Synthesis of Benzo-Fused Benzodiazepines Employed as Probes of the Agonist Pharmacophore of Benzodiazepine Receptors

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The synthesis and *in vitro* evaluation of benzo-fused benzodiazepines 1–6 are described. These "molecular yardsticks" were employed to probe the spatial dimensions of the lipophilic pocket L_2 in the benzodiazepine receptor (BzR) cleft and to determine the effect of occupation of L_2 with respect to agonist activity. Of the new analogs synthesized, the 7,8-benzo-fused benzodiazepine 6 displayed moderately high affinity for the BzR (IC₅₀ = 55 nM) and exhibited both anticonvulsant (ED₅₀ ≈ 15 mg/kg) and muscle relaxant (ED₅₀ ≈ 15 mg/kg) activity. As expected, 2 and 4 interacted with the repulsive regions of interaction, S₁ and S₂, and exhibited low affinities for BzR. The rigid nature of these molecular yardsticks (especially 6, Figure 7) has been employed to probe the depth of L₂. Moreover, in the case of 6 full occupation of L₂ has resulted in an increase in the muscle relaxant effect at the expense of the anticonvulsant/anxiolytic effect.

Introduction

Since the introduction of Librium in 1960^1 and the subsequent discovery of its mode of action¹ via γ -aminobutyric acid receptors ($GABA_A R$), the benzodiazepines have enjoyed widespread use rivaled by few other classes of compounds. The GABAA receptors are a heterooligomeric group of ligand-gated ion channels that constitute the major inhibitory neurotransmitter system in the mammalian central nervous system (CNS).² The identification of multiple α , β , and γ subunits³⁻⁵ is consistent with pharmacological evidence of multiple GABA_A receptor isoforms in the CNS.6 Molecular biological studies have established that expression of either two (α, γ) or three (α, β, γ) subunits are necessary to constitute a functional receptor which mimics many of the pharmacological, biochemical, and electrophysiological properties of native receptors.⁷⁻⁹ However, neither the stoichiometry nor the composition of native GABA_A receptors in the CNS has been evinced.

SAR data available for a number of structurally diverse ligands has led to the development of several different models of the benzodiazepine receptor (BzR) pharmacophore.^{10–17} A common feature of these models attempts to explain ligand efficacy (that is, GABA positive, GABA neutral, GABA negative) as a function of ligand-receptor interaction at the molecular level. For example, on the basis of the *in vitro* and *in vivo* profiles of pyridodiindoles (2-methoxy-7,12-dihydropyridodiindole, 2-chloro-7,12-dihydropyridodiindole), β -carbolines (β CCM, β CCE, DMCM), pyrazoloquinolinones (CGS-8216), and the thienylpyrazoloquinolinones (TPQ), as well as computer modeling studies [alignment rule], a model of the pharmacophore for inverse agonists/antagonists was developed in our laboratory (Figure 1).^{18,19}

Recently, a preliminary model for the agonist pharmacophore^{20,21} has been designed *via* a chemical- and computer-assisted approach analogous to that employed for inverse agonists (Figure 2). Three points were employed initially for the least-squares fitting of each ligand, and these pharmacophoric descriptors were termed L₁, H₁, and H₂ (Figure 2).²⁰ In addition, lipophilic area L₂ which represents the region of overlap of the substituents (Cl, OCH₃, Me, Et) on the D rings of the pyrazoloquinolinones (CGS) and the thienylpyrazoloquinolinones (TPQ), respectively, as well as the C1 and NO₂ groups at position 7 of the typical 1,4-benzodiazepines (diazepam, etc.), has been defined. Interaction at H₁, H₂, L₁, and L₂ is critical for potent agonist activity. In the case of the 1,4-benzodiazepines (flunitrazepam, diazepam, etc.), the 5-phenyl group (C ring) interacts with a third lipophilic area termed L₃. An area of negative steric interaction has been termed S₁ and has been described in a previous report.^{20,21}

To account for the bidirectional effect of GABA on agonist and inverse agonist binding to BzR, Skolnick et al.^{22,23} postulated a domain hypothesis for ligand interaction wherein both classes of compounds were proposed to bind to different areas of the same binding region. Consistent with this hypothesis, the pharmacophoric descriptors H_1 and L_1 are common to the site for both inverse agonists and agonists; however, the pharmaco-and/or L_3) and inverse agonist (H₁, A₂, and L₁) activity are clearly different (see Figures 1 and 2).²⁴ The overlap of the two pharmacophores depicted in Figure 3 represented as the total included volume (agonists = green, inverse agonists = violet) provides a better representation of the binding site at BzR especially with regard to ligand efficacy in vivo (Figure 3).

Recent evidence suggests that full occupation of L_3 by the phenyl ring (C-6) of ZK-93423 resulted in a full agonist spectrum of activity (anxiolytic, anticonvulsant, muscle relaxant, sedative-hypnotic),^{20,21,25} while partial occupation of this same region with a propyl group (C-6) resulted in an anxiolytic/anticonvulsant [6-(propyloxy)-4-(methoxymethyl)- β -carboline acid ethyl ester, 6PBC] response devoid of muscle-relaxant activity, a so-called partial agonist profile.²¹ Clearly much work must be carried out to confirm this hypothesis. In order to determine the size of lipophilic region L_2 and the effect of occupation of L_2

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Figure 1. The superposition of 12 inverse agonist ligands and the included volume analysis of the inverse agonist pharmacophore at the benzodiazepine binding site (β CCE, DMCM, 3-ethoxy- β -carboline, 3-propionyl- β -carboline, CGS-8216, 7,12-dihydropyrido-[3,2-b:5,4-b']diindole, 2-methoxy-7,12-dihydroxypyrido[3,2-b:5,4-b']diindole, 2-thienylpyrazolo[3,4-c]quinolin-3-one, 2-(4'-methyl-thienyl)pyrazolo[3,4-c]quinolin-3-one, 3-thienylpyrazolo[3,4-c]quinolin-3-one, 3-(5'-methylthienyl)pyrazolo[3,4-c]quinolin-3-one, and 3-(4'-methylthienyl)pyrazolo[3,4-c]quinolin-3-one). The inverse agonist pharmacophoric descriptors H₁ and H2 represent hydrogen bond donor sites on the protein; A₂ represents a hydrogen bond acceptor site on the protein; L₁ represents a lipophilic pocket. The illustration on the right side of the picture (orthographic stereoview) originates from rotation of the pharmacophore 90° to the left.



Figure 2. The superposition of 24 different agonist ligands representing 70 different agonists and the included volume analysis of the agonist pharmacophore at the benzodiazepine receptor binding site (diazepam, brotizolam, delorazepam, midazolam, triazolam, norflunitrazepam, 7-aminoflurazepam, 7,2'-dichloro-thieno[2,3-e][1,4]benzodiazepine, 1-methyl-8-chloro-2'-fluoro-s-triazolo[4,3-a]-[1,4]benzodiazepine, 2,9-dichloropyrimido[5,4-d][2]benzazepine, 4-chloro-5-(dibutylamino)-3-aryl-1,2,4-triazolo[3,4-a]phthalazine, 2-benzoyl-5-methoxy-7-ethylimidazo[1,2-a]quinoline, 2-benzoyl-5-(methylthio)-6-methyl-7-ethylimidazo[1,2-c]pyrimidine, 2-(4'-chlorophenyl)pyrazolo[3,4-c]quinolin-3-one, 2-(5'-methylthienyl)pyrazolo[3,4-c]quinolin-3-one, 2-(5'-butylthienyl)pyrazolo[3,4-c]quinolin-3-one, 2-(4',5'-dimethylthienyl)pyrazolo[3,4-c]quinolin-3-one, 3-(5'-butylthienyl)pyrazolo[3,4-c]quinolin-3-one, 2-(4',5'-dimethylthienyl)pyrazolo[3,4-c]quinolin-3-one, 3-(5'-butylthienyl)- β -carboline-3-carboxylic acid ethyl ester, 6-(benzyloxy)-4-(methoxymethyl)- β -carboline-3-carboxylic acid ethyl ester, 6-(popyloxy)-4-(methoxymethyl)- β -carboline-3-carboxylic acid ethyl ester, 6-(popyloxy)-4-(methoxymethyl)- β -carboline-3-carboxylic acid ethyl ester, 6-(popyloxy)-4-(methoxymethyl)- β -carboline-3-carboxy

on agonist activity, a series of benzo-fused benzodiazepines has been designed (Figure 4).

The use of "molecular yardsticks" in the diindole series to define the boundary of the repulsive region S_1 was recently reported.^{24,26} Potential 7,8-disubstituted molec-

ular yardsticks in the 1,4-benzodiazepine series are depicted in Figure 5. The complementary probes in the 6,7and 8,9-benzo-fused systems are illustrated here only for the benzo-fused benzodiazepines 1 and 2 (Figure 4). Molecular yardsticks (benzo-fused rings) employed here



Figure 3. The included volume of agonist ligands is shown in green while the included volume of inverse agonists is represented in violet. The illustration on the right side of the picture (orthographic stereview) originates from rotation of the pharmacophore 90° to the left.



Figure 4. Benzo-fused 1,4-benzodiazepines.

represent rigid probes to define the dimensions of the lipophilic pockets of the BzR in the absence of complications introduced by rotational freedom, simplifying the molecular modeling. Even in the cases of the 7,8-dimethyl, 7,8-di-*tert*-butyl, or 7,8-bis(trihalo) analogues rotational freedom of the symmetrically substituted carbon atoms does not complicate the molecular modeling.²⁷

The SAR of the classical 1,4-benzodiazepines (diazepam, flunitrazepam, nitrazepam, etc.) has been extensively reported.²⁸ It is well documented that substitution of an electron-withdrawing group at position 7 (L2) and a halogen atom at position $2'(H_2)$ for a hydrogen atom increases the affinity and efficacy at the BzR in this series. Moreover, the phenyl ring at C(5) of diazepam is also required (L₃) for a full agonist spectrum of activity.^{20,21} On the basis of the above SAR, the proposed interaction between the benzo-fused 1,4-benzodiazepine system and the agonist pharmacophore/receptor model is illustrated in two dimensions in Figure 6. All of these ligands contain the required functional groups to form hydrogen bonds at H1 and H_2 of the receptor protein, as well as fulfill the requirements of L_1 and L_3 . As indicated, the linear 7,8benzo-fused ligand (panel B) should just fit into the region L_2 and bind to the BzR as an agonist, whereas the 8,9benzo-fused ligand (panel A) would interact in the region of negative steric repulsion (S_1) with little or no affinity at the BzR. The 6,7-benzo-fused ligand (panel C) does not occupy L_2 and should, therefore, exhibit little or no agonist activity. This ligand may elicit weak antagonist activity; however, if the in vitro affinities of 2 and 5 are low, this will help to better outline the area S_2 . This is defined as a region of negative steric interaction at the boundary between lipophilic pockets L_2 and L_3 , as illustrated in Figure 6.

Chemistry

The present series of compounds were prepared in order to better define the dimensions of the proposed lipophilic pocket (L₂) and the effect of its occupation on the profile of in vivo activity. The benzo-fused 1,4-benzodiazepines 1-3 were synthesized by methods outlined in the review by Fryer.¹² In this sequence, the preparation of the necessary α -aminobenzophenones 7–9 is required and is illustrated in Scheme 1.29 Conversion of 1-nitronaphthalene 10 into 1-amino-2-naphthonitrile 12 was accomplished via the method of Tomioka et al.³⁰ This novel transformation constitutes a one-pot sequence to convert an arvlnitro compound into an ortho-substituted aminoaryl nitrile. The 1-nitronaphthalene 10 was heated in a mixture of ethyl cyanoacetate, potassium cyanide, and potassium hydroxide for 36 h at 50 °C. This process was followed by hydrolysis as depicted in Scheme 1 to furnish the desired 1-amino-2-naphthalenecarbonitrile (12) in 60% yield. The 2-nitro analog 11 was converted into 2-amino-1-naphthalenecarbonitrile (13) under conditions analogous to those described above in 56% yield. Regiospecific orthocyanation of the nitronaphthyl derivative with concomitant reduction of the nitro moiety had occurred in the same simple process.

The 1-amino-2-naphthonitrile (12) was stirred with 3 equiv of phenylmagnesium bromide, and this was followed by hydrolysis to provide 1-amino-2-benzoylnaphthalene (7) in 85% yield. The reaction of 2-amino-1-naphthonitrile (13) with 3 equiv of phenylmagnesium bromide in ether was followed by hydrolysis with 6 N aqueous HCl at reflux to furnish 2-amino-1-benzoylnaphthalene (8) in 86% yield. The intermediate in this process, an unusually stable imine (C=NH), could not be hydrolyzed in 2 N aqueous HCl (5 h at 30 °C); consequently, more vigorous conditions were required. The 2-amino-3-benzoylnaphthalene derivative 9 was synthesized from commercially available 3-amino-



Figure 5. Two-dimensional molecular yardsticks. Distances cited are between the centroid of the benzene ring and the edge of the van der Waals field of the protons.



Figure 6. H_1 , H_2 are the hydrogen bond donor sites on the receptor protein. L_1 , L_2 , and L_3 , are the lipophilic pockets in the protein at the binding site. S_1 and S_2 are the areas of negative interaction between the ligand and the protein at the binding site.

Scheme 1



2-naphthoic acid (14). This acid 14 was stirred with 3 equiv of phenyllithium at 25 °C to provide the desired α -aminobenzophenone 9 in 51% yield, accompanied by 10% of the diphenyl tertiary alcohol 15.

The three α -aminobenzophenones 7–9 were converted into the target benzo-fused benzodiazepines 1-3, as illustrated in Scheme 2. In brief, acylation of α -aminobenzophenone 7 with 1.1 equiv of bromoacetyl bromide gave the corresponding 1-(N-(bromoacetyl)amino)-2-benzoylnaphthalene 16 in 94% yield. A solution of the amide 16 was stirred in a saturated solution of ammonia in methanol at reflux to produce the benzo-fused benzodiazepine derivative 5-phenyl-1,3-dihydronaphtho[1,2-e]-[1,4] diazepin-2-one (17) in 74% yield. Methylation of 17 with methyl iodide in the presence of sodium hydride gave the desired N(1)-methyl-5-phenyl-1,3-dihydronaphtho-[1,2-e][1,4]diazepin-2-one (1, 87%). Acylation of α -aminobenzophenone 8 with 1.1 equiv of bromoacetyl bromide gave the corresponding 2-(N-(bromoacetyl)amino)-1-benzoylnaphthalene 18 in 89% yield. A solution of the amide 18 in methanol was reacted with ammonia to produce the benzo-fused benzodiazepine derivative 5-phenyl-1,3-dihydronaphtho[2,1-e][1,4]diazepin-2-one (19) in 39% yield and the quinoline byproduct (20) in 44% yield. It is believed that in 19 the 5-phenyl ring and the 6,7-fused benzene ring experience a negative steric interaction which

Scheme 2^s



^a (a) BrCH₂COBr/NaHCO₃, 0 °C, CHCl₃; (b) NH₃/MeOH reflux; (c) NaH/MeI, DMF.

retarded the cyclization of 18 to 19, to the benefit of byproduct 20. The benzoquinoline 20 would arise from attack of the methylene group of 18 on the ketone, followed by dehydration to form the more stable aromatic quinoline system. Presumably, ammonia has displaced the bromine atom in 18 before this quinoline 20 was formed. Methylation of 19 with methyl iodide in the presence of sodium hydride gave the desired N(1)-methyl-5-phenyl-1,3-dihydronaphtho[2,1-e][1,4]diazepin-2-one (2) in 90% yield. Acylation of α -aminobenzophenone 9 was followed by the amination/cyclization process, as described above, to produce the benzo-fused benzodiazepine derivative 5-phenyl-1,3-dihydronaphtho[2,3-e][1,4]diazepin-2-one (22) in

Table 1. In Vitro IC_{50} Values of New Ligands at the BzR



^a See the Experimental Section for details.

Scheme 3



78% yield. Methylation of 22 with methyl iodide in the presence of sodium hydride gave the desired N(1)-methyl-5-phenyl-1,3-dihydronaphtho[2,3-e][1,4]diazepin-2-one (3) in 88% yield.

The three analogs were screened for in vitro affinity to benzodiazepine receptor sites on rat cortical membranes, the data from which is depicted in Table 1. As can be seen from the data in Table 1, none of these analogs exhibited potent affinity to BzR. This is not surprising, for examination of the ligand-receptor fit illustrated in Figure 6 for 1-3 indicates that there is little room to spare in the binding site at S_1 , L_2 , and S_2 , respectively. It is known, however, that substitution of fluorine for hydrogen at the 2'-position of the 1.4-benzodiazepines greatly enhances affinity and efficacy at the BzR.²⁸ This is particularly important with reference to ligands 1-3 for the 2'-fluorine substituent could interact at H_2 in place of N(4), permitting some ligand flexibility (plasticity) in the binding cleft. For this reason attention turned toward the synthesis of benzo-fused ligands 4-6.

When naphthonitrile 12 or amino acid 14 was reacted (individually) with the anion of $o-C_6H_4BrF/n$ -BuLi (1:1) [(o-fluorophenyl)lithium] at low temperature (-75 °C to -50 °C for 5 h), only starting materials were recovered, respectively. When the temperature was elevated to -30 °C to 25 °C, only starting materials and biphenylene were obtained in reasonable amounts (Scheme 3). The structure of biphenylene was confirmed by comparison of its properties to those of an authentic sample (see the Experimental Section). These results indicated that the nitrile and carboxylate moieties in the two series were not electrophilic enough to react with the anion at low temperature. Unfortunately, at higher temperatures (above -30 °C), the (o-fluorophenyl)lithium underwent Scheme 4



Scheme 5



1,2-elimination to form benzyne which dimerized to produce biphenylene (Scheme 3).

In order to circumvent this difficulty, the amino acid 14 was stirred with benzoyl chloride at 170 °C to provide the 2-phenyl-4H-naphtho[2,3-d]-1,3-oxazin-4-one 23 in 91% yield, according to the procedure of Clemence et al.³¹ Treatment of the oxazin-4-one 23 with 1 equiv of (ofluorophenyl)lithium at -78 °C furnished the desired 2'fluorophenyl ketone 24 in 51% yield,³² accompanied by 15% of the bis(2'-fluorophenyl) alcohol 25. Increasing the ratio of the lithium reagent to the naphthoxazinone 23 only increased the yield of the tertiary alcohol 25 (Scheme 4). When the amide 24 was heated in the presence of base (5-10% aqueous NaOH) to effect hydrolysis, the benzoacridone derivative 28 was obtained in more than 80% yield. However, hydrolysis of benzamide 24 under acidic conditions furnished the desired α -amino ketone 26 in 97% yield. The formation of the benzoacridone 28 is interesting and worthy of brief comment. Presumably, the benzamide 24 is converted in base into the anion, as illustrated in Scheme 5. Since the fluorine atom is activated to displacement by the neighboring carbonyl group, the intramolecular nucleophilic attack takes place smoothly and in high yield to furnish acridine derivative 27. Hydrolysis of the benzamide function in situ then led to the 9-oxobenz[b]acridine 28. This sequence may provide a facile route to ring A substituted benzacridones.

In order to prepare the α -amino-2'-fluorobenzophenone required for the synthesis of benzo-fused 1,4-benzodiazepine 4, 1-amino-2-naphthonitrile 12, which was readily available by the process of Tomioka *et al.*,³⁰ was hydrolyzed with 20% NaOH³³ to provide the corresponding 1-amino-2-naphthoic acid 29 in 85% yield. This amino acid 29 was heated with benzoyl chloride at 170 °C to provide the corresponding naphthoxazinone 30 in 91% yield. The naphthoxazinone 30 was stirred with 1 equiv of (ofluorophenyl)lithium at -78 °C to provide the keto amide intermediate 31 (85%) as the only product. This process was followed by hydrolysis (48% HBr/AcOH, Δ) to furnish the desired amine 32 in 95% yield (Scheme 6).

As described earlier, 1-amino-2-naphthonitrile 12 did not react with (o-fluorophenyl)lithium at low temperature. Moreover, all attempts to hydrolyze 2-amino-1-naphthonitrile (13) to the corresponding amino acid failed. When 13 was treated under various conditions (20–40% NaOH, Δ ; 50–75% H₂SO₄, Δ), the product of decarbox-

Scheme 6



Scheme 7



Scheme 8^s



^a (a) BrCH₂COBr/NaHCO₃, 0 °C, CHCl₃; (b) NH₃/MeOH reflux; (c) NaH/MeI, DMF.

ylation,³⁴ 2-aminonaphthalene, was obtained as the only isolable material. Since the starting amino acid related to 13 was not easily obtained, a related intermediate 33 from the process developed by Tomioka *et al.*³⁵ was prepared (Scheme 7). Hydrolysis of the nitrile 33 in sulfuric acid provided the 2-(dicyanomethylene)naphthoxazinone 34. This naphthoxazinone was then stirred with 2 equiv of (o-fluorophenyl)lithium at -78 °C to generate intermediate 35, and this step was followed by hydrolysis to furnish the desired fluorine-substituted 1-(2'fluorobenzoyl)-2-aminonaphthalene 36 in 71% yield.

The syntheses of the 2'-fluorobenzo-fused 1,4-benzodiazepines 4-6 were carried out by the methods of Sternbach³⁶ and Fryer,¹² as illustrated in Scheme 8. Amino ketone 32 was acylated with bromoacetyl bromide to provide the bromo amide 37 in 92% yield. When this amide 37 was heated in a solution of methanol saturated with ammonia the 8,9-benzo-fused 1,4-benzodiazepine 38 was obtained. Methylation under standard conditions, as described above, provided the target N(1)-methyl-5-(2'-fluorophenyl)-1,3-dihydronaphtho[1,2-e][1,4]diazepin-2-one (4) in excellent yield. Conversion of amino ketone 36 into bromo amide 39 was carried out under conditions analogous to those described above. The conversion of the N(1)-H benzodiazepine 40 into the N(1)-methyl-5(2'-fluorophenyl)-1,3-dihydronaphtho[2,1-e][1,4]diazepin-2-one (5) was executed as indicated in Scheme 8. The 7,8-benzo-fused system, N(1)-methyl-5-(2'-fluorophenyl)-1,3-dihydronaphtho[2,3-e][1,4]diazepin-2-one (6), was prepared in excellent yield by reaction of amino ketone 26 with bromoacetyl bromide, as shown, to generate 41, followed by amination/cyclization (see 42) and N(1)methylation, as illustrated in Scheme 8.

Biological Results and Discussion

The affinities of benzo-fused 1,4-benzodiazepines at BzR were evaluated by previously reported methods.^{21,24} Illustrated in Table 1 are the IC₅₀ values of these new "molecular yardsticks". The 8,9-benzo-fused ligands 1 and 17 exhibited very little (IC₅₀ > 1000 nM) or no affinity to BzR, and this can be attributed to a negative steric interaction with the receptor protein at S₁, which is consistent with the results obtained in the pyridodiindole and pyridoimidazole series.³⁷ The low affinity of these 8,9-benzo-fused ligands confirms the location of S₁ in the receptor binding cleft, previously reported.²⁴

The 6,7-benzfused ligands 2 and 19 have IC₅₀ values >1000 nM, supporting the location of S_2 (a negative area of steric interaction between the boundaries of L_2 and L_3). These findings are in agreement with the recent results obtained with the pyridoimidazoles by Martin et al.24,26,37 The low IC_{50} values of the linear 7,8-benzo-fused ligands 3 and 22 indicate only a very weak interaction at the BzR. Again, the rigid phenyl ring must be interacting with the receptor protein (Figure 6), presumably in lipophilic pocket L_2 . Because the fit of the 7,8-benzo-fused ring of 3 and 22 in lipophilic pocket L_2 was anticipated as a near acceptable interaction (see Figure 6), an additional modification of these rigid probes was required. It has been well documented, as mentioned above, that substitution of a fluorine atom for hydrogen at the 2'-position of the 1,4-benzodiazepines enhanced the affinity and efficacy of ligands at the BzR; consequently, the 2'-fluoro analogs 4-6 were screened. The effect of a fluorine substituent (2') on the activity of the 8,9-benzo-fused compounds (see 4 and 38, Table 1) resulted in an increase in potency, while the effect on the 6,7-benzo-fused compounds (see 5 and 40) was minimal. Substitution of the 2'-hydrogen atom with fluorine in the linear N(1)-methyl 7,8-benzo-fused system (see 3, >1000 nM), however, resulted in a significant enhancement in affinity with the 2'-fluoro ligand 6 exhibiting an IC_{50} value of 55 nM. The increase in binding potency is significant in the context of the agonist pharmacophore/receptor model. The 2'-fluorine substituent is in close proximity to the required hydrogen bonding site H_2 in the proposed ligand binding cleft. It is possible that the required agonist hydrogen bonding interaction at H_2 with 6 now occurs via the 2'-fluorine atom rather than the imine nitrogen atom at position 4. This permits 6 to move in the binding site just enough to fit into L_2 without loss of the important interactions at H_1 , H_2 , L_1 , and L₃. This plasticity (flexibility) in the binding cleft is permitted because of the interaction of H_2 with the 2'fluorine atom.

Because of the high affinity of 6 to the BzR as compared to the activity of the desfluoro analogs, it was chosen for *in vivo* evaluation. Pharmacological studies in mice indicate that N(1)-methyl-5-(2'-fluorophenyl)-1,3-dihydronaphtho[2,3-e][1,4]diazepin-2-one (6) exhibits a full agonist spectrum of activity, analogous to that previously







reported for diazepam.²¹ The ED₅₀ for the anticonvulsant effect of 6 was $\approx 15 \text{ mg/kg}$, and the ED₅₀ for the myorelaxant effect was also ≈ 15 mg/kg. In comparison to diazepam, ligand 6 exhibited a less potent anticonvulsant effect and a comparable ataxic effect. Apparently, full occupation of L_2 has potentiated the muscle relaxant effect of 6 evidently at the expense of the potency of the anticonvulsant/anxiolytic effect. This is somewhat similar to the spectrum of activity elicited by the full agonist ZK 93423 (6-(benzyloxy)-4-(methoxymethyl)-β-carboline-3-carboxylic acid ethyl ester) vs the partial agonist 6PBC.²¹ In this latter case, partial occupation of L_3 (6PBC) furnished an agent with anxiolytic and anticonvulsant activity devoid of muscle relaxant activity.^{21,25} Although speculative, it is reasonable to predict that ligand selectivity and intrinsic activity (efficacy) at different GABA_A receptor isoforms will stem from different interactions in the lipophilic pockets of the BzR(s) receptor binding cleft(s) effected by selective BzR ligands. While it is not known whether transfected cells expressing various GABA_A subunits assemble them with the same stoichiometry as native receptors, future studies with recombinant receptors should provide additional insights into the validity of this hypothesis.

For comparison to 6, depicted in Table 2 is a list of disubstituted 1,4-benzodiazepines which have been previously reported to bind to the BzR.28,38 The 7,8disubstituted ligands 43, 44, and 45 exhibit high affinities at the BzR in vitro and two of these ligands elicit potent agonist activity. However, ligand 46 (7,8-dimethyl) exhibits only weak agonist activity because it is devoid of the electron-withdrawing group at position 7 required for potent in vivo activity of the 1,4-benzodiazepines.²⁸ However, this 7,8-dimethyl analog does fit into region L_2 of the BzR binding site. Illustrated in Figure 7 is the fit of the new ligand 6 and the 7,8-dichloro analog 44 (agonist, 3.6 nM) into the previously developed pharmacophore/ receptor model. As clearly illustrated in Figure 7, the lipophilic boundary of the receptor protein readily accepts 44 (X = F, 3.6 nM) but barely permits the binding of 6 [compare 3 (X = H, >1000 nM) to 6 (X = F, 55 nM)];

consequently, the depth of L_2 is certainly close to that defined by the rigid ring of 6. Substitution of a phenyl group for a chlorine atom at position 7 of diazepam results in ligand 51, which elicits only weak activity at the BzR. In contrast, the ligand 50 substituted with an ethylene moiety at position 7 binds to the BzR *in vitro* at 24 nM. The lack of affinity of 51 as compared to 50 can be attributed to the inability of region L_2 to accept the large phenyl ring of 51. This is entirely consistent with the volume of L_2 defined by molecular yardstick 6.

As mentioned above, the benzo-fused rings at C(8) and C(9) of 1 and 4 interacted with region S₁ and exhibited poor affinity at the BzR [IC₅₀(s) <1000 and 260 nM, respectively]. The 7,9-dichloro-1,4-benzodiazepine 48 (Ro 20-8065) is a full agonist and exhibits an activity comparable to diazepam (see Table 2). From this correlation, it is clear that region L₂ can tolerate a chlorine atom or methyl group at C(9) but not the large benzene ring of 4 which extends into region S₁. The 6,7-benzo-fused ring in 2 and 5 (IC₅₀ >1000 nM) extends into the region S₂ illustrated as the boundary between lipophilic regions L₂ and L₃ (see Figure 6). In agreement with this, 1,4benzodiazepines which bear substituents at position 6 (52, 53) do not exhibit high affinities at the BzR compared to the 6(H)-substituted congeners (Figure 8).²⁸

A logical extension of this "molecular yardsticks" approach is the use of (o-dimethyl-substituted benzene)or naphthalene-substituted 1,4-benzodiazepines to probe the dimensions (depth) of the lipophilic regions of the receptor site (see Figure 5 for details). The distance from the center of the benzene (A) ring (L_1) of the 1,4benzodiazepine nucleus to the end of the fused benzene ring differs from the distance to the terminus of the methyl groups (4.499 Å) or to the end of the fused naphthalene ring (8.224 Å), as illustrated in Figure 5.²⁷ Once the in vitro affinities of a number of these "molecular yardsticks" have been determined, these values can be employed with computer-aided molecular graphics to determine the exact dimensions of lipophilic pockets L_2 and L_3 by simple difference methods. Correlation of the occupation of these pockets with in vivo activity can then be made in order to design agents more selective for anxiolytic activity.

The two different pharmacophore/receptor models illustrated in Figures 1 and 2 are important with regard to agonist and inverse agonist activity, respectively, in vivo at BzR. Since in vitro binding data employed for this work was determined on rat cortical membranes, the potencies likely represent the weighted average of several GABA_A receptor isoforms. The agonist pharmacophore illustrated in Figure 2 represents an inclusive pharmacophore of "diazepam-sensitive" (DS) sites which is clearly different from that of the "diazepam-insensitive" (DI) receptor/model (the major isoform of DI receptors contains an α_6 subunit) reported earlier from this laboratory.⁴² The subtle topological differences (i.e., L₂, L₃, S₁, S₂, etc.) between DS GABA_A receptor subtypes can be determined when enough ligands are developed with high selectivity for a specific isoform. Within this context, both the stoichiometry and composition of native receptors must also be evinced. At this juncture it will be possible to subtract (via modeling) the volume of ligands of different isoforms from the inclusive model in order to discover the topological differences between the various GABA_A receptor isoforms. Ligands with rigid rings related to 6, as well as molecular yardsticks similar to those in Figure 5



Figure 7. The 7,8-benzo-fused benzodiazepine (6) and the dichlorobenzodiazepine (44) fitted into the agonist pharmacophore. The magenta dotted areas represent the van der Waals radii of 6.



Figure 8. Superposition of the agonists diazepam, Ro-05-4435, brotizolam, etizolam, midazolam, CGS-9896, and 6 with the negative controls 4 (magenta), and 5 (green). The regions of S_1 and S_2 (orange) were derived from subtraction of the union of the positive volumes of diazepam, Ro-05-4435, brotizolam, midazolam, CGS-9896, and 6 from the union of the negative control volumes of 4 and 5.

(see also footnotes 27 and 37), may be important in determining the differences between native BzR subtypes. Such studies are underway and will be reported in due course.

Experimental Section

In Vitro. The potencies of test compounds to displace [³H]flunitrazepam from benzodiazepine receptors were determined through a modification of previously described procedures.^{19,21,24} In brief, rats were killed by decapitation, and the cerebral cortex was removed. Tissues were disrupted in 100 volumes of Tris-citrate buffer (50 mM, pH 7.4) using a Brinkman Polytron (15 s, setting 6). Tissues were centrifuged for 20 min (4 °C) at 20000g. The supernatant was discarded and the tissue pellet resuspended in an equal volume of buffer. This "washing" procedure was repeated three times. Tissues were either used fresh or stored at -70 °C until used. Incubations (0.5 mL) consisted of tissue suspension (0.1 mL, ~0.1 mg of protein), 0.05 mL of NaCl solution (2.5 M), 0.05 mL of [³H]flunitrazepam (final concentration, ~1 nM, sp. act. 83.4 Ci/mmol), and drugs and/or

buffer to equal volume of Ro 15-1788 (final concentration 10 μ M). Incubations (0-4 °C) were initiated by addition of radioligand and teminated after 60 min by rapid filtration under vacuum through GF/B filters with two 5-mL washes of ice-cold buffer. IC₅₀ values were estimated using InPlot 4.0 (GraphPAD, San Diego, CA) with at least six concentrations of inhibitor. Values represent $X \pm$ SEM of at least three determinations. Compounds with potencies >1000 nM were generally only tested twice.

In Vivo. Adult male NIH/Swiss mice (25-30 g) were injected intraperitoneally (ip) with graded doses of the compounds (0.1 mL; diluted Emulphor/saline, 1.9) or an equal volume of vehicle (0.1 mL, diluted Emulphor/saline, 1.9). Groups of three to eight mice were injected in graded doses and 12 min later were suspended by their forepaws on a 1.5-mm-thick wire 60 cm above the bench top to assess muscle relaxation; three falls in <1 min was positive for muscle relaxation. At 15 min postinjection mice were injected with PTZ (80 mg/kg) to assess anticonvulsant activity or (40 mg/kg) to assess the proconvulsant activity. Groups of three to eight mice were injected ip with three or four graded doses of drug or vehicle, followed 10 min later by administration of diazepam (2.5 mg/kg ip). After 5 min, the animals were injected

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with PTZ (80 mg/kg) to assess the antagonist activity. In vehicle treated mice, 80 mg/kg PTZ produced tonic and clonic convulsions in 100% of the animals, while the incidence of seizes at 40 mg/kg was $\sim 10\%$. The dose of diazepam (2.5 mg/kg) protected 100% of the mice from PTZ-induced convulsions and also produced muscle relaxation in 100% of the animals tested.

Molecular Modeling. These studies were performed on an Evans & Sutherland PS390 graphics workstation and a Silicon Graphics Personal Iris 4D/35 workstation using SYBYL version 5.5 (Tripos Associates, St. Louis, MO). The starting geometries of the ligands were taken either from X-ray crystallographic structures^{13,39-42} or generated using CONCORD.⁴³ All bond lengths and valence angles of these structures were fully optimized with Gaussian 9044 or 9245 ab initio calculations (Gaussian Inc., Carnegie-Mellon University, Pittsburgh, PA) at the 3-21G level on a Cray X-MP supercomputer or IBM RS-6000 Model 560 workstation. Substituent groups were then added to the parent compounds to generate the remaining analogs using SYBYL. For example, geometries of 1-6 were arrived at by fusing a rigid benzene ring to diazepam. The side chains were optimized (holding the heterocyclic core structures fixed) using MacroModel BatchMin version 3.5 (Columbia University, New York, NY).46 Cartessian coordinates for these structures are deposited in the supplementary material of previous publications from this laboratory^{42,47} or the present work. Calculations of ring centroids, least-squares fitting, and included volume analyses⁴⁸ were also carried out using SYBYL. The lengths of hydrogen-bond extension vectors (HBV) were set to 1.84 Å, while the C-N-HBV and C=O-HBV valence angles used were set to 120 and 135° respectively, to mimic the geometry of an ideal hydrogen bond.⁴⁹⁻⁵⁶ The receptor modeling strategy employed here has been applied earlier for the inverse agonist/antagonist and agonist pharmacophores.19,20

Materials. Melting points were taken on a Thomas-Hoover melting point apparatus or an Electrothermal Model IA8100 digital melting point apparatus and are reported uncorrected. Proton and carbon NMR spectra were recorded on a Bruker 250-MHz multiple-probe instrument (62.9 MHz for carbon) or a GE 500-MHz spectrometer. Infrared spectra were recorded on a Nicolet Dx FTIR DX V5.07 spectrometer or a Mattson Polaris IR-10400 instrument. Low-resolution mass spectral data (EI/ CI) were obtained on a Hewlett-Packard 5985 B GC-mass spectrometer, while high-resolution mass spectral data were obtained on a Finnigan HR mass spectrometer. Microanalyses were performed on a Perkin-Elmer 240C carbon, hydrogen, and nitrogen analyzer. Analytical TLC plates employed were E. Merck Brinkman UV active silica gel (Kieselgel 60 F254) on plastic, and silica gel 60b for flash chromatography was purchased from E. M. Laboratories. All chemicals were purchased from Aldrich Chemical Co. unless otherwise stated. All reactions were carried out under an atmosphere of nitrogen.

1-Amino-2-naphthalenecarbonitrile (12),³⁰ 2-amino-1-naphthalenecarbonitrile (13),³⁰ 2-[(ethoxycarbonyl)amino]naphthalene-1-carbonitrile (33),³⁵ and 3-(dicyanomethylene)-3,4-dihydro-1*H*-naphth[2,1-d][1,3]oxazin-1-one (34),³⁵ were prepared according to the method of Tomioka *et al.*^{30,35} The spectral properties of these compounds were identical to the reported values.^{30,35}

1-Amino-2-benzoylnaphthalene (7) (Procedure a). A solution of 1-amino-2-naphthalenecarbonitrile (12) (1 g, 6 mmol) in dry ethyl ether (20 mL) was added to PhMgBr (18 mmol) in dry ethyl ether (100 mL) [which had been prepared from bromobenzene (2.83 g, 18 mmol) and magnesium (0.5 g, 20 mmol)]. The solution was heated to reflux for 1 h, and then aqueous 2 N HCl (100 mL) was added. The mixture was stirred at 30 °C for 2 h. After the solution was neutralized with aqueous NaOH (10%), the ether layer was separated and the water layer was extracted with ether $(2 \times 100 \text{ mL})$. The ether layer was washed with water and dried (Na₂SO₄). The ether layer was concentrated under reduced pressure, and the residue was purified by flash chromatography (silica gel) with CHCl₈ to provide 7. The solid was recrystallized from CH₈OH to furnish 7 as yellow crystals (1.27 g, 85%): mp 111-112 °C; IR (KBr) 3430, 3402 (NH₂), 1595 (C=O), 1539, 1496, 1307, 1243, 751 cm⁻¹; ¹H NMR (DMSO-d₆) δ 6.92 (d, 1H, J = 9 Hz), 7.28 (d, 1H, J = 9 Hz), 7.48–7.56 (m, 6H), 7.61 (t, 1H, J = 8 Hz), 7.75 (d, 1H, J = 8 Hz), 8.44 (d, 1H, J = 8 Hz), 8.61 (br s, 2H, NH₂); ¹³C NMR (CDCl₃) δ 199.1 (s,

C=O), 150.1 (s), 140.9 (d), 136.1 (d), 131.0 (s), 130.0 (d), 129.1 (s), 128.9 (d), 128.5 (d), 128.1 (s), 125.4 (d), 123.1 (s), 121.7 (d), 114.8 (s), 111.3 (d); MS (EI) m/e 247 (M⁺, 74), 246 (100), 217 (6), 170 (15), 115 (21). Anal. (C₁₇H₁₈NO) C, H, N.

1-Benzoyl-2-aminonaphthalene (8). 2-Amino-12-naphthalenecarbonitrile (13) (3.6 g, 21 mmol) was treated as described in procedure a, although the hydrolysis required heating with aqueous 6 N HCl for 5 h. The solid was purified by flash chromatography (silica gel) with hexane/ethyl acetate (4:1) to provide 8 as yellow crystals (4.5 g, 86%): mp 169-170 °C; IR (KBr) 3431, 3283 (NH₂), 3056, 1597 (C=O), 1542, 1461, 1247, 783, 703 cm⁻¹; ¹H NMR (DMSO-d₆) δ 5.89 (br s, 2H, NH₂), 702-7.17 (m, 4H), 7.45 (t, 2H, J = 7.6 Hz), 7.56-7.64 (m, 3H), 7.68-7.72 (m, 1H), 7.76 (d, 1H, J = 8.9 Hz); ¹³C NMR (CDCl₃) δ 198.97 (s, C=O), 145.40 (s), 139.58 (s), 132.85 (d), 132.91 (s), 132.58 (d), 129.70 (d), 128.57 (d), 114.56 (s); MS (EI) m/e 247 (M⁺, 100). Anal. (C₁₇H₁₃NO) C, H, N.

2-Amino-3-benzoylnaphthalene (9). 3-Amino-2-naphthoic acid (14) (1 g, 5.35 mmol) was dissolved in dry THF (50 mL), and phenyllithium (11 mL of 2.5 M, 21.4 mmol) was added into the solution at 0 °C. The mixture was then stirred for 2 h at 25 °C. Aqueous saturated NH4Cl solution (20 mL) was added to the mixture, after which the THF layer was separated and the water layer was extracted with ether $(2 \times 50 \text{ mL})$. The THF and ether extracts were combined and purified by flash chromatography with hexane/EtOAc (6:1) to provide 9 (0.61 g, 51%) and diphenyl 2-(3-aminonaphthyl)]methanol (15) (0.18g, 10% yield). 9: light yellow crystals; mp 119-120 °C (CH₃OH); IR (KBr) 3477, 3371 (NH), 1643 (C=O), 1630, 1571, 890, 759 cm⁻¹; ¹H NMR (DMSO d_6) δ 6.33 (br s, 2H, NH₂), 7.08 (s, 1H), 7.10 (t, 1H, J = 7.4 Hz), 7.39 (t, 1H, J = 7.4 Hz), 7.53–7.59 (m, 3H), 7.64–7.72 (m, 4H), 7.89 (s, 1H); MS (EI) m/e 247 (M⁺, 43), 246 (47), 230 (4), 217 (9), 170 (10), 142 (17), 115 (100). Anal. (C17H18NO) C, H, N.

15: mp 160–161 °C (hexane/EtOAc); IR (KBr) 3449 (OH), 3386, 3354 (NH), 3053, 1635, 1610, 1455, 769, 701 (cm⁻¹); ¹H NMR (DMSO- d_6) δ 5.38 (br s, 2H, D₂O exchangeable, NH₂), 6.77 (s, 1H), 6.90 (s, 1H), 7.00 (dt, 1H, J = 1, 7.0 Hz), 7.03 (s, 1H, D₂O exchangeable, OH), 7.36–7.20 (m, 11H), 7.49 (d, 1H, J = 8.15Hz); MS (EI) m/e 325 (M⁺, 14), 306 (100), 276 (2), 246 (4), 230 (31), 202 (6), 115 (29), 105 (23).

2-Phenyl-4H-naphth[2,3-d][1,3]oxazin-4-one (23) (Procedure b). 3-Amino-2-naphthoic acid (14) (3 g, 17.8 mmol) was dissolved in benzoyl chloride (50 mL), and the mixture was heated to 170 °C for 3 h. The mixture was then cooled to room temperature, whereupon crystals formed. The solid was collected and washed with hexane/ether (2:1) to give 23 (3.8 g, 91%) as colorless crystals: mp 227-228 °C; IR(KBr) 1753 (C=O), 1611, 1282, 1170, 751, cm⁻¹; ¹H NMR (CDCl₃) δ 7.48-7.70 (m, 5H), 7.98 (d, 1H, J = 8.5 Hz), 8.03 (d, 1H, J = 8.5 Hz), 8.15 (s, 1H), 8.32-8.36 (m, 2H), 8.87 (s, 1H); MS(CI) m/e 274 (M⁺ + 1, 100). Anal. (C₁₈H₁₁NO₂) C, H, N.

2-(2'-Fluorobenzoyl)-3-(N-benzoylamino)naphthalene (24) (Procedure c). A solution of 2-bromofluorobenzene (1.54 g, 8.82 mmol) in dry THF (20 mL) was cooled to -78 °C, and n-BuLi (6.1 mL of 1.6 M, 9.7 mmol) was added dropwise to the solution. After the mixture was stirred for 15 min at -78 °C, it was transferred into a solution of 2-phenylnaphth[2,3-d]oxazin-4one 23 (2.5 g, 9.1 mmol) in dry THF (250 mL) which was precooled to -78 °C. The mixture was then stirred at -78 °C for 20 min. Aqueous saturated NH₄Cl solution (50 mL) was added to the reaction mixture, and it was warmed to room temperature. The organic layer was separated, washed with water, and dried (MgSO₄). After the THF was removed under reduced pressure, the residue was purified by flash chromatography with hexane/ ethyl acetate (95:5) to provide 24 (1.71 g, 51%) and bis(2'fluorophenyl)[3-(N-benzoylamino)-2-naphthyl]methanol (25) (0.6 g, 14%). 24: mp 188-189 °C (hexane/EtOAc); IR (KBr) 3298 (NH), 3056, 1681, 1633, 1546, 1303, 757 (cm⁻¹); ¹H NMR (CDCl₈) δ 7.24 (t, 1H, J = 8.5 Hz), 7.31 (dt, 1H, J = 1, 8 Hz), 7.41 (dt, 1H, J = 1, 8 Hz), 7.46-7.61 (m, 6H), 7.72 (d, 1H, J = 8.2 Hz), 7.90 (d, 1H, J = 8.2 Hz), 8.12–8.15 (m, 3H), 9.40 (s, 1H), 12.12 (br s, 1H, NH); ¹⁹F NMR (CDCl₃) δ (CF₃CO₂H, external -41.30 (s); MS (EI) $m/e 369 (M^+, 23), 264 (1.5), 246 (20), 105 (100)$. Anal. (C₂₄H₁₆-FNO₂) C, H, N.

25: mp 210-211 °C (hexane/EtOAc); IR (KBr) 3395 (OH),

3234 (NH), 3043, 1638 (C=O), 1546, 1384, 855, 702 cm⁻¹; ¹H NMR (CDCl₃) δ 4.49 (t, 1H, J = 7.8 Hz), 7.02–7.30 (m, 7H), 7.31–7.52 (m, 10H), 7.88 (d, 1H, J = 8.3 Hz), 9.01 (s, 1H), 10.2 (br s, 1H); MS (CI) m/e 467 (M⁺ + 1, 35), 466 (M⁺, 27), 449 (100).

2-Amino-3-(2'-fluorobenzoyl)naphthalene (26) (Procedured). The (N-benzoylamino)naphthalene 24 (1g, 3.77 mmol) was dissolved in glacial acetic acid (50 mL), and 48% HBr (25 mL) was added to the solution. The mixture was heated to reflux for 10 h, after which the solvent was removed under reduced pressure. The residue was then dissolved in EtOAc (50 mL) and washed with aqueous NaHCO₃ solution (5%) followed by water and then dried $(MgSO_4)$. After the EtOAc was removed under reduced pressure, the residue was purified by a wash column which was eluted with hexane/EtOAc (3:1) to afford 26 (0.73 g, 97%) as yellow crystals: mp 108-109 °C; IR (KBr) 3483, 3372 (NH), 3062, 1628 (C=O), 1605, 1308, 765 cm⁻¹; ¹H NMR (DMSOd₆) δ 6.12 (br s, 2H, NH₂), 7.24 (s, 1H), 7.35–7.48 (m, 3H), 7.52 (dt, 1H, J = 1, 6.6 Hz), 7.65 (dt, 1H, J = 1, 6.6 Hz), 7.72-7.82 (m, 100)4H), 8.17 (d, 1H, J = 2 Hz); ¹⁹F NMR (CDCl₃) δ (CF₃CO₂H, external) -42.19 (s); MS (EI) m/e 265 (M⁺, 84), 264 (52), 245 (32), 170 (16), 142 (23), 115 (100). Anal. (C₁₇H₁₂FNO) C, H, N.

1-Amino-2-naphthoic Acid (29). 1-Amino-2-cyanonaphthalene (12) (5 g, 30 mmol) was dissolved in ethanol (150 mL), and aqueous 20% NaOH solution (50 mL) was added. The mixture was heated to reflux for 10 h. After the ethanol was removed under reduced pressure, the aqueous solution was brought to pH 6.5 with aqueous concentrated HCl to furnish a white precipitate. The solid was collected, washed with water, and dried under vacuum to provide 29 (4.2 g, 85%): mp 270 °C [(dec) lit.⁵⁷ mp: 198–199 °C]; IR (KBr) 3161, 3156, 3018, 2896, 2867, 2792 (RCO₂-RNH₃+), 1677 (C=O), 1617, 1442 cm⁻¹; ¹H NMR (DMSO-d₆) δ 7.66–7.77 (m, 2H), 7.86 (d, 1H, J = 8.7 Hz), 8.01 (d, 2H, J = 8.7 Hz), 8.90 (d, 1H, J = 7.4 Hz); MS (EI) m/e187 (M⁺, 16), 141 (19).

2-Phenyl-4H-naphth[1,2-d][1,3]oxazin-4-one (30). 1-Amino-2-naphthoic acid (**29**) (4.2 g 22 mmol) was reacted with benzoyl chloride under conditions analogous to that described in procedure b to provide the title compound **30** as a white solid (5.87 g, 91%): mp 192–193 °C; IR (KBr) 3055, 1754 (C=O), 1607, 1567, 758, 700 cm⁻¹; ¹H NMR (CDCl₃) δ 7.64 (m, 3H), 7.65–7.80 (m, 2H), 7.82–8.00 (m, 2H), 8.13 (d, 1H, J = 8.7 Hz), 8.45 (m, 2H), 9.06 (m, 1H); MS (EI) *m/e* 273 (M⁺, 59), 245 (2), 229 (13), 196 (17), 140 (9), 126 (23), 105 (100). Anal. (C₁₈H₁₁NO₂) C, H, N.

1-(*N*-Benzoylamino)-2-(2'-fluorobenzoyl)naphthalene (31). The 2-phenylnaphth[1,2-d]oxazin-4-one 30 (3.5 g, 12.8 mmol) was treated under conditions analogous to those of procedure c to provide 31 (4.1 g, 85%) as bright yellow crystals (hexane/EtOAc): mp 169–170 °C; IR (KBr) 3278 (NH), 3070, 1661 (C=O), 1610, 1517, 1302, 1101, 837, 758 cm⁻¹; ¹H NMR (CDCl₃) δ 7.06–7.23 (m, 2H), 7.40–7.65 (m, 8H), 7.73 (d, 1H, J = 8 Hz), 7.86 (dd, 1H, J = 1, 8 Hz), 7.95–8.10 (m, 3H), 10.03 (br s, 1H); MS (EI) m/e 369 (M⁺, 7), 264 (2), 246 (33), 235 (3), 140 (2), 105 (100). Anal. (C₂₄H₁₆FNO₂) C, H, N.

1-Amino-2-(2'-fluorobenzoyl)naphthalene (32). 1-(*N*-Benzoylamino)-2-(2'-fluorobenzoyl)naphthalene (31) (3.05 g, 8.3 mmol) was treated according to procedure d to afford 32 (2.2g, 95%) as light green-yellow crystals: mp 119–121 °C; IR (KBr) 3499, 3377 (NH₂), 3058, 1612 (C=O), 1520, 1483, 913, 815, 741 cm⁻¹; ¹H NMR (CDCl₃) δ 6.94 (d, 1H, J = 8.3 Hz), 7.11–7.30 (m, 3H), 7.41–7.51 (m, 3H), 7.57 (dt, 1H, J = 1.2, 8.3 Hz), 7.96 (d, 1H, J = 8.4 Hz); MS (EI) m/e 265 (M⁺, 91), 264 (87), 246 (30), 170 (36), 115 (100). Anal. (C₁₇H₁₂FNO) C, H, N.

1-(2'-Fluorobenzoyl)-2-aminonaphthalene (36). 3-(Dicyanomethylene)-3,4-dihydro-1*H*-naphth[2,1-*d*][1,3]oxazin-1one (34) (1.3 g, 5 mmol) was treated as described in procedure c with 2 equiv of (o-fluorophenyl)lithium, and this was followed by treatment analogous to procedure d to afford 36 (0.93 g, 71%) as light brown crystals (hexane/EtOAc): mp 98–99 °C; ¹H NMR (CDCl₃) δ 5.60 (br s, 2H, NH₂), 6.90 (d, 1H, J = 9 Hz), 6.98–7.17 (m, 4H), 7.17–7.40 (m, 2H), 7.26 (d, 1H, J = 9 Hz), 7.62 (dd, 1H, J = 1.5, 9 Hz), 7.72 (d, 1H, J = 9 Hz); IR (KBr) 3494, 3381 (NH₂), 3064, 1645, 1620, 1602 (C=0), 818, 747 cm⁻¹; MS (EI) *m/e* 265 (M⁺, 100), 264 (71), 248 (20), 246 (25), 170 (75), 142 (30), 115 (90). Anal. (C₁₇H₁₂FNO) C, H, N.

General Procedure e To Prepare Bromoacetyl Amides. 1-[N-(Bromoacetyl)amino]-2-benzoylnaphthalene (16). 1-Amino-2-benzoylnaphthalene (7) (0.7 g, 2.8 mmol) and NaHCO3 (1 g, 11 mmol) were suspended in dry CHCl₃ (50 mL), and a solution of bromoacetyl bromide (0.63 g, 3.1 mmol) in dry CHCl₃ (10 mL) was added dropwise at 0 °C. The mixture was stirred at 0 °C for 30 min. The CHCl₃ solution was washed with aqueous NaHCO₃ solution (2%) and dried (MgSO₄). After the CHCl₃ was removed under reduced pressure. the oily residue was purified by a wash column on silica gel [hexane/EtOAc (4:1)] to provide 16 as colorless crystals (1.03 g, 94%): mp 199-201 °C; IR (KBr) 3268 (NH), 3015, 1665 (C=O), 1525, 814 cm⁻¹; ¹H NMR (CDCl₃) δ 3.93 (s, 2H), 7.42-7.49 (m, 3H), 7.26-7.56 (m, 3H), 7.77-7.93 (m, 5H), 9.30 (br s, 1H, NH); MS (EI) m/e 369 (M⁺, 18), 367 (M⁺, 18), 264 (26), 246 (100), 217 (38), 105 (37). Anal. (C18H14BrNO) C. H. N.

2-[N-(Bromoacetyl)amino]-1-ben zoylnaphthalene (18). 2-Amino-1-benzoylnaphthalene (8) (2.6 g, 10.5 mmol) was treated as described in procedure e to provide 18 as yellow needles (3.4 g,89%): mp 157–158 °C; IR (KBr) 3241 (NH), 3063, 1673 (C-O), 1583, 1539 (C=O), 828 cm⁻¹; ¹H NMR (DMSO- $d_{\theta} \delta$ 3.79 (s, 2H), 7.46–7.48 (m, 4H), 7.53 (m, 1H), 7.61–7.66 (m, 4H), 8.02 (d, 1H, J = 8.5 H), 8.10 (d, 1H, J = 8.5 Hz), 10.19 (br s, 1H); MS (EI) m/e 369 (M⁺, 39), 367 (M⁺, 40), 264 (97), 262 (100), 246 (72), 217 (64), 183 (77), 105 (56). Anal. (C₁₉H₁₄BrNO) C, H, N.

2-[N-(Bromoacetyl)amino]-3-benzoylnaphthalene (21). 2-Amino-3-benzoylnaphthalene (9) (1.2 g, 4.9 mmol) was treated as described in procedure e to provide 21 as light yellow crystals (1.7 g, 94%): mp 145–146 °C; IR (KBr) 3241 (NH), 3062, 1670 (C=O), 1637 (C=O), 1537, 761 cm⁻¹; ¹H NMR (CDCl₃) δ 4.07 (s, 2H), 7.69–7.38 (m, 5H), 7.70–7.85 (m, 3H), 7.78 (d, 1H, J = 8.5 Hz), 8.11 (s, 1H), 9.01 (s, 1H), 11.31 (br s, 1H, NH); MS (EI) m/e369 (M⁺, 34), 367 (M⁺, 34), 246 (68), 217 (89), 105 (100). Anal. (C₁₉H₁₄BrNO) C, H, N.

1-[N-(Bromoacetyl)amino]-2-(2'-fluorobenzoyl)naphthalene (37). 1-Amino-2-(2'-fluorobenzoyl)naphthalene (32) (2.2 g, 8.3 mmol) was treated as described in procedure e to provide 37 as colorless crystals (2.95 g, 92%): mp 169–172 °C; IR (KBr) 3281 (NH), 3069, 1669 (C=O), 1650, 1606, 1519, 756 cm⁻¹; ¹H NMR (CDCl₃) δ 3.96 (s, 2H), 7.14 (dt, 1H, J = 0.7, 9.4 Hz), 7.25 (dt, 1H, J = 0.8, 7.6 Hz), 7.64–7.48 (m, 4H), 7.67 (dt, 1H, J = 0.8, 7.6 Hz), 7.80 (d, 1H, J = 8.6 Hz), 7.88 (m, 1H), 7.97 (m, 1H), 9.55 (br s, 1H, NH); MS (EI) m/e 387 (M⁺, 16), 385 (M⁺, 16), 292 (6), 264 (68), 246 (14), 183 (20), 140 (23), 123 (100), 115 (27). Anal. (C₁₉H₁₃BrFN₂O) C, H, N.

2-[*N*-(**Bromoacety**])**amino**]-1-(2'-fluorobenzoy])**naphtha** lene (39). 2-Amino-1-(2'-fluorobenzoy])**naphtha**lene (36) (0.73 g, 2.8 mmol) was treated as described in procedure e to provide 39 as colorless crystals (0.98 g, 92%): mp 139–141 °C; IR (KBr) 3281 (NH), 3057, 1650 (C=O), 1556, 1362, 825, 743 cm⁻¹; ¹H NMR (CDCl₃) δ 3.99 (s, 2H), 7.08 (t, 1H, J = 8 Hz), 7.16 (t, 1H, J = 7.8 Hz), 7.20–7.55 (m, 4H), 7.63 (t, 1H, J = 7.8 Hz), 7.97 (d, 1H, J = 8.1 Hz), 8.24 (d, 1H, J = 8.1 Hz), 9.51 (br s, 1H, NH); MS (EI) *m/e* 387 (M⁺, 20), 385 (M⁺, 21), 264 (100), 235 (28), 183 (63), 123 (59), 115 (24). Anal. (C₁₉H₁₃BrFN₂O) C, H, N.

2-[*N*-(**Bromoacety**])**amino**]-**3-**(2'-**fluorobenzoy**])**naphthalene** (41). 2-Amino-3-(2'-fluorobenzoy])**naphthalene** (26) (0.39 g, 1.1 mmol) was treated as described in procedure e to provide 41 as colorless crystals (0.295 g, 90%): mp 181–182 °C (hexane/EtOAc); IR (KBr) 3208 (NH), 1665 (C=O), 1641, 1533, 1300, 760 (cm⁻¹); ¹H NMR (CDCl₃) δ 4.01 (s, 2H), 7.21 (m, 1H), 7.31 (dt, 1H, J = 1.1, 7.1 Hz), 7.42 (dt, 1H, J = 1.1, 6.9 Hz), 7.63–7.53 (m, 3H), 7.72 (d, 1H, J = 8.2 Hz), 7.87 (d, 1H, J = 8.2 Hz), 8.08 (d, 1H, J = 2.3 Hz), 9.11 (s, 1H), 11.58 (br s, 1H, NH); MS (EI) *m/e* 387 (M⁺, 62), 385 (M⁺, 62), 292 (13), 264 (62), 246 (12), 235 (31), 196 (14), 123 (100). Anal. (C₁₉H₁₈BrFN₂O) C, H, N.

General Procedure f for Amination followed by Cyclization To Prepare the Benzo-Fused 1,4-Benzodiazepines. 5-Phenyl-1,3-dihydronaphtho[1,2-e][1,4]diazepin-2-one (17). The bromoacetyl amide 16 (0.11 g, 0.3 mmol) was dissolved in a saturated solution of ammonia in CH₃OH (150 mL) and the mixture was heated to reflux for 10 h. After the methanol was removed under reduced pressure, the solid which remained was purified by a wash column (silica gel) eluted with hexane/EtOAc (3:1). The purified material was recrystallized from CHCl₃/CH₃-OH to provide the benzo-fused benzodiazepine 17 (0.078 g, 74%) as colorless crystals: mp 245–246 °C dec; IR (KBr) 3212 (NH), 3078, 1658 (C=O), 1363, 821, 751 cm⁻¹; ¹H NMR (DMSO- d_6) δ 3.79 (d, 1H, J = 9.8 Hz), 4.58 (d, 1H, J = 9.8 Hz), 7.23 (d, 1H, J = 8.6 Hz), 7.40–7.54 (m, 5H), 7.66–7.72 (m, 3H), 7.99 (m, 1H), 8.36 (m, 1H); ¹³C NMR (DMSO- d_6) δ 169.79, 138.92, 135.92, 134.25, 130.19, 129.27, 128.28, 128.25, 126.93, 126.31, 125.71, 123.89, 123.71, 123.43, 57.23; MS (EI) m/e 286 (M⁺, 12), 257 (86), 230 (100), 140 (62); MS(CI) m/e 287 (M⁺, 89). Anal. (C₁₉H₁₄N₂O) C, H, N.

5-Phenyl-1,3-dihydronaphtho[2,1-*e*][1,4]diazepin-2-one (19). The *N*-(bromoacetyl)-1-benzoyl-2-naphthylamine 18 (3.2 g, 8.7 mmol) was treated as described in procedure f to provide 19 as colorless crystals (0.97 g, 39%) accompanied by 2-hydroxy-3-amino-4-phenylbenzo[f]quinoline 20 (1.09 g, 44%). 19: mp 259–259.8 °C (hexane/EtOAc); IR (KBr) 3213 (NH), 3056, 1681 (C==O), 1625, 1606, 1364, 744 cm⁻¹; ¹H NMR (DMSO-d₆) δ 3.89 (d, 1H, J = 10 Hz), 4.56 (d, 1H, J = 10 Hz), 7.23–7.44 (m, 9H), 7.93 (d, 1H, J = 9 Hz), 8.09 (d, 1H, J = 9 Hz), 10.76 (br s, 1H); ¹³C NMR (DMSO-d₆) δ 170.85, 168.47, 140.19, 138.56, 131.99, 131.03, 129.81, 120.70, 128.36, 128.28, 128.19, 127.07, 126.60, 125.05, 120.57, 57.51; MS (EI) *m/e* 286 (M⁺, 100), 285 (37), 257 (60), 230 (29), 183 (50), 155 (23). Anal. (C₁₉H₁₄N₂O) C, H, N.

20: mp 328 °C dec; IR (KBr) 3465, 3375, 3110, 3050, 1655 (C=O), 1570, 808 cm⁻¹; ¹H NMR (DMSO- d_6) δ 4.67 (br s, 2H, NH₂), 6.93 (m, 1H), 7.06 (d, 1H, J = 8.7 Hz), 7.27 (t, 1H, J = 6.8 Hz), 7.32 (m, 2H), 7.48–7.76 (m, 4H), 7.70 (d, 1H, J = 8.8 Hz), 7.80 (d, 1H, J = 7.8 Hz), 10.46 (br s, 1H, NH); ¹³C NMR (DMSO- d_6) δ 156.54 (s), 138.74 (s), 135.54 (s), 130.66 (s), 130.25 (s), 130.09 (d), 129.09 (d), 128.75 (d), 128.66 (s), 127.97 (d), 126.27 (d), 124.92 (d), 124.77 (d), 123.65 (d), 120.36 (d), 116.75 (d), 114.13 (s); MS (EI) m/e 286 (M⁺, 100), 267 (13), 255 (12), 240 (30), 202 (16), 120 (10).

5-Phenyl-1,3-dihydronaphtho[2,3-*e*][1,4]diazepin-2-one (22). The bromoacetyl amide 21 (0.52 g, 1.4 mmol) was treated as described in procedure f to provide 22 (0.35 g, 78%) as colorless crystals: mp 271-274 °C; IR (KBr) 3194 (NH), 3050, 2975, 1682 (C==O), 1632, 1607, 882 cm⁻¹; ¹H NMR (CDCl₃) δ 4.37 (s, 2H), 7.32-7.51 (m, 4H), 7.52-7.63 (m, 4H), 7.75 (d, 1H, J = 10 Hz), 7.83 (d, 1H, J = 6.7 Hz), 7.85 (s, 1H), 8.87 (br s, 1H, NH); ¹³C NMR (CDCl₃) δ 171.39 (s), 169.76 (s), 139.52 (s), 136.40 (s), 133.92 (s), 131.16 (d), 130.22 (d), 129.24 (d), 128.58 (d), 128.29 (d), 128.19 (d), 126.75 (d), 126.35 (s), 125.71 (d), 117.46 (d), 56.60 (dd); MS (EI) *m/e* 286 (M⁺, 24), 258 (37), 257 (36), 230 (37), 202 (35), 140 (100), 127 (96). Anal. (C₁₉H₁₄N₂O) C, H, N.

5-(2-Fluorophenyl)-1,3-dihydronaphtho[1,2-*e*][1,4]diazepin-2-one (38). N-(Bromoacetyl)-2-(2'-fluorobenzoyl)naphthylamine (37) (3.2 g, 8.3 mmol) was treated as described in procedure f to provide 38 as colorless crystals (2 g, 80%): mp $255-256 \,^{\circ}$ C, ¹H NMR (DMSO-*d*₆) δ 4.44 (br s, 2H), 7.05 (dt, 1H, J = 0.8, 9.4 Hz), 7.23 (t, 1H, J = 6.6 Hz), 7.42 (m, 1H), 7.50–7.70 (m, 4H), 7.88 (dd, 1H, J = 2.5, 6.9 Hz), 8.22 (dd, 1H, J = 2.2, 7.1Hz), 9.24 (br s, 1H, NH); MS (EI) *m/e* 304 (M⁺, 100), 275 (88), 200 (30), 154 (32), 137 (38), 127 (79), 114 (48). Anal. (C₁₉H₁₃-FN₂O) C, H, N.

5-(2-Fluorophenyl)-1,3-Dihydronaphtho[2,1-*e*][1,4]diazepin-2-one (40). The *N*-(bromoacetyl)-1-(2'-fluorobenzoyl)-2-naphthylamine (39) (0.7 g, 1.8 mmol) was treated as described in procedure f to provide 40 as colorless crystals (0.495 g, 90%): mp 259 °C dec; IR (KBr) 3200 (NH), 1680 (C=O), 1625, 1600, 1445, 1350, 750 cm⁻¹; ¹H NMR (CDCl₃) δ 4.00 (d, 1H, J = 10.3Hz), 4.94 (dd, 1H, J = 1.8, 10.3 Hz), 6.85 (m, 1H), 7.16 (dt, 1H, J = 0.9, 7.5 Hz), 7.20–7.40 (m, 4H), 7.44 (d, 1H, J = 8.5 Hz), 7.62 (dt, 1H, J = 1.6, 7.5 Hz), 7.82 (d, 1H, J = 8.1 Hz), 7.94 (d, 1H, J = 8.8 Hz), 9.02 (br s, 1H); MS (EI) *m/e* 304 (M⁺, 100), 284 (22), 258 (11), 255 (14), 142 (11), 114 (17). Anal. (C₁₉H₁₃FN₂O) C, H, N.

5-(2-Fluorophenyl)-1,3-dihydronaphtho[2,3-e][1,4]diazepin-2-one (42). N-(bromoacetyl)-3-(2'-fluorobenzoyl)-2naphthylamine (41) (0.21 g, 5.4 mmol) was treated as described in procedure f to provide 42 as colorless crystals (0.14 g, 85%): mp 263 °C dec; IR (KBr) 3200 (NH), 1675 (C=O), 1625, 1440, 755 cm⁻¹; ¹H NMR (CDCl₃) δ 4.41 (s, 2H), 7.02 (m, 1H), 7.25 (dt, 1H, J = 1.1, 8.5 Hz), 7.40–7.51 (m, 2H), 7.54 (m, 1H), 7.53 (s, 1H), 7.64 (dt, 1H, J = 1, 8.5 Hz), 7.72 (d, 1H, J = 8.8 Hz), 7.74 (s, 1H), 7.77 (d, 1H, J = 8.8 Hz), 8.43 (br s, 1H, NH); ¹³C NMR (CDCl₃) δ 172.33 (s), 167.98 (s), 160.57 (d, J_{CF} = 252 Hz), 134.49 (s), 134.40 (s), 131.90 (dd, $J_{CCCCF} = 8.1$ Hz), 131.43 (d), 130.74 (d), 129.46 (s), 128.55 (d), 128.34 (s), 127.72 (s), 127.05 (d), 126.22 (d), 124.26 (dd, $J_{CCCF} = 3$ Hz), 117.99 (d), 116.23 (dd, $J_{CCF} = 22$ Hz), 56.35 (t); MS (EI) m/e 304 (M⁺, 100), 285 (18), 276 (87), 248 (19), 220 (10), 127 (28). Anal. (C₁₉H₁₃FN₂O) C, H, N.

General Procedure g for N-Methylation of the 1.4-Benzodiazepines. 1-Methyl-5-phenyl-1,3-dihydro-naphtho-[1,2-e][1,4]diazepin-2-one (1). The 8,9-benzo-fused 1,4-benzodiazepine 17 (0.51 g, 1.78 mmol) was dissolved in dry DMF (40 mL), and NaH (46 mg, 1.92 mmol) was added to the solution in small portions. After the mixture which resulted was stirred at 25 °C for 10 min, CH₃I (0.27 g, 1.95 mmol) was added and the slurry was stirred for 30 min. The DMF was then removed under reduced pressure. The residue was purified by flash chromatography [hexane/ethyl acetate (10:1)] to provide the title compound 1 (0.485 g, 87%) as colorless crystals: mp 165-167 °C; IR (KBr) 3057, 1670 (C=O), 1599, 1650, 832 cm⁻¹; ¹H NMR $(CDCl_3) \delta 3.44$ (s, 3H), 3.84 (d, 1H, J = 10.2 Hz), 4.88 (d, 1H, J= 10.2 Hz), 7.31 (d, 1H, J = 8.6 Hz), 7.39-7.48 (m, 3H), 7.62-7.72(m, 5H), 7.92 (m, 1H), 8.01 (m, 1H); MS (EI) m/e 300 (M⁺, 74),299 (72), 272 (100), 255 (8), 229 (5), 165 (8). Anal. (C₂₀H₁₆N₂O-1/3H2O) C, H, N.

1-Methyl-5-phenyl-1,3-dihydronaphtho[2,1-e][1,4]diazepin-2-one (2). The 6,7-benzo-fused 1,4-benzodiazepine 19 (0.6 g, 2.1 mmol) was treated as described in procedure g to provide 2 (0.564 g, 90%) as colorless crystals: mp 188–189 °C; IR (KBr) 3063, 2988, 1688 (C==O), 1606, 1506, 988, 750 (cm⁻¹); ¹H NMR (DMSO-d₆) δ 3.39 (s, 3H), 3.90 (d, 1H, J = 10.3 Hz), 4.62 (d, 1H, J = 10.3 Hz), 7.24–7.40 (m, 8H), 7.75 (d, 1H, J = 9.0 Hz), 8.00 (d, 1H, J = 10.3 ltz), 7.24–7.40 (m, 8H), 7.75 (d, 1H, J = 9.0 Hz), 8.00 (d, 1H, J = 8.1 Hz), 8.20 (d, 1H, J = 9 Hz); ¹³C NMR (DMSO-d₆) δ 170.13 (s), 168.26 (s), 141.98 (s), 139.80 (s), 132.01 (d), 130.26 (s), 130.13 (d), 128.58 (d), 128.36 (d), 128.12 (d), 127.12 (d), 126.92 (s), 125.79 (d), 120.95 (s), 120.31 (d), 57.25 (dd), 34.14 (q); MS (EI) *m/e* 300 (M⁺, 100), 299 (35), 272 (76), 255 (15), 197 (46), 182 (8). Anal. (C₂₀H₁₆N₂O) C, H, N.

1-Methyl-5-phenyl-1,3-dihydronaphtho[2,3-e][1,4]diazepin-2-one (3). The 7,8-benzo-fused 1,4-benzodiazepine 22 (0.22 g, 0.77 mmol) was treated as described in procedure g to provide 3 as colorless crystals (0.2g, 87%): mp 167.5-168.7 °C; IR (KBr) 3058, 2857, 1671 (C=O), 1634, 1608, 893, 730 cm⁻¹; ¹H NMR (DMSO- d_{6}) δ 3.51 (s, 3H, NCH₃), 3.86 (d, 1H, J = 10.8 Hz), 4.76 (d, 1H, J = 10.8 Hz), 7.35-7.51 (m, 4H), 7.58 (t, 1H, J = 7.7 Hz), 7.63-7.68 (m, 2H), 7.73 (s, 1H), 7.75 (d, 1H, J = 8.4 Hz), 7.81 (s, 1H), 7.86 (d, 1H, J = 8.4 Hz); ¹³C NMR (CDCl₃) δ 171.29 (s), 170.43 (s), 141.31 (s), 139.36 (s), 134.22 (s), 131.0 (d), 130.47 (d), 129.65 (d), 129.25 (s), 128.49 (d), 128.29 (d), 128.01 (s), 127.30 (d), 36), 299 (32), 272 (54), 255 (27), 202 (43), 127 (100). Anal. (C₂₀H₁₈N₂O) C, H, N.

1-Methyl-5-(2'-fluorophenyl)-1,3-dihydronaphtho[1,2-*e*]-[1,4]diazepin-2-one (4). The 8,9-benzo-fused 1,4-benzodiazepine 38 (0.6 g, 2 mmol) was treated as described in procedure g to provide 4 (0.543 g, 91%) as colorless crystals: mp 178–180 °C; IR (KBr) 3062, 2931, 1681 (C=O), 1613, 1588, 1450, 763 cm⁻¹; ¹H NMR (CDCl₃) δ 3.43 (s, 3H), 3.86 (d, 1H, J = 10.5 Hz), 4.93 (d, 1H, J = 10.5 Hz), 7.05 (m, 1H), 7.18 (dd, 1H, J = 0.6, 8 Hz), 7.26 (dt, 1H, J = 1, 8 Hz), 7.45 (m, 1H), 7.56–7.70 (m, 2H), 7.72 (dt, 1H, J = 1, 8 Hz), 7.89 (m, 1H), 8.00 (m, 2H); MS (EI) m/e318 (M⁺, 86), 317 (87), 299 (37), 290 (100), 168 (19), 145 (29), 127 (47). Anal. (C₂₀H₁₆FN₂O) C, H, N.

1-Methyl-5-(2'-fluorophenyl)-1,3-dihydronaphtho[2,1-e]-[1,4]diazepin-2-one (5). The 6,7-benzo-fused 1,4-benzodiazepine 40 (0.13 g, 0.5 mmol) was treated as described in procedure g to provide 5 (0.122 g, 91%) as colorless crystals: mp 145–147 °C; IR (KBr) 3075, 2994, 1675 (C=O), 1606, 1513, 819, 750 cm⁻¹; ¹H NMR (CDCl₃) δ 3.49 (s, 3H), 3.93 (d, 1H, J = 10.3 Hz), 4.90 (d, 1H, J = 10.3 Hz), 6.85 (ddd, 1H, J = 1, 7.2, 10.8 Hz), 7.20 (dt, 1H, J = 1.2, 7.6 Hz), 7.25 (dt, 1H, J = 1.4, 7.7 Hz), 7.30–7.50 (m, 4H), 7.60 (dt, 1H, J = 1.9, 7.7 Hz), 7.82 (d, 1H, J = 9.0 Hz); MS (EI) m/e 318 (M⁺, 100), 299 (18), 290 (70), 269 (11), 197 (83), 168 (55), 127 (55). Anal. (C₂₀H₁₆FN₂O) C, H, N.

1-Methyl-5-(2'-fluorophenyl)-1,3-dihydronaphtho[2,3-e]-[1,4]diazepine-2-one (6). The 7,8-benzo-fused 1,4-benzodiazepine 42 (0.11 g, 0.35 mmol) was treated as described in procedure g to provide 6 (0.105 g, 91%) as colorless crystals: mp 136-137 °C (hexane/EtOAc); IR (KBr) 1676 (C=O), 1635, 1612, 1445, 1317, 750 cm⁻¹; ¹H NMR (CDCl₃) δ 3.52 (s, 3H), 3.88 (d, 1H, J = 10.7 Hz), 4.80 (d, 1H, J = 10.7 Hz), 7.01 (ddd, 1H, J = 1, 2, 9.3 Hz), 7.24 (dt, 1H, J = 1.1, 7.6 Hz), 7.38–7.50 (m, 2H), 7.55 (dt, 1H, J = 1.3, 7.7 Hz), 7.71 (s, 1H), 7.71 (m, 2H), 7.72 (s, 1H), 7.84 (d, 1H, J = 8.4 Hz); ¹³C NMR (CDCl₃) δ 170.82 (s), 167.52 (s), 160.00 (d, $J_{CF} = 252$ Hz), 140.22 (s), 134.28 (s), 132.04 (dd, $J_{CCCF} = 7$ Hz), 131.38 (d), 129.21 (d), 128.48 (d), 127.36 (d), 126.54 (d), 124.38 (dd, $J_{CCCCF} = 3$ Hz), 118.87 (d), 116.24 (dd, $J_{CCF} = 21$ Hz), 56.77 (dd), 35.61 (q); MS (EI) m/e 318 (M⁺, 100), 299 (27), 290 (C), H, N.

Attempted Conversion of (Fluorobenzoyl)naphthalene 24 into (Fluorobenzoyl)aminonaphthalene 26. 2-(2'-Fluorobenzoyl)-3-(N-benzoylamino)naphthalene (24) (100 mg, 0.27 mmol) was dissolved in ethanol (30 mL), and 5% NaOH solution was added. The mixture was heated to reflux for 2 h. After the ethanol was removed under reduced pressure, the aqueous solution was extracted with $CHCl_3$ (20 mL \times 3) and dried over MgSO₄. After the CHCl₃ was removed under reduced pressure, the residue was purified by a wash column which was eluted with hexane/EtOAc (3:1) to afford benz[b]acridin-12(5H)-one⁵⁸ (28) as light brown crystals (57 mg, 86%): mp 298 °C dec (lit.⁵⁸ mp 303 °C); IR (KBr) 3257 (NH), 1050, 1640, 1627, 1590 (C=O), 1335, 1104, 743 cm⁻¹; ¹H NMR (DMSO- d_6) δ 7.20 (dt, 1H, J = 1.9, 7.8 Hz), 7.42 (dt, 1H, J = 1.9, 7.9 Hz), 7.52 (d, 1H, J = 8.3Hz), 7.59 (dt, 1H, J = 2, 7.8 Hz), 7.74 (dt, 1H, J = 2, 7.9 Hz), 7.93 (s, 1H), 7.99 (d, J = 8.4 Hz), 8.15 (d, 1H, J = 8.3 Hz), 8.24 (d, 1H, J = 8.3 Hz)J = 8.1 Hz, 8.92 (s, 1H), 11.2 (br s, NH); MS (EI) m/e 245 (M⁺, 100), 216 (31), 189 (20), 140 (12).

Attempted Conversion of Aminonaphthalenecarbonitrile 12 and Amino Acid 14 into (Fluorobenzoyl)aminonaphthalene 26. A solution of 2-bromofluorobenzene (1.5 g, 8.8 mmol) in dry THF (30 mL) was cooled to -78 °C and n-BuLi (6 mL of 1.6 M, 9.6 mmol) was added dropwise to the solution. After the mixture was stirred for 20 min at -78 °C, a solution of naphthylnitrile 12 (0.54 g, 2.8 mmol) or 14 (individually) in 50 mL THF was added. After the mixture had been stirred for 5 h at -78 °C, the solution was stirred at -50 °C for three h (in both cases, the reaction was monitored by TLC and only starting material was observed). When the temperature was raised to -30 °C, the light yellow solution turned to brown. The reaction was then quenched with aq. saturated NH_4Cl solution (30 mL). The reaction mixture was worked up to provide starting 12 or 14 accompanied by biphenylene (213 mg) mp 112-114 °C (lit. $113-114)^{59}$; ¹H NMR (CDCl₃) δ 7.65 (dd, 4H, J = 2.8, 6.2 Hz), 8.65 $(dd, 4H, J = 2.8, 6.2 Hz); MS(EI) m/e 152 (M^+, 100).$

Supplementary Material Available: The *ab initio* optimized coordinates, connection tables, and Mulliken charges for the benzo-fused 1,4-benzodiazepines (1-3) and the parent 1-methyl-5-phenyl-1,4-benzodiazepin-2-one (3 pages). Ordering information given on any current masthead page.

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Three-dimensional molecular yardsticks to measure the volume of a receptor pocket in definite increments. The distances pictured are the van der Waals field range in the direction orthogonal to the plane of the paper.

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