-a]pyrrolo[2,1-c][1,4]benzodiazepine-1-carboxylate 10.

A solution of benzodiazepine **4b** (278 mg, 0.67 mmol) in toluene (10 mL) was degassed by passing pure dry nitrogen through the solution for 20 min. The mixture was heated to 140 °C under nitrogen after which tetrakis(triphenylphosphine)palladium(0) (77 mg, 0.067 mmol, 10 mol %) and 2-(tributylstannyl)thiophene (750 mg, 2.01mmol) were added at once. The mixture was heated to reflux under nitrogen. After 12 h, the mixture was allowed to cool to rt and the precipitate which resulted was removed by vacuum filtration. The filtrate was concentrated under reduced pressure and the residue was treated with a saturated aq solution of $NaHCO_3$ (30 mL) and extracted with CH_2Cl_2 (3 x 25 mL). The

combined extracts were washed with brine and dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue was purified by gradient column chromatography (silica gel, EtOAc/hexane to EtOAc) to provide a white solid. (189 mg, 68 %). **10**: mp 177-180°C; IR (KBr) 2966, 1709, 1636, 1495, 1442, 1255, 1511 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.66 (s, 9H), 2.29 (m, 3H), 3.52 (m, 1H), 3.65 (m, 1H), 3.86 (m, 1H), 4.80 (d, 1H, J = 6.7 Hz), 7.17 (dd, 1H, J = 3.7 Hz and 5.0 Hz), 7.40 (m, 2H), 7.45 (d, 1H, J = 3.5 Hz), 7.85 (dd, 1H, J = 2.0 Hz and 8.2 Hz), 8.35 (d, 1H, J = 2.1 Hz); MS (EI) m/e (relative intensity) 421 (M^+, 7), 365 (44), 347 (47), 319 (100), 291 (20) 237 (15). Anal. Calcd. for $C_{23}H_{23}N_3O_3$ S: C, 65.54; H, 5.50; N, 9.97. Found: C, 65.01; H, 5.39; N, 9.76.

tert-Butyl (S)-11,12,13,13a-tetrahydro-7-phenyl-9-oxo-9*H*-imidazo[1,5-a]pyrrolo[2,1-c][1,4]benzodiazepine-1-carboxylate 11.

A solution of benzodiazepine **4b** (278 mg, 0.67 mmol) in toluene (10 mL) was degassed by passing pure dry nitrogen through the solution for 20 min. The mixture was heated to 140 °C under nitrogen after which tetrakis (triphenylphosphine) palladium (0) (77 mg, 0.067 mmol, 10 mol %) and tributylphenyltin (760 mg, 2.01mmol) were added at once. The mixture was heated to reflux under nitrogen. After 12 h, the mixture was allowed to cool to rt and the precipitate which resulted was removed by vacuum filtration. The filtrate was concentrated under reduced pressure and the residue was treated with a saturated aq solution of $NaHCO_3$ (30 mL) and extracted with CH_2Cl_2 (3 x 25 mL). The combined extracts were washed with brine and dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue was purified by gradient column chromatography (silica gel, EtOAc/hexane,EtOAc) to provide a white solid. (196 mg, 71 %). **11**: mp 160-164°C; IR (KBr) 2975, 1712, 1635, 1487, 1454, 1367, 1255 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.67 (s, 9H), 2.26 (m, 3H), 3.52 (m, 1H), 3.61 (m, 1H), 3.84 (m, 1H), 4.82 (d, 1H, J = 6.7 Hz), 7.48 (m, 4H), 7.67 (d, 2H, J = 7.04 Hz), 7.85 (dd , 1H, J = 6.1 Hz and 8.3 Hz), 7.89 (s, 1H), 8.35 (d, 1H, J = 2.2 Hz); MS (EI) m/e (relative intensity) 415 (M^+, 10), 359 (97), 341 (49), 313 (100), 285 (32) 247 (19), 231 (24). Anal. Calcd. for $C_{25}H_{25}N_3O_3 \bullet 1/3\ H_2O$: C, 71.24; H, 6.13; N, 9.96. Found: C, 71.46; H, 6.07; N, 9.94.

2,2,2-Trifluoroethyl-(S)-11,12,13,13a-tetrahydro-7-bromo-9-oxo-9*H*-imidazo[1,5-a] pyrrolo[2,1-c][1,4]benzodiazepine-1-carboxylate 12.

To the solution of carbonyl diimidazole (1.71 g, 10.54 mmol) in anhydrous DMF (50 mL) was added 11,12,13,13a-tetrahydro-7-bromo-9-oxo-9*H*-imidazo[1,5-a]pyrrolo-[2,1-c][1,4]-benzo-diazepine-1-carboxylic acid **5** (1.96 g, 5.27 mmol). The solution was stirred for 2 h at rt. Analysis by TLC (silica gel) indicated the absence of starting material. To the solution which resulted was then added 2,2,2-trifluoroethanol (1.58 g, 15.8 mmol) in dry DMF (2 mL) as well as DBU (0.88 g, 5.80 mmol) in dry DMF (2 mL) at rt. The mixture was stirred at rt for 10 h until analysis by TLC (silica gel) indicated the disappearance of starting material. The reaction mixture was then poured into ice water (150 mL) and extracted with CH_2Cl_2 (3 x 150 mL). The combined organic layer was washed with H_2O (5 x 150 mL), brine and dried (Na_2SO_4). The solvent which resulted was removed under reduced pressure and the residue was purified by flash chromatography (silica gel, EtOAc/hexanes to EtOAc) to provide **12** (1.65 g) as a white solid in 70% yield. **12**: mp 231-234 °C; IR (NaCl) 1733,1635, 1159, 730 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.25(m, 3H), 3.46(m, 1H), 3.55(m, 1H), 3.84(m, 1H), 4.76(m, 3H), 7.23(d, 1H, J= 6.06 Hz), 7.78(d, 1H, J= 2.31 Hz), 7.99(s, 1H, J= 3.0 Hz), 8.31(s, 1H). MS (EI) *m/e* (relative intensity) 443 (M^+, 7.6), 442(9), 389(15), 388(14), 345(58), 315(99), 316(100), 289(22). Anal. Calcd. for $C_{17}H_{13}BrF_3N_3O_3$: C, 45.97; H, 2.95; N, 9.46. Found: C, 45.82; H, 2.97; N, 9.36.

2,2,2-Trifluoroethyl-(S)-11,12,13,13a-tetrahydro-7-[(trimethylsily)-ethynyl]-9-oxo-9*H*-imidazo[1,5-a] pyrrolo[2,1-c][1,4]benzodiazepine-1-carboxylate 13.

This benzodiazepine was prepared from **12** analogous to the procedure employed for the preparation of **6** and purified by flash column chromatography (yield 70%). **13**: mp 204-206°C; IR (KBr) 2960, 2133, 2241, 1734, 1636, 1497, 1438 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.28 (s, 9H), 2.25 (m, 3H), 3.48(m, 1H), 3.61 (m, 1H), 3.81(s, 1H), 4.75(s,3H), 7.35 (d, 1H, J = 8.4 Hz), 7.71 (dd, 1H, J = 8.3 Hz and 1.9 Hz), 7.89 (s, 1H), 8.20 (s, 1H); MS (EI) m/e (relative intensity) 461 (M^+, 12), 361 (35), 333 (100), 305 (9), 159 (11). Anal. Calcd. for $C_{22}H_{22}F_3N_3O_3Si$: C, 57.25; H, 4.80; N, 9.10. Found: C, 57.04; H, 4.84; N, 8.97.

2,2,2-Trifluoroethyl-(S)-11,12,13,13a-tetrahydro-7-acetylenyl-9-oxo-9*H*-imidazo[1,5-a] pyrrolo[2,1-c][1,4]benzodiazepine-1-carboxylate 14.

This benzodiazepine was prepared from **13** analogous to the procedure employed for the preparation of **7** and purified by flash column chromatography (yield 30 %). **14**: mp 158-164°C; IR (KBr) 3296, 2972, 1734, 1637, 1496 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.27 (m, 3H), 3.34 (s, 1H), 3.57 (m, 1H), 3.64 (m, 1H), 3.78 (m, 1H), 4.72 (m, 3H), 7.35 (d, 1H, J = 7.5 Hz), 7.76 (d, 1H, J = 6.4 Hz), 8.00 (s, 1H), 8.35 (s, 1H); MS (EI) m/e (relative intensity) 389 (M^+, 12), 333(16), 289 (50), 261 (100), 233 (21),138 (20). Anal. Calcd. for $C_{19}H_{14}F_3N_3O_3 \bullet 1/4\ H_2O$: C, 57.97; H, 3.71; N, 10.67. Found: C, 57.82; H, 3.64; N, 10.45.

2,2,2-Trifluoroethyl-(S)-11,12,13,13a-tetrahydro-7-vinyl-9-oxo-9*H*-imidazo[1,5-a] pyrrolo[2,1-c][1,4]benzodiazepine-1-carboxylate 15.

This benzodiazepine was prepared from **12** analogous to the procedure employed for the preparation of **8**, followed by flash column chromatography (yield 36%). **15**: mp 251-253°C; IR (KBr) 2916,1734,1618, 1594, 1498, 1447, 1276 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.26 (m, 3H), 3.46 (m, 1H), 3.83 (m, 1H), 4.73 (m, 3H), 5.46 (d, 2H, J = 10.9 Hz), 5.93 (d, 1H, J = 17.5 Hz), 6.81 (m, 1H), 7.41 (d, 1H, J = 8.3 Hz), 7.47 (dd, 1H, J = 8.3 Hz and 2.0 Hz), 7.70 (s, 1H), 7.96 (d, 1H, J = 1.9 Hz); MS (EI) m/e (relative intensity) 391 (M^+, 11), 335 (14), 291 (37), 263(100),235 (19), 140(17). Anal. Calcd. for $C_{16}H_{22}F_3N_3O_3$: C, 57.46; H, 4.23; N,10.58. Found: C, 57.21; H, 4.09; N, 10.31.

2,2,2-Trifluoroethyl-(S)-11,12,13,13a-tetrahydro-7-furan-9-oxo-9*H*-imidazo[1,5-a] pyrrolo[2,1-c][1,4]benzodiazepine-1-carboxylate 16.

This benzodiazepine was prepared from **12** analogous to the procedure employed for the preparation of **9**, followed by flash column chromatography (yield 36%). **16**: mp 228-230°C; IR (KBr) 2964, 1802, 1734, 1636, 1498, 1437, 1276, 1156 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.25 (m, 3H), 3.44 (m, 1H), 3.65 (m, 1H), 4.82 (m, 1H), 6.54 (dd, 1H, J = 1.8 Hz and 3.4 Hz), 6.85 (d, 1H, J = 6.7 Hz), 7.44 (d, 1H, J = 8.4 Hz), 7.54 (d, 1H, J= 1.25 Hz), 7.95 (dd, 1H, J = 2.07 Hz and 8.4 Hz), 8.05 (s, 1H), 8.46 (s, 1H); MS (EI) m/e (relative intensity) 431 (M^+, 19), 375 (9), 331 (17), 303 (100), 275 (13), 83 (19). Anal. Calcd. for $C_{21}H_{16}F_3N_3O_4 \bullet 2/3\ H_2O$: C, 56.89; H, 3.94; N, 9.47. Found: C, 56.96; H, 3.69; N, 9.19.

2,2,2-Trifluoroethyl-(S)-11,12,13,13a-tetrahydro-9-oxo-9*H*-imidazo[1,5-a] pyrrolo[2,1-c][1,4]benzodiazepine-1-carboxylate 17.

A solution of benzodiazepine **12** (222 mg, 0.5 mmol) in DMF (5 mL) was degassed by passing pure dry nitrogen through the solution for 20 min. The mixture was heated to 100 °C under nitrogen after which tetrakis (triphenylphosphine) palladium (0) (58 mg, 0.05 mmol, 10 mol %) and HCO_2Na (68 mg, 1 mmol) were added at once. The mixture was heated under nitrogen for 4 h, the mixture was allowed to cool to rt. The reaction mixture was then poured into ice water (50 mL) and extracted with CH_2Cl_2 (3 x 40 mL). The combined organic layer was washed with H_2O (5 x 50 mL), brine and dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue was purified by flash chromatography to provide **22** (186 mg) as a white solid in 86 % yield. **17**: mp 118-124°C; IR (KBr) 3094, 2973, 2875, 1735, 1639, 1499 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.23 (m, 3H), 3.44 (m, 3H), 3.45 (m, 1H), 3.62 (m, 1H), 3.85 (m, 1H), 4.75 (m, 3H), 7.42 (d, 1H, J = 7.9 Hz), 7.51-7.72 (m, 1H), 8.12 (s, 1H), 8.14 (dd, 1H, J = 1.5 Hz and 7.7 Hz); MS (EI) m/e (relative intensity) 365 (M^+, 9), 309 (19), 277 (87), 265 (46), 237 (100) 183 (25), 154 (20).). Anal. Calcd. for $C_{17}H_{14}F_3N_3O_3$: C, 55.89; H, 3.86; N, 11.50. Found: C, 55.62; H, 3.59; N, 11.19.

2,2,2-Trifluoroethyl-(S)-11,12,13,13a-tetrahydro-7-phenyl-9-oxo-9*H*-imidazo[1,5-a] pyrrolo[2,1-c][1,4]benzodiazepine-1-carboxylate 18.

This benzodiazepine was prepared from bromide **12** analogous to the procedure employed for the preparation of **11**, followed by flash column chromatography on silica gel(EtOAc/Hexane to EtOAc, yield 65 %). **18**: mp 200-203°C; IR (KBr) 2975, 2358, 1737, 1540, 1278, 1117 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.27 (m, 3H), 3.47 (m, 1H), 3.57(m, 1H), 3.82 (m, 1H), 4.75 (m, 3H), 7.50 (m, 4H), 7.68 (d, 1H, J = 6.9 Hz), 7.88 (dd, 1H, J = 8.4 Hz and 2.2 Hz), 7.95 (s, 1H), 8.38 (d, 1H, J = 2.1 Hz); MS (EI) m/e (relative intensity) 441 (M^+, 12), 341 (32), 313 (100), 285 (15), 152(22). Anal. Calcd. for $C_{23}H_{18}F_3N_3O_3$: C, 62.58; H, 4.11; N, 9.52. Found: C, 62.41; H, 4.12; N, 9.40.

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