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Syntheses of 5-thienyl- and 5-furyl-substituted benzodiazepines: probes of the pharmacophore for benzodiazepine receptor agonists

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Summary — The synthesis of 5-thienyl- and 5-furyl-substituted benzodiazepines is described. These compounds were employed to probe the lipophilic pocket (L_3) of the benzodiazepine receptor (BzR) and to determine the effect of occupation of L_3 on biological activity. Of the new analogs synthesized, the 5-(2-thienyl)-benzodiazepines **6a** and **7a** displayed high affinity for the BzR (IC_{50} 28 and 18 nM, respectively) and exhibited both anticonvulsant (ED_{50} ~ 9 and 3 mg/kg) and muscle relaxant (ED_{50} ~ 10 and 7 mg /kg) activity. The 5-(3-thienyl)benzodiazepines **6d** and **7d** displayed only moderate affinity for the BzR (IC_{50} 140 and 110 nM) and exhibited no biological activity (no anticonvulsant or muscle relaxant activity) at doses up to 40 mg/kg. The 5-(2-furyl)benzodiazepines (**6b**, **7b**, **19b** and **20b**) exhibit low affinities for the BzR. These *in vitro* and *in vivo* findings are consistent with our model suggesting that pocket L_3 is very sensitive to lipophilic effects. Thus, decreasing the lipophilicity of functional groups which occupy this region decreases ligand affinity at BzR. The 2'-halogen (F or Cl) substituent of the 5-phenylbenzodiazepines increases ligand affinity *in vitro* because the active conformation of the phenyl N(4)=C(5)-C(1')=C(2') moiety is *syn* rather than *anti*. The *syn* conformation permits the 2'-halogen (F or Cl) atom to interact at the hydrogen bonding site H_2 and form a stable three-centered hydrogen bond in the proposed ligand binding cleft. The 3-thienyl and 2-furyl groups decrease the lipophilicity of the substituent which occupies L_3 but do not form a hydrogen bond at H_2, thus resulting in a diminished affinity at BzR.

benzodiazepine receptor / agonist pharmacophore / 5-furylbenzodiazepine / 5-thienylbenzodiazepine / structure–activity relationship

Introduction

Several medically important classes of compounds (*eg*, benzodiazepines, barbiturates, neuroactive steroids, and inhalation agents) enhance activity at a family of ligand-gated ion channels collectively known as $GABA_A$ receptors [2]. In view of the therapeutic actions of compounds that affect $GABA_A$ receptors, this family of ligand-gated ion channels remains an important target for drug development. Chemically diverse classes of compounds (*eg*, benzodiazepines [3] β-carbolines [4], triazolopyridazines [5] and pyrazoloquinolinones [6]) bind with high affinities [7, 8] to a modulatory site on $GABA_A$ receptors originally referred to as the benzodiazepine receptor (BzR) [9, 10]. The pharmacological actions of BzR ligands span a continuum ranging from sedation and muscle relaxation (agonists) to seizures and anxiety (inverse agonists) [11, 12]. This spectrum of action results from the bidirectional modulation of GABA-gated chloride channels by BzR ligands. Thus, BzR agonists (*eg*, diazepam) augment while inverse agonists (*eg*, 3-methoxycarbonyl-β-carboline) inhibit the ability of GABA to hyperpolarize neuronal membranes [13].

Recently, an inclusive pharmacophore for ligand binding to benzodiazepine receptors has been described [7, 14, 15]. In comparison to the pharmacophore for inverse agonists, the agonist model contains one additional hydrogen bonding site of interaction (H_2) as well as two additional areas of lipophilic interaction (L_2 and L_3). Three areas of negative steric interaction (S_1, S_2 and S_3) between the ligand and the receptor-binding protein have also been defined [7, 14, 16]. Recent evidence suggests that full occupation of

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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) [7, 17, 18], while partial occupation of the same region with a propyl group (C-6) resulted in an anxiolytic/ anticonvulsant (6-propyloxy-4-methoxymethyl-β-carboline carboxylic acid ethyl ester, 6PBC) response devoid of muscle-relaxant activity, a so-called partial agonist profile [7, 17]. In agreement with this hypothesis, flunitrazepam, triazolam, brotizolam, midazolam, and diazepam are full agonists and contain, for example, a phenyl group at the 5-position which can fully occupy lipophilic area L_3. Imidazobenzodiazepines such as Ro 15-4513, Ro 15-1788, Ro 14-7437, Ro 15-3505, Ro 19-4603, Ro 16-6028, and Ro 17-1812, are devoid of this large phenyl ring at area L_3 and they exhibit antagonist, partial agonist or partial inverse agonist activities (table I) [3, 7, 19]. It appears these compounds cannot fully occupy the lipophilic region L_3 of the BzR (fig 1). One hypothesis resulting from these findings is that full interaction of BzR ligands at L_3 together with the agonist requirement (H_1, H_2, L_1 and L_2) leads to full agonist activity, and partial interaction at L_3 results in a partial agonist response [7, 14, 17]. In order to determine the effect of occupation of L_3 on pharmacological action, a series of 5-thienyl- and 5-furyl-substituted benzodiazepines have been designed and synthesized.

Chemistry

The present series of compounds were prepared in order to better define the characteristics of proposed lipophilic pocket (L_3) and its effects on the profile of *in vivo* activity. The synthetic strategies employed here have been reported in a previous paper [14, 20].

The 2-phenyl-6-halo-4*H*-benzo[2,3-*d*]-1,3-oxazin-4-ones **1a,b** were prepared by following work reported earlier [14, 20, 21]. Treatment of **1a** and **1b** (individually) with 1.2–1.3 equivalents of the lithium reagent at –30°C furnished the desired ketones **2a,b,c** accompanied by bis-(aryl) alcohol byproducts **3a,b,c**, respectively (scheme 1). Hydrolysis of the ketoamides **2a,b,c** (individually) under alkaline or acidic conditions provided the α–aminobenzophenones **4a,b,c**, respectively. The aminobenzophenones were readily converted into benzodiazepines **6a,b,c** and **7a,b,c** by following the earlier methods of Fryer and Sternbach (scheme 2) [14, 22, 23].

Attempts to prepare the 3-thienylaminophenylketone **4d** under the conditions described above were not successful. When the 3-bromothiophene was stirred with *n*-BuLi at –78°C [24] and then reacted with lactone **1a** at –30°C, a mixture of thienyl-substituted ketoamides was produced which was difficult to separate at this stage. Consequently, this mixture was hydrolyzed, acylated, and treated with ammonia as mentioned above [14, 22, 23], after which the components were separated to furnish two new benzodiazepines, **6a** and **6e**. The desired benzodiazepine **6d** was not isolated from this mixture. Evidently, when 3-bromothiophene was treated with *n*-BuLi, 3-thienyllithium **8** was formed by a lithium-halogen exchange reaction (see scheme 3). Under the reaction conditions, the 3-thienyllithium **8** then reacted with excess 3-bromothiophene to provide **9** and thiophene. The 3-thienyllithium **8** then reacted with the newly formed thiophene to generate the more stable isomeric 2-thienyllithium **10**. Both lithium reagents **9** and **10** reacted with lactone **1a** and the mixture of ketones so formed was converted into the benzodiazepines **6a** and **6e**, according to the method of Fryer [22]. The structures were confirmed by IR, MS, and proton NMR decoupling experiments.

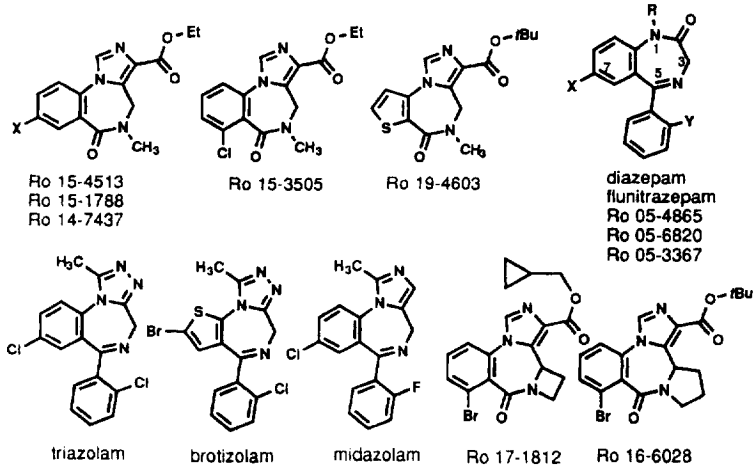
In order to circumvent this problem, 4-chloroaniline was converted into the pivoylamide **11** and this amide was treated with 2.1 equivalents of *n*-BuLi [25]. The mixture that resulted was stirred with 3-thienylaldehyde to produce the desired alcohol **12** in 85% yield. The alcohol **12** was oxidized to ketone **13** by PDC and subsequent hydrolysis provided the aminoketone **4d** (scheme 4). This material was then converted under the conditions of Fryer and Sternbach [14, 22, 23] into benzodiazepines **6d** and **7d** (individually) in excellent yield (scheme 2).

The naphthoxazone **14** [14, 20] was reacted (individually) with 2-thienyl or 2-furyllithium to furnish ketoamides **15a, b** in 65 and 54% yields, respectively. The amide **15a** was readily converted into benzodiazepines **19a** and **20a** by following the strategies mentioned above (scheme 5). However, the amide **15b** decomposed under both alkaline or acidic conditions required for the hydrolysis. In order to circumvent this problem, the 3-amino-2-naphthoic acid **21** was converted into 2-chloromethyl naphthoxazinone **22** by reaction with chloroacetyl chloride and the product was reacted with 2-furyllithium to furnish the acetoamide **18b** (scheme 6). The acetoamide **18b** was then stirred with ammonia to provide benzodiazepine **19b** and this was followed by methylation (NaH, CH_3I) to produce the desired 5-furyl analog **20b** (scheme 5).

Biological results and discussion

The affinities of these new 1,4-benzodiazepines at the BzR were evaluated by previously reported methods [14, 16]. Illustrated in table II are the IC_{50} values of these 5-substituted analogs. The 2-thienyl-substituted heterocycles **6a** and **7a** displaced [^{3}H]flunitrazepam from rat cortical BzR with high affinity (IC_{50} = 28 and 18 nM). When a bromine atom was substituted for hydrogen at the 4'-position of the thienyl ring, the

Table I. The *in vitro* and *in vivo* activity of imidazobenzodiazepines and 5-phenylbenzo[1,4]diazepines [3, 19].



Ligands	X	Y	R	IC_{50}(nM)	Profiles
Ro 15-4513	N_3			7.3±1.6	partial inverse agonist[19]
Ro 15-1788	F			1.1±0.1	antagonist[19]
Ro 14-7437	H			1.8±0.1	antagonist[19]
Ro 15-3505				0.3±0.0	partial inverse agonist[19]
Ro 19-4603				0.3±0.0	partial inverse agonist[19]
Ro 16-6028				0.7±0.1	partial agonist[19]
Ro 17-1812				0.1±0.0	partial agonist[19]
Ro 05-4865	F	H	CH_3	17	agonist[3]
Ro 05-6820	F	F	H	7.4	agonist[3]
Ro 05-3367	Cl	F	H	2.0	agonist[3]
flunitrazepam	NO_2	F	CH_3	3.8	full agonist[3]
triazolam				1.1±0.1	full agonist[3, 19]
brotizolam				0.6±0.1	full agonist[3, 19]
midazolam				1.1±0.1	full agonist[3, 19]
diazepam	Cl	H		8.1	full agonist[3, 19]

analog (**6e**) exhibited low affinity (IC_{50} = 462 nM). In comparison to the 2-thienyl-substituted congeners (**6a** and **7a**), the 3-thienyl-substituted analogs (**6d** and **7d**) also exhibited moderate affinities at BzR (IC_{50} = 140 and 110 nM); the 3-thienyl analogs are approximately five times less potent. The furyl analogs (**6b** and **7b**) exhibited low affinities for BzR. The rank order of potencies of 5-substituted benzodiazepines listed in tables I and II follows the order of 2-halophenyl > phenyl > 2-thienyl > 3-thienyl > 2-furyl.

Usually furan and thiophene are considered to be bioisosteres of a phenyl ring (flat aromatic ring) [26]. Classically, furan and thiophene are considered to be electron-rich π systems [27]. The size [28] of these aromatic rings follows the order phenyl ≥ thienyl > furyl and the lipophilic area L_3 of the receptor should accept the thiophene or furan ring readily based on steric considerations. It had been suggested that replacement of the 5-phenyl ring of diazepam with a thiophene ring might reduce steric interactions and enhance ligand affinity at BzR [29]. However, the *in vitro* results obtained here are not consistent with this hypothesis [29].

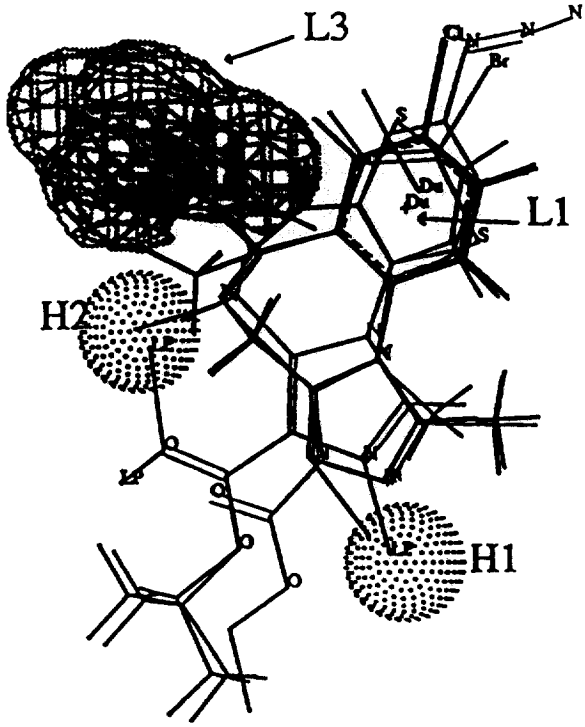
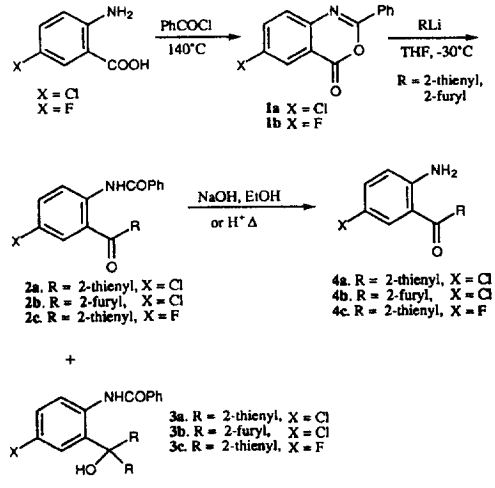
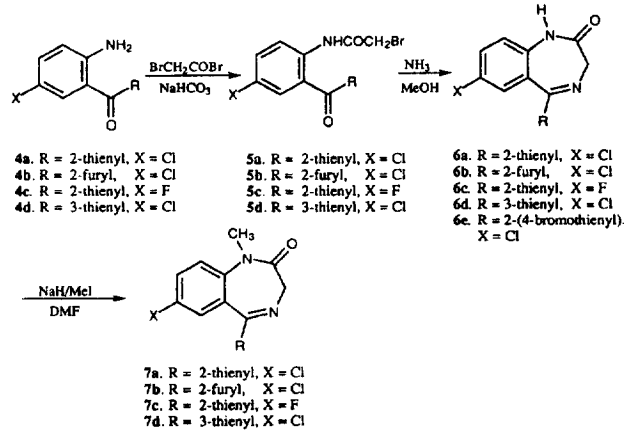


Fig 1. The volume of region L_3 for full agonists (full occupation of this region as well as interactions at H_1, H_2, L_1 and L_2 is believed necessary for a ligand to exhibit a full agonist profile). The volume was derived from the subtraction of the combined antagonist, partial inverse agonist, and partial agonist imidazobenzodiazepine volumes of Ro 15-1788, Ro 15-4513, Ro 17437, Ro 15-3505, Ro 16-6028, and Ro 19-4603 at region L_3 from the combined volumes of the full agonists triazolam, midazolam, brotizolam, flunitrazepam, and diazepam at region L_3.

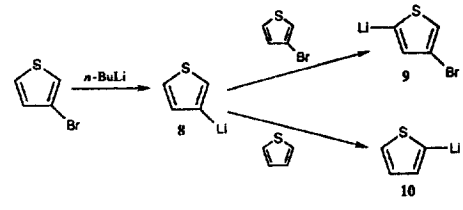
A CoMFA [30] study was initiated to understand the affinities of the analogs represented in tables I and II. The alignment employed here was identical to that reported earlier in the agonist and inclusive pharmacophores [7, 14, 15]. Three points were employed in the least squares fitting of these structures. These points were the centroid of ring-A, the lone pair of electrons on the nitrogen atoms of ring-D (N2 or N3) or the C=O of diazepam, and the lone pair of electrons on the B-ring imine nitrogen atom (N5). The length of the lone pair of electrons of the nitrogen atoms N2, N3, and N5 was extended to 1.84 Å to mimic an ideal hydrogen bond [31–36]. For brotizolam and triazolam, the imine nitrogen atom N3 interacts with the common receptor site descriptor H_1. When ring-D was replaced with an imidazole heterocycle as in midazolam, the interaction with H_1 occurred through the imine nitrogen atom (N2).



Scheme 1.

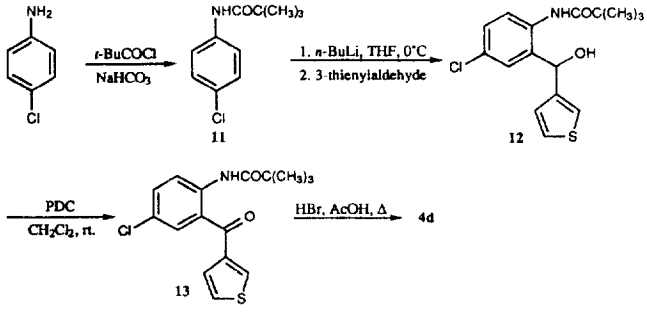


Scheme 2.

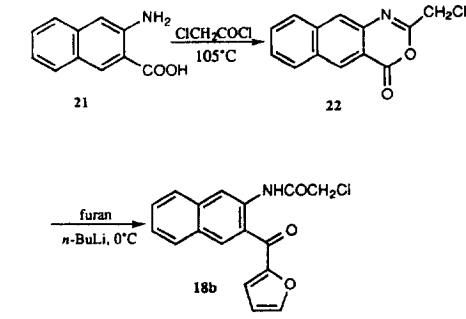


Scheme 3.

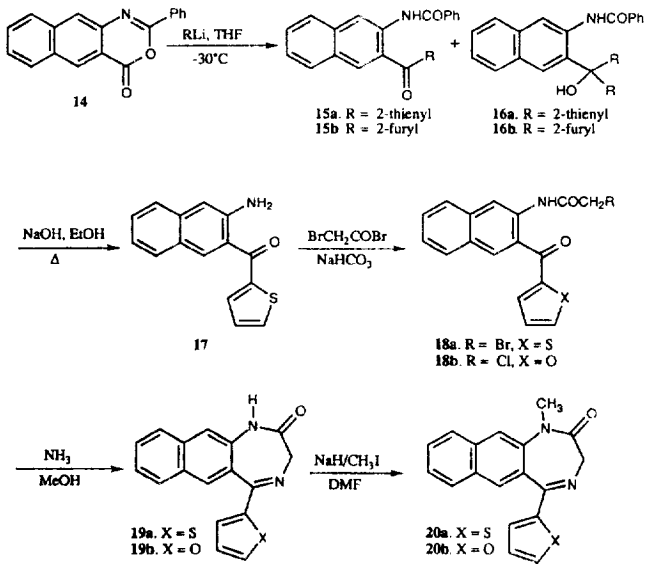
One important issue is the conformation of the 2'-substituted phenyl, thienyl and furyl rings at the 5- or 6-position in the benzodiazepine analogs listed in



Scheme 4.



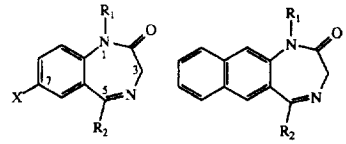
Scheme 6.



Scheme 5.

tables I and II, respectively. To strictly define the relative stability of *syn* and *anti* conformations for the 5-arylbenzodiazepines, some of the model benzodiazepines as shown in table III were calculated using both empirical MM2 and *ab initio* methods (see *Experimental protocols*) [36, 37] and compared with those observed in the X-ray crystallographic structures. The results demonstrated that there is a surprisingly good correlation between the N4=C5-C1'-C2' torsional angle observed in the *ab initio* 6-31G* optimized structures and the *average* torsional angle observed in the X-ray crystallographic structures (table III). The relative energy differences between *syn* and *anti* conformations are consistent and relatively small from both MM2 and *ab initio* calculations. This established that MM2 can be reliably used to predict the relative energy differences between *syn* and *anti* conformations for the compounds listed in tables I and II. Examination of energies *via* MM2 calculations shows the low energy conformations of **7a** and **7b** are *syn* [N(4)=C(5)-C(1')-S(O) torsion angle less than 90° (**7a**, 15.3°; **7b**, 13.4°); ΔE (*syn* – *anti*) = –3.86, –2.29 kcal/mol, respectively]. The low energy conformation of **7d** is *anti* [(N(4)=C(5)-C(1')-C(2') greater than 90° but less than 270°] which is –2.19 kcal/mol lower in energy than the *syn* conformer. The conformation of the 2'-substituted phenyl ring was calculated to be *anti* [(N(4)=C(5)-C(1')-C(2') greater than (90°)] which is similar to that reported in the literature [29] and is due to the steric and the electrostatic (repulsion) interactions between the electronegative substituent (halogen) and the imine nitrogen atom [29]. However, the bioactive conformation of these ligands may not be the global minimum energy conformation [29]. In the calculations employed here, the ΔE (*anti* – *syn*) in these 2'-halogen (F or Cl) analogs is less than –0.5 kcal/mol. Therefore, it is possible that the active conformation of the 2'-halogen (F or Cl) substituted phenyl ring at C(5) of the benzodiazepines is *syn* [N(4)=C(5)-C(1')-C(2') torsion angle less than 90°]. In the *syn* conformation, these halogen atoms apparently act as a hydrogen bonding auxiliary for the imine nitrogen atom N5 (designated N4 in diazepam) and can interact at H_2 to form a more stable, three-centered hydrogen bond which enhances ligand affinity. This type of hydrogen bond has been observed in the crystal structure of the hydrochloride salt of a 5-(2'-fluorophenyl)-1,4-benzodiazepine by Petcher and Widmer [37]. The formation of this stable three-centered hydrogen bond more than compensates for the small energy changes (*anti* to *syn*) in the 2'-halogen-substituted phenyl ring. This plasticity (flexibility) [14] in the binding cleft is permitted

Table II. *In vitro* and *in vivo* data of new benzodiazepine ligands at the BzR.



19a-b and 20a-c

Ligands	R_1	R_2	X	IC_{50} (nM)[a]	anticonvulsant ED_{50} (mg/kg)	muscle relaxation ED_{50} (mg/kg)
6a	H	2-thienyl	Cl	28±7	9	10
6b	H	2-furyl	Cl	267±17	*n.t.*	*n.t.*
6c	H	2-thienyl	F	130±13	*n.t.*	*n.t.*
6d	H	3-thienyl	Cl	140±25	> 40	> 40
6e	H	4-Br-2-thienyl	Cl	462±40	*n.t.*	*n.t.*
7a	CH_3	2-thienyl	Cl	18±3	3	7
7b	CH_3	2-furyl	Cl	269±13	*n.t.*	*n.t.*
7c	CH_3	2-thienyl	F	73±3	*n.t.*	*n.t.*
7d	CH_3	3-thienyl	Cl	110±5	> 40	> 40
nordiazepam		phenyl	Cl	9.4[3]		
diazepam	CH_3	phenyl	Cl	8.1[3]		
delorazepam	H	2-chlorophenyl	Cl	1.8[3]		
Ro 05-3367	H	2-fluorophenyl	Cl	2[3]		
bromazepam	H	2-pyridyl	Br	18[3]		
20a	H	2-thienyl		226±4	*n.t.*	*n.t.*
19a	CH_3	2-thienyl		814±50	*n.t.*	*n.t.*
19b	H	2-furyl		> 1000	*n.t.*	*n.t.*
20b	CH_3	2-furyl		> 1000	*n.t.*	*n.t.*
20c[14]	CH_3	2-fluorophenyl		55±2	15	15

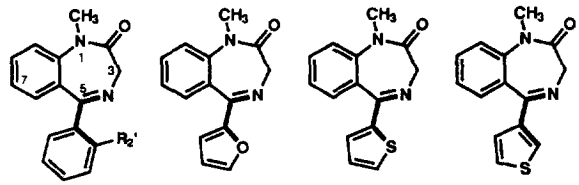
[a]Values for new (previously unpublished) compounds are listed with statistical limits and represent $\bar{X}$ of three or more experiments. Ligands with IC_{50} > 200 nM were generally not tested *in vivo* in this series. *nt* = not tested.

because of the interaction of H_2 with the 2'-halogen atom as well as the N(4) nitrogen atom and these ligands fit into the BzR binding site without loss of the important interactions at H_1, H_2, L_1, L_2 and L_3.

On the basis of this analysis, the final CoMFA statistics indicate a good correlation (r^2 = 0.841). In the steric CoMFA map (fig 2), there is a region of negative steric interaction. The 4'-bromine atom in **6e** interacts with this negative steric region and consequently this ligand exhibited low affinity at the BzR.

From the electrostatic map (fig 3), it would be predicted that increasing negative electrostatic potential in an area around the imine (N4) nitrogen atom and the 2'-position would increase ligand affinity. The analogs **6a** and **6b** have an electronegative atom (sulfur or oxygen) close to the region. Because the sulfur or oxygen atoms are in the aromatic ring (thiophene or furan) and one of the lone pairs of electrons on the sulfur or oxygen atoms participates in the aromatic system (delocalization), these atoms do not

Table III. Relative energies and N4=C5-Ar torsional angles of the *syn* and *anti* conformers of the fully geometry optimized 5-phenyl, 5-(2'-furyl), 5-(2'-thienyl), and 5-(3'-thienyl)-1,4-benzodiazepine derivatives and comparisons with the torsional angles observed in X-ray crystallographic structures.



5-(2'-furyl) 5-(2'-thienyl) 5-(3'-thienyl)

R_2'	torsion angle (degrees)[1]			relative energy (kcal/mol)	
	X-ray	MM2*	6-31G*	MM2*	6-31G*
H	-28 ± 9 (n = 21)[2]	-41.5	-29.8	N/A[5]	N/A[5]
"	150 ± 8 (n = 21)[2]	136.4	148.0	"	"
F		-47.4	-49.6	0.44	1.56
"	133 ± 6 (n = 2)[3]	130.9	136.8	0.00	0.00
Cl		-56.0	-65.3	0.60	1.09
"	116 ± 10 (n = 3)[4]	121.2	123.5	0.00	0.00
Br		-58.9	N/C[6]	0.69	N/C[6]
"		118.4	"	0.00	"
I		-61.0	"	0.56	"
"		118.6	"	0.00	"
5-(2'-furyl)		-13.8	-15.9	0.00	0.93
"		160.4	163.5	2.18	0.00
5-(2'-thienyl)		-18.9	-15.8	0.00	0.00
"		139.4	150.8	0.19	1.85
5-(3'-thienyl)		-34.4	-27.6	0.43	1.16
"		160.5	159.2	0.00	0.00

[1]For 5-phenyl derivatives, torsion angle is defined using the N4=C5-C1'-C2' atoms, and for the 5-(2'-furyl), 5-(2'-thienyl), and 5-(3'-thienyl) analogs, the torsion angle is defined by the N4=C5-C2'-O1', N4=C5-C2'-S1', and N4=C5-C3'-C2' atoms respectively. [2]CSD reference codes (see *Experimental protocols* for details): BAZCLH, BEDZPN10, BIZSAE, BOMMUL, CHABZN, DCDAZP, DIZPAM10, FLDAZP-1, FLDAZP-2, FULWUE, FUMZES-1, FUMZES-2, PRAZAM-1, PRAZAM-2, SABJEK-1, SABJEK-2, VERZEX, VICFIW, ZZZAUS20-1, ZZZAUS20-2, ZZZAUS20-3. [3]CSD reference codes: FIMPIA, GIPKEV. [4]CSD reference codes: CLDZPB, FAFNEF, JIPHAR. [5]N/A = not applicable (since the *syn* and *anti* conformers for R_2' = H are degenerate). [6]N/C = not calculated.

exhibit the necessary electrostatic contribution to form a hydrogen bond at H_2 [38-41]. Although examination of MNDO calculations indicates a charge on sulfur (thienyl) of +0.344 and on oxygen (furyl) of –0.101, it is well recognized [38-41] that a hydrogen bond between an active proton and the heteroatom of furan or thiophene is substantially weak or negligible. This helps to explain why the thienyl and furyl analogs do not bind as tightly as their 2'-halo-substituted phenyl analogs do at the BzR.

Furthermore, as expected, the lipophilicity of the 5-substituent that interacts with L_3 seems to play an important role. The lipophilicity of the phenyl, thienyl and furyl rings follows the order phenyl > thiophene > furan [42]. Increasing the lipophilicity of the aromatic substituents that occupy L_3 increases the affinity (*eg*, diazepam > **7a** > **7b**, see table II). These results further demonstrate the lipophilic nature of this region of the binding site. If the electronegative atom near the H_2 hydrogen bonding site can interact with H2 (2'-F or 2'-Cl), it will enhance ligand affinity. On the other hand, if this electronegative atom does not or only weakly interacts with H_2 (oxygen or sulfur atom in the furan or thiophene ring) its presence only reduces the lipophilicity of the 5-substituent and ligand affinity will be reduced. Bromazepam has a

highly polar 2'-pyridine ring at C(5) of the 1,4-benzodiazepine nucleus and exhibits high affinity for BzR (IC_{50} = 18 nM [3]), presumably because the nitrogen atom in the pyridine ring can form a strong hydrogen bond at the H_2 hydrogen bonding site. In contrast, the 4'-pyridyl analog does not bind tightly to the BzR [43]. Similarly, analogs **6d** and **7d** exhibit lower affinity than **6a** and **7a** suggesting that L_3 cannot tolerate a hydrophilic group deep in this lipophilic pocket.

We have recently reported [14] that a 7,8-benzofused benzodiazepine **20c** with a 2'-fluorine substituent (molecular yardstick) exhibits both high affinity and a full agonist profile of activity at BzR. The new benzofused analogs **20a, b** exhibit low affinity *in vitro* and follow the same pattern (2'-fluorophenyl > phenyl > 2'-thienyl > 2'-furyl) as the 7-halo series (Ro 05-3367, diazepam, **7a**, and **7b**) described here. The effects of lipophilicity with regard to L_3 are consistent with the results mentioned above.

Pharmacological studies indicate that **6a** and **7a** are full agonists [17]. The ED_{50} for the anticonvulsant effects of **6a** and **7a** was 9 and 3 mg/kg, respectively, and the ED_{50} for the myorelaxant effects was 10 and 7 mg/kg, respectively. Apparently, the thiophene fully interacts with the lipophilic area L_3 and results in full agonist activity; thiophene is a much better bioisostere for phenyl than furan. The furyl analogs **6d** and **7d** do not exhibit anticonvulsant activity and myorelaxant effects in mice even at does up to 40 mg/kg presumably because of low affinity.

Since rat cortical membranes were used to estimate ligand affinities, the reported potencies are likely to represent the weighted average of several $GABA_A$ receptor isoforms. Although speculative, it is possible to predict that both ligand potency 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). While it is not known whether transfected cells expressing varions $GABA_A$ 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. Although the differences are small, it is important to note that the potency of the anticonvulsant effects of **7a** have increased at the expense of the muscle relaxant effects in contrast to the 7,8-benzofused benzodiazepine **20c** reported earlier [14]. Attempts to correlate the muscle relaxant effects of these agonists with lipophilic pockets L_2 and L_3 *via* receptor subsite selectivity are underway.

Both the *in vitro* and *in vivo* data contained herein are consistent with the previously reported agonist pharmacophore [7, 14, 15]. The interaction at L_3 of the BzR is a lipophilic interaction. Decreasing the lipophilicity of ligands in this region will reduce the

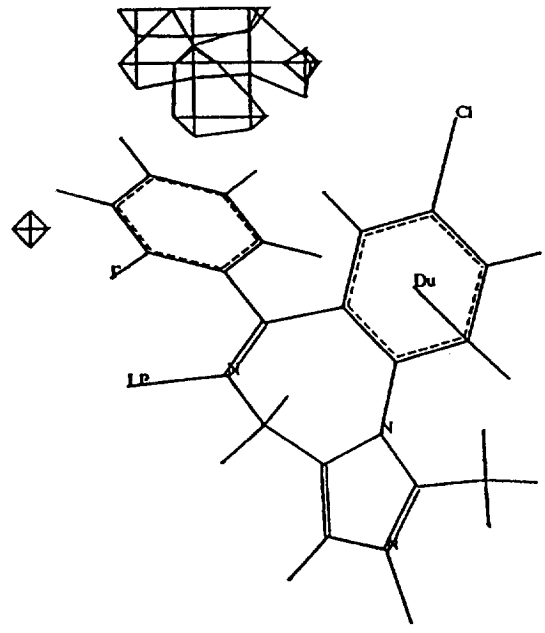


Fig 2. Agonist steric CoMFA map. The contours define regions wherein a higher steric interaction is predicted to decrease affinity to BzR.

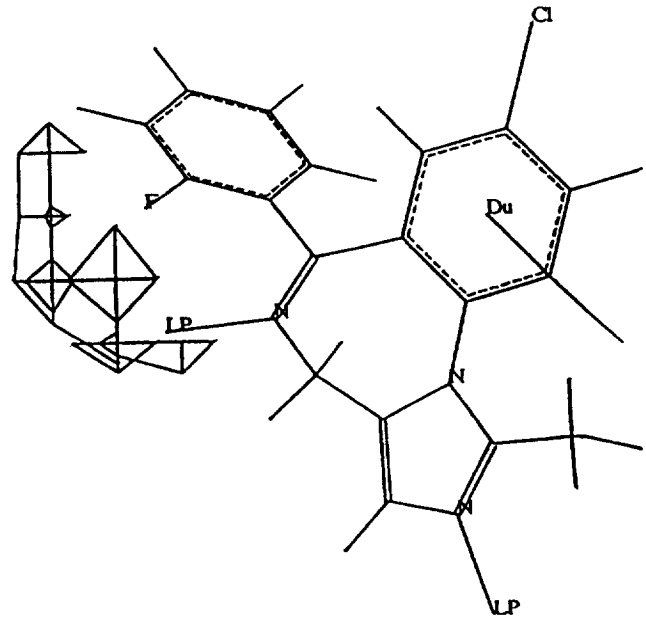


Fig 3. Agonist electrostatic CoMFA map. The contours define regions wherein a more negative electrostatic interaction is predicted to increase affinity to BzR.

affinity at BzR unless the polar group can form a hydrogen bond at H_2. The 2'-halogen (F or Cl) substituent on the 5-phenyl ring of the 1,4-benzodiazepines assists in formation of a three-centered hydrogen bond at H_2 in the binding site at BzR and increases affinity. Therefore, the active conformation of the 2'-halogen (F or Cl) substituted 5-phenyl rings of the 1,4-benzodiazepines, imidazobenzodiazepines, and the triazolobenzodiazepines is believed to be *syn* [N(4)=C(5)-C(1')-S torsion angle less than 90°] rather than the global minimum energy conformation [*anti*, N(4)=C(5)-C(1')-S torsion angle greater than 90°] [29]. This is in complete agreement with the previous hypothesis put forth from this laboratory [44, 45]; ligands which can rotate to a planar or pseudoplanar topography exhibit potent affinity at the BzR [44, 45]. The analogs **6a** and **7a** exhibit full agonist activity because the size of the thienyl and phenyl rings is similar. Further studies of the relationship between the lipophilic area L_3, ligand efficacy and subtype selectivity are in progress.

Experimental protocols

In vitro methods

The potencies of test compounds to displace [^{3}H]flunitrazepam from benzodiazepine receptors were determined through a modification of previously described procedures [15, 16, 46]. 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 20 000 *g*. 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 use. Incubations (0.5 ml) consisted of tissue suspension (0.1 ml, ~0.1 mg protein), 0.05 ml NaCl solution (2.0 M), 0.05 ml [^{3}H]flunitrazepam (final concentration, ~1 nM, Spec Act 83.4 Ci/mmol), and drugs and/or buffer to equal volume. Ro 15-1788 was used to determine non-specific binding (final concentration 10 μM). Incubations (0–4°C) were initiated by addition of radioligand and terminated after 60 min by rapid filtration under vacuum through GF/B filters with two 5 ml washes of ice-cold buffer. IC_{50} values were estimated using InPlot 4.0 (GraphPAD, San Diego, CA) with at least six concentrations of inhibitor. Values represent X ± SEM of at least 3 determinations. Compounds with potencies > 1000 nM were generally only tested twice.

In vivo methods

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 3–8 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 < 1 min was positive for muscle relaxation. Fifteen minutes post injection mice were injected with PTZ (80 mg/kg) to assess anticonvulsant activity. In vehicle-treated mice, 80 mg/kg PTZ produced tonic and clonic convulsions in 100% of the animals. 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

The Cambridge Structural Database (CSD) 1,4-benzodiazepine substructure searches were performed using the 3/3/94 update of the database (120 481 entries) and Quest Version 5.7 [47]. Structures in which the N4 nitrogen atom was either complexed with a metal, protonated, or engaged in a hydrogen bonding interaction were excluded from the averages listed in table III. The starting geometries of the ligands were taken either from X-ray crystallographic structures [19, 48-51] or generated using Concord [52]. All bond lengths and valence angles of these structures were fully optimized with Gaussian 90 [53] or 92 [54] *ab initio* calculations (Gaussian Inc Carnegie-Mellon University, Pittsburgh, PA, USA) at the 3-21G or 6-31G* 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 (version 5.5, Tripos Associates, Saint Louis, MO, USA). The side chains were optimized (holding the heterocyclic core structures fixed) using MacroModel BatchMin version 4.0 (Columbia University, New York, NY, USA) [55]. Calculations of ring centroids, least squares fitting, and included volume analyses [56] 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 degrees, respectively, to mimic the geometry of an ideal hydrogen bond [31–36]. The receptor modeling strategy employed here has been applied earlier for the inverse agonist/antagonist and agonist pharmacophores, [7, 14, 15, 46]. The molecular mechanics calculations were performed using the MM2 force field [57] contained within MacroModel version 4.5 [55] (available from Columbia University New York, NY 10027), and the default Polak-Ribiere conjugate gradient minimizer followed by a final optimization with the full matrix Newton Raphson method. Both the Sybyl and MacroModel calculations were performed on a Silicon Graphics Indigo Extreme Workstation or on a Silicon Graphics Personal Iris 4D/35 Workstation.

Chemistry

Melting points were taken on 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). Infrared spectra were recorded on a Nicolet DX FTIR spectrophotometer or a Beckman Acculab-1 or a Mattson Polaris IR-10400. Mass spectral data (EI/CI) were obtained on a Hewlett-Packard 5885 mass spectrometer or 5985B GC-mass spectrometer. Microanalyses were performed on an F and M Scientific Corp model 185 or Perkin-Elmer 240C carbon, hydrogen, and nitrogen analyzer and analyses indicated by the symbols of elements or functions were within ±0.4% of theoretical values. Analytical TLC plates employed were E Merck Brinkman UV active silica gel (Kieselgel 60 F254) on plastic. Flash chromatography was carried out on silica gel 60b purchased from EM Laboratories. All chemicals were purchased from Aldrich Chemical Co unless otherwise stated. All reactions were run under a nitrogen atmosphere.

6-Chloro-2-phenyl-4H-benzo[2,3-d]-1,3-oxazin-4-one **1a**
The 2-amino-5-chlorobenzoic acid (85 g, 0.5 M) was treated with benzoyl chloride (400 ml) at 140°C for 3 h. After the reaction mixture was cooled to rt, the crystals which formed were collected by filtration and were washed with hexane to provide **1a** as colorless needles (125 g, 92%): mp 201–202.7°C; IR (KBr) 3060, 1757 (C=O), 1618, 1467, 1253, 1044, 778, 685 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.40–7.60 (m, 3H), 7.63 (d, 1H, J = 8.6 Hz), 7.75 (dd, 1H, J = 3.2, 8.6 Hz), 8.19 (d, 1H, J = 2.4 Hz), 8.28 (m, 2H); ^{13}C-NMR ($CDCl_3$) δ 158.39 (s), 157.30 (s), 145.47 (s), 136.79 (d), 133.62 (s), 132.65 (d), 129.86 (s), 128.85 (d), 128.77 (d), 128.43 (d), 127.92 (d), 118.08 (s); MS (EI) *m/e* 259 (M^+, 7), 257 (M^+, 20),105 (100); anal $C_{14}H_8ClNO_2$ (C, H, N).

6-Fluoro-2-phenyl-4H-benzo[2,3-d]-1,3-oxazin-4-one **1b**
The 2-amino-5-fluorobenzoic acid (10 g, 64.5 mmol) was treated with benzoyl chloride (50 ml) under conditions analogous to the preparation of **1a** to provide **1b** as a colorless solid (14.6 g, 93%): mp 136–137°C; IR (KBr) 3108, 1752 (C=O), 1625, 1575, 937, 873 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.52 (m, 4H), 7.69 (dd, 1H, J = 4.9, 8.9 Hz), 7.87 (dd, 1H, J = 3, 7.8 Hz), 8.27 (m, 2H); MS (EI) *m/e* 241 (M^+, 69), 197 (52), 164 (13), 108 (53), 105 (100); anal $C_{14}H_8FNO_2$ (C, H, N).

4-Chloro-2-(2'-thienylcarbonyl)-N-benzoylaniline **2a** *and bis-(2'-thienyl)[5-chloro-2-(N-benzoyl)amino]phenylmethanol* **3a**. *Procedure a*
The benzoxazinone **1a** (5 g, 19 mmol) was dissolved in dry THF (50 ml) and cooled to –30°C. The thienyllithium (9.4 ml of 2.5 M solution, 23.5 mmol) was added over 5 min and the mixture was stirred at –30°C for 20 min. Saturated aq NH_4Cl solution (20 ml) and ethyl ether (30 ml) were then added. The organic layer was separated, washed with water, and dried ($MgSO_4$). After the solvent was removed under reduced pressure, the residue was purified *via* flash chromatography (hexane/EtOAc (4:1)) to provide **2a** as light-yellow crystals (4.1 g, 62%) and **3a** (1.4 g, 17%).

2a: mp 117–118.8°C (hexane/EtOAc); IR (KBr) 3318 (NH), 3084, 1681, 1598, 1289, 914, 697 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.21 (dd, 1H, J = 4, 4.9 Hz), 7.64 (m, 5H), 7.78 (dd, 1H, J = 1, 4.9 Hz), 7.84 (d, 1H, J = 2.4 Hz), 7.98 (dd, 2H = 1.4, 7.7 Hz), 8.76 (d, 1H, J = 9 Hz), 11.21 (br s, 1H, NH); ^{13}C-NMR ($CDCl_3$) δ 189.00 (s), 165.50 (s),143.32 (s), 138.41 (s), 135.90 (d), 135.51 (d), 134.15 (s), 133.72 (d), 132.21 (d), 131.42 (d), 128.87 (d), 128.33 (d), 127.71 (s), 127.33 (d), 125.44 (s), 123.30 (d); MS (EI) *m/e* 341 (M^+, 3), 332 (1), 230 (3), 111 (3), 105 (100); anal $C_{18}H_{12}ClNO_2S$ (C, H, N).

3a: mp 146.6°C (dec, hexane/EtOAc); IR (KBr) 3375 (OH), 3302 (NH), 3105, 1656, 1576, 1527, 827, 710 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 3.87 (br s, 1H, OH), 6.78 (m, 2H), 6.83 (d, 1H, J = 2.5 Hz), 6.94 (m, 2H), 7.38–7.30 (m, 6H), 7.63 (d, 2H, J = 7.1 Hz), 8.47 (d, 1H, J = 8.8 Hz), 9.84 (br s, 1H, NH); MS (EI) *m/e* 425 (M^+, 1), 407 (2), 302 (5), 111 (11), 105 (100).

4-Chloro-2-(2'-furoyl)-N-benzoylaniline **2b** *and bis-(2'-furyl)-[5-chloro-2-(benzoyl)amino]phenylmethanol* **3b**
The 2-bromofuran (1.69 g, 11.5 mmol) was dissolved in dry THF (10 ml) and *n*-BuLi (5.1 ml of 2.5 M solution, 13 mmol) was added to the solution at –78°C. After 10 min, the solution was added to a solution of the lactone **1a** (3 g, 11.5 mmol) in dry THF (150 ml) which had been precooled to –30°C. The sequence was then executed according to *Procedure a* to provide **2b** (2.16 g, 58%) and **3b** (0.64g, 14%), respectively.

2b: mp 103–104.3°C (hexane/EtOAc); IR (KBr) 3359 (NH), 3125, 1670 (C=O), 1630, 1516, 1387, 906, 709 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 6.64 (dd, 1H, J = 2, 3.8 Hz), 7.28 (dd, 1H, J = 0.8, 3.8 Hz), 7.29–7.61 (m, 4H), 7.77 (m, 1H), 8.00 (m, 3H), 8.80 (d, 1H, J = 9.2 Hz), 11.50 (br s, 1H); ^{13}C-NMR ($CDCl_3$) δ 183.18 (s, C=O), 165.58 (s), 151.72 (s), 148.23 (d), 139.11 (s), 134.20 (s), 134.04 (d), 132.21 (d), 131.13 (d), 128.87 (d), 127.73 (s), 127.36 (d), 124.28 (s), 123.10 (d), 122.42 (d), 112.74 (d); MS (EI): 327 (M^+, 1), 325 (M^+, 4), 230 (2), 105 (100); anal $C_{18}H_{12}ClNO_3$ (C, H, N).

3b: mp 153°C (dec, hexane/EtOAc); IR (KBr) 3287, 3067, 1655 (C=O), 1577, 1519, 1397, 739 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 9.89 (br s, 1H, NH), 8.42 (d, 1H, J = 8.8 Hz), 7.67–7.63 (m, 2H), 7.47–7.44 (m, 3H), 7.41–7.35 (m, 4H), 6.35–6.32 (dd, 2H, J = 1.8, 3.3 Hz), 6.07 (dd, 2H, J = 0.7, 3.2 Hz), 3.76 (br s, 1H, OH); MS (EI) *m/e* 393 (M^+, 1), 375 (2), 270 (2),105 (100).

4-Fluoro-2-(2'-thienylcarbonyl)-N-benzoylaniline **2c**
The lactone **1b** (7 g, 29 mmol) was reacted with 2-thienyllithium (35 ml of 1 M solution, 35 mmol) analogous to the conditions under *Procedure a* to provide **2c** (6.72 g, 71%) as light-yellow crystals: mp 126–128°C (hexane/EtOAc); IR (KBr) 3353, 3107, 1680, 1672, 1616, 955, 815 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.19 (dd, 1H, J = 3.9, 5.0 Hz), 7.35 (m, 1H), 7.57 (m, 4H), 7.64 (dd, 1H, J = 1.1, 3.9 Hz), 7.78 (dd, 1H, J = 1.1, 5.0 Hz), 7.97 (m, 2H), 8.75 (m, 1H), 11.11 (br s, 1H); MS (EI) *m/e* 325 (M^+, 7), 220 (1), 214 (7), 148 (2), 105 (100); anal $C_{18}H_{12}FNO_2S$ (C, H, N).

4-Chloro-2-(2'-thienylcarbonyl)aniline **4a**, *Procedure b*
The amide **3a** (4 g, 11.7 mmol) was dissolved in ethanol (100 ml) and 10% NaOH solution (20 ml) was added. The mixture was heated to reflux for 5 h and the ethanol was removed under reduced pressure. The mixture was extracted with $CHCl_3$ (50 ml x 2) and the $CHCl_3$ solution was washed with water and dried ($MgSO_4$). After the $CHCl_3$ was removed, the residue was purified *via* a wash column on silica gel (hexane/EtOAc (3:1)) to provide **4a** as dark-green crystals (2.52 g, 90%): mp 100.2–101.5°C (lit [58] 95–97°C).

4-Chloro-2-(2'-furoyl)aniline **4b**
The amide **2b** (1 g, 3 mmol) was hydrolyzed as described in *Procedure b* to produce **4b** (0.51 g, 74%) as yellow crystals: mp 111–112°C (lit [58] 113–115°C).

4-Chloro-2-(3'-thienylcarbonyl)aniline **4d**
The *t*-butylketoamide **13** (1 g, 3.1 mmol) was treated analogous to *Procedure b* to provide **4d** (680 g, 95%) as orange crystals: mp 128–129°C (hexane/EtOAc); IR (KBr) 3416, 3311 (NH_2), 3107, 1623 (C=O), 1539, 1251, 814, 759 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 5.80 (br s, 2H), 6.66 (d, 1H, J = 8.7 Hz), 7.22 (dd, 1H, J = 2.5, 8.7 Hz), 7.37 (dd, 1H, J = 2.9, 5 Hz), 7.45 (dd, 1H, J = 1.3, 5 Hz), 7.60 (d, 1H, J = 2.5 Hz), 7.8 (dd, 1H, J = 1.3, 2.8 Hz); MS (EI) *m/e* 237 (M^+, 46), 220 (13), 204 (100), 164 (12), 126 (21), 111 (91); anal $C_{11}H_8ClNOS$ (C, H, N).

4-Chloro-2-(2'-thienylcarbonyl)-N-bromoacetylaniline **5a**. *Procedure c*
The thienylaniline **4a** (2 g, 8.4 mmol) and $NaHCO_3$ (2 g, 24 mmol) were suspended in dry $CHCl_3$ (50 ml) and cooled to 0°C. A solution of bromoacetyl bromide (2.1 g, 9.5 mmol) in dry $CHCl_3$ (5 ml) was added dropwise over 5 min at 0°C and the mixture was stirred at 0°C for another 20 min. The $CHCl_3$ solution was then washed with aq $NaHCO_3$ solution (5%) and dried ($MgSO_4$). After the $CHCl_3$ was removed, the oily residue was purified *via* a wash column on silica gel eluted with

hexane/EtOAc (4:1) to provide **5a** as light-yellow crystals (2.91 g, 97%): mp 151–152 °C (hexane/EtOAc); IR (KBr) 3234, 1680 (C=O), 1599, 1508, 1053, 834; ^{1}H-NMR ($CDCl_3$) δ 3.97 (s, 2H), 7.20 (dd, 1H, *J* = 1, 4.8 Hz); 7.54 (dd, 1H, *J* = 2.4, 9.0 Hz), 7.61 (dd, 1H, *J* = 1.1, 4.8 Hz), 7.79 (d, 1H, *J* = 2.4 Hz), 7.80 (dd, 1H, *J* = 1, 4.4 Hz), 8.47 (d, 1H, *J* = 9 Hz), 10.81 (br s, 1H); ^{13}C-NMR ($CDCl_3$) δ 188.01 (s), 164.74 (s), 143.10 (s), 136.60 (s), 135.96 (d), 135.77 (d), 133.28 (d), 131.08 (d), 128.70 (s), 128.36 (d), 126.44 (s), 123.31 (d), 29.23 (t); MS (EI) *m/e* 359 (M^+, 40), 357 (M^+, 29) 278 (17), 248 (14), 236 (100), 180 (62); anal $C_{13}H_9ClNO_2SBr$ (C, H, N).

4-Chloro-2-(2'-furoyl)-N-bromoacetylaniline 5b
The furylaniline **4b** (0.7 g, 3.1 mmol) was reacted with bromoacetyl bromide analogous to the conditions of *Procedure c* to provide **5b** as white crystals (0.996 g, in 94% yield): mp 101–103°C (hexane/EtOAc); IR (KBr) 3446, 3087, 1755 (C=O), 1621, 1469, 776, cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 3.98 (s, 2H), 6.64 (dd, 1H, *J* = 1.8, 3.7 Hz), 7.28 (d, 1H, *J* = 3.5 Hz), 7.54 (dd, 1H, *J* = 2.5, 8.9 Hz), 7.75 (d, 1H, *J* = 1.4 Hz), 7.92 (d, 1H, *J* = 2.5 Hz) 8.50 (d, 1H, *J* = 8.9 Hz), 11.09 (br s, 1H); ^{13}C-NMR ($CDCl_3$) δ 182.32 (s), 164.82 (s), 151.62 (s), 148.27 (d), 137.49 (s), 133.60 (d), 130.93 (d), 128.72 (s), 125.22 (s), 123.11 (d), 122.39 (d), 112.76 (d), 29.22 (t); MS (EI) *m/e* 343 (M^+, 36), 341 (M^+, 29), 262 (12), 248 (33), 246 (10), 220 (100), 180 (75); anal $C_{13}H_9NO_3BrCl$ (C, H, N).

4-Fluoro-2-(3'-thienylcarbonyl)-N-bromoacetylaniline 5c
The amide **2c** (3.25 g, 10 mmol) was hydrolyzed under conditions analogous to those of *Procedure b* and acylated according to *Procedure c* to provide **5c** (3.2 g, 94%) as light-yellow crystals: mp 98–100°C (hexane/EtOAc); IR (KBr) 3260, 3070, 1690, 1612, 1529, 858, 728 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 3.91 (s, 2H), 7.19 (m, 1H), 7.30 (m, 1H), 7.51 (dd, 1H, *J* = 1, 5 Hz), 7.62 (dd, 1H, *J* = 1, 3.8 Hz), 7.80 (dd, 1H, *J* = 1, 5 Hz), 8.46 (dd, 1H, *J* = 5, 9.3 Hz), 10.70 (br, 1H); MS (EI) *m/e* 343 (M^+, 29), 341 (M^+, 29), 262 (17), 188 (29), 164 (66), 111 (65); anal $C_{13}H_9FNO_2SBr$ (C, H, N).

7-Chloro-5-(2'-thienyl)-1,3-dihydrobenzo[e][1,4]diazepine 6a. Procedure d
The bromoacetyl amide **5a** (2 g, 5.6 mmol) was dissolved in a saturated solution of anhydrous ammonia in CH_3OH (150 ml) and the mixture was heated to reflux for 6 h. After the methanol was removed under reduced pressure, the solid which remained was purified by a wash column (silica gel, hexane/EtOAc (3:1)) to provide **6a** (1.36 g, 88%) as colorless crystals: mp 202–204°C (dec, hexane/EtOAc; lit [59] 212–214°C); IR (KBr) 3203, 1684, 1591, 1480, 822 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 4.16 (br s, 2H), 7.06 (m, 3H), 7.46 (m, 2H), 7.66 (d, 1H, *J* = 2.4 Hz), 8.62 (br s, 1H); ^{13}C-NMR ($CDCl_3$) δ 171.87 (s), 163.33 (s), 143.20 (s), 137.00 (s), 132.11 (d), 131.53 (d), 130.54 (s), 130.23 (d), 129.12 (s), 127.65 (d), 122.91 (d, 2C), 55.95 (t); MS (EI) *m/e* 276 (M^+, 85), 248 (100), 220 (13), 185 (16), 163 (11); anal $C_{13}H_9ClN_2OS$ (C, H, N).

7-Chloro-5-(2'-furyl)-1,3-dihydrobenzo[e][1,4]diazepine-2-one 6b
The amide **5b** (0.5 g, 1.5 mmol) was converted into **6b** (0.31 g, 83%) according to the conditions of *Procedure d*. **6b**: mp 244°C (dec, hexane/EtOAc; lit [59] 245–246°C); IR (KBr) 3209, 1678, 1597, 1481, 1388, 1011, 979 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 4.28 (br s, 2H), 6.48 (dd, 1H, *J* = 1.8, 3.4 Hz), 6.67 (d, 1H, *J* = 3.5 Hz), 7.12 (d, 1H, *J* = 8.6 Hz), 7.46 (dd, 1H, *J* = 2.4, 8.6 Hz), 7.57 (d, 1H, *J* = 1 Hz), 7.63 (d, 1H, *J* = 2.3 Hz), 9.60 (s, 1H); MS (EI) *m/e* 260 (M^+, 49), 232 (100), 203 (11), 168 (22); anal $C_{13}H_9N_2O_2Cl$ (C, H, N).

7-Fluoro-5-(2'-thienyl)-1,3-dihydrobenzoate][1,4]diazepine 6c
The amide **5c** (2 g, 5.85 mmol) was reacted with ammonia as described in *Procedure d* to provide **6c** (1.31 g, 86%) as light-yellow crystals: mp 225–227°C (hexane/EtOAc); IR (KBr) 3191, 3072, 2973, 1675, 1602, 1574, 836, 716 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 3.80 (br, 1H), 4.30 (br, 1H), 7.11 (m, 1H), 7.16 (dd, 1H, *J* = 1, 3.6 Hz), 7.25 (dd, 1H, *J* = 5, 8.9 Hz), 7.50 (m, 2H), 7.74 (dd, 1H, *J* = 1, 5 Hz), 10.49 (s, 1H); MS (EI) *m/e* 260 (M^+, 75), 232 (100), 122 (17), 108 (11), 102 (13); anal $C_{13}H_9FN_2OS$ (C, H, N).

7-Chloro-5-(3'-thienvl)-1,3-dihydrobenzo[e][1,4]diazepine 6d
The thienylaniline **4d** (0.5 g, 2.2 mmol) was treated as described in *Procedure c* and the product employed in *Procedure d* to furnish **6d** (0.52 g, 86%) as colorless crystals: mp 227–228°C (hexane/EtOAc); IR (KBr) 3193, 3117, 2959, 1675 (C=O), 1599, 821 cm^{-1}; ^{1}H-NMR($CDCl_3$) δ 4.26 (br s, 2H), 7.12 (d, 1H, *J* = 8.5 Hz), 7.33 (dd, 1H, *J* = 2.9, 5.1 Hz), 7.47–7.52 (m, 4H), 9.29 (br s, 1H); MS (EI) *m/e* 276 (M^+, 60), 248 (100), 220 (25), 140 (46); anal $C_{13}H_9N_2ClOS$ (C, H, N).

7-Chloro-5-(4'-bromo-2'-thienyl)-1,3-dihydrobenzo[e][1,4]-diazepine 6e
The 3-bromothiophene (1.2 g, 7.4 mmol) was dissolved in dry THF (10 ml) and *n*-BuLi (3.1 ml of 2.5 M solution, 7.8 mmol) was added to the solution at –78°C. After 10 min, the solution which resulted was added to a solution of the lactone **1a** (1.8 g, 7 mmol) in dry THF (100 ml) which had been precooled to –30°C. The mixture which resulted was treated according to *Procedure a* to provide a mixture of components which were very difficult to separate. The mixture was, therefore, treated according to *Procedures b, c,* and *d* and the components were then separated *via* flash chromatography (hexane/EtOAc (5:1)) to furnish two benzodiazepines **6a** (124 mg) and **6e** (49 mg). The spectral properties of **6a** were identical to those reported above. The overall yield of **6e** was 9%. **6e**: mp 223–225°C (hexane/EtOAc); IR (KBr) 3191, 3100, 1694 (C=O), 1595, 1420, 1005, 850, 829 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 4.20 (br s, 2H, 3-H), 7.01 (d, 1H, *J* = 1.3 Hz, 5'-H), 7.05 (d, 1H, *J* = 8.7 Hz, 9-H), 7.36 (d, 1H, *J* =1.3 Hz, 3'-H), 7.50 (dd, 1H, *J* = 2.4, 8.7 Hz, 8-H), 7.64 (d, 1H, *J* = 2.4 Hz, 6-H), 8.01 (br s, 1H, 1-H); MS (EI) *m/e* 356 (M^+, 53), 354 (M^+, 45), 328 (100), 275 (31), 183 (22), 138 (68); anal $C_{13}H_8BrClN_2OS$ (C, H, N).

Methyl-7-chloro-5-(2'-thienyl)-1,3-dihydrobenzo[e][1,4]diazepine 7a. Procedure e
The benzodiazepine **6a** (350 mg, 1.3 mmol) was dissolved in DMF (10 ml) and NaH (35 mg, 1.5 mmol) was added to the solution in small portions. The slurry was then stirred for 5 min at rt and CH_3I (213 mg, 1.5 mmol) was added to the mixture. After the mixture had been stirred for 30 min at rt, the DMF was removed under reduced pressure. The residue was purified by flash chromatography (hexane/EtOAc (5:1)) to provide the title compound **7a** (0.338 g, 89%) as colorless crystals: mp 164–166°C (hexane/EtOAc); IR (KBr) 3079, 2924, 1680 (C=O), 1588, 1483, 1321, 801 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 3.35 (s, 3H), 3.75 (d, 1H, *J* = 11.1 Hz), 4.72 (d, 1H, *J* = 11.1 Hz), 7.06 (t, 1H, *J* = 5 Hz), 7.18 (m, 1H), 7.26 (d, 1H, *J* = 8.9 Hz), 7.51 (m, 2H), 7.62 (d, 1H, *J* = 2.5 Hz); ^{13}C-NMR ($CDCl_3$) δ 170.10 (s), 162.70 (s), 143.10 (s), 142.16 (s), 131.67 (d, 2C), 131.40 (d), 130.54 (d), 129.50 (d), 129.21 (s), 127.59 (d), 122.65 (d), 56.37 (dd), 34.88 (q); MS (EI) *m/e* 292 (M^+, 22), 290 (M^+, 61), 289 (64), 262 (100), 199 (12), 127 (15); anal $C_{14}H_{11}ClN_2OS$ (C, H, N).

1-Methyl-7-chloro-5-(2'-furyl)-1,3-dihydrobenzo[e][1,4]diazepine-2-one 7b
The benzodiazepine **6b** (0.2 g, 0.8 mmol) was methylated according to the conditions of *Procedure e* to provide **7b** (0.18 g, 86%) as light-yellow crystals: mp 143–144°C (hexane/EtOAc); IR (KBr) 3124, 2994, 1668, 1599, 1482, 888, 781 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 3.35 (s, 3H), 3.77 (d, 1H, *J* = 10.9 Hz), 4.80 (d, 1H, *J* = 10.9 Hz), 6.51 (dd, 1H, *J* = 1.8, 3.5 Hz), 6.74 (d, 1H, *J* = 3.5 Hz), 7.26 (d, 1H, *J* = 8.9 Hz), 7.52 (dd, 1H, *J* = 2.6, 8.9 Hz), 7.59 (m, 2H); ^{13}C-NMR ($CDCl_3$) δ 169.95 (s), 158.44 (s), 151.40 (s), 145.47 (d), 142.31 (s), 131.71 (d), 129.54 (s), 129.23 (d), 128.52 (s), 122.59 (d), 115.74 (d), 111.86 (d), 56.46 (dd), 34.90 (q); MS (EI) *m/e* 274 (M^+, 45), 246 (100), 231 (12), 218 (14),154 (14); anal $C_{14}H_{11}N_2O_2Cl$ (C, H, N).

1-Methyl-7-fluoro-5-(2'-thienyl)-1,3-dihydrobenzo[e][1,4]diazepine 7c
The benzodiazepine **6c** (0.26 g, 1 mmol) was treated with CH_3I/NaH (1.1 eq) according to *Procedure e* to provide **7c** (0.23 g, 84%) as yellow crystals: mp 154–156°C (hexane/EtOAc); IR (KBr) 3079, 2980, 1680, 1574, 1497, 977, 843 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 3.35 (s, 3H), 3.76 (d, 1H, *J* = 11 Hz), 4.71 (d, 1H, *J* = 11 Hz), 7.06 (m, 1H), 7.20 (d, 1H, *J* = 3.5 Hz), 7.30 (m, 3H), 7.48 (d, 1H, *J* = 5.1 Hz); MS (EI) *m/e* 274 (M^+, 74), 246 (100), 229 (13), 203 (11), 134 (11),109 (25); anal $C_{14}H_{11}FN_2OS$ (C, H, N).

1-Methyl-7-chloro-5-(3'-thienyl)-1,3-dihydrobenzo[e][1,4]diazepine 7d
The thienylbenzodiazepine **6d** (0.546 g, 2 mmol) was treated as described in *Procedure e* to provide **7d** (0.455 g, 79%) as colorless crystals: mp 161–162°C (hexane/EtOAc); IR (KBr) 3087, 2977, 1682 (C=O), 1591, 1481, 859, 827 (cm^{-1}); ^{1}H-NMR ($CDCl_3$) δ 3.35 (s, 3H), 3.74 (d, 1H, *J* = 10.9 Hz), 4.74 (d, 1H, *J* = 10.9 Hz), 7.26 (d, 1H, *J* = 9.7 Hz), 7.34 (dd, 1H, *J* =2.9, 4.9 Hz), 7.47–7.52 (m, 4H); MS (EI) *m/e* 290 (M^+, 13), 262 (100), 222 (26), 199 (13), 171 (14); anal $C_{14}H_{11}ClN_2OS$ (C, H, N).

2-(4'-Chloro-N-t-butylcarbonyl)aniline-3-thienylmethanol 12
The *t*-butylaniline **11** (4.12 g, 19 mmol) was dissolved in dry THF and the solution was cooled to –78°C. BuLi (17 ml of 2.5 M solution, 42 mmol) was added to the solution at –78°C and the mixture was stirred at 0°C for 3 h. The 3-thienylaldehyde (2.19 g, 19 mmol) in 10 ml THF was then added to the mixture dropwise over 3 min and the mixture was stirred at 0°C for another 2 h. After saturated aq NH_4Cl solution (20 ml) was added to quench the reaction, ether (50 ml) was then added and the organic layer was separated, washed with water, brine, and dried ($MgSO_4$). After the solvent was removed, the residue was purified by a wash column on silica gel (hexane/EtOAc (3:1)) to provide **12** as a colorless oil (4.7 g, 76%): ^{1}H-NMR ($CDCl_3$) δ 1.06 (s, 9H), 3.26 (br s, 1H), 5.83 (s, 1H), 6.91 (dd, 1H, *J* = 1, 5.1 Hz), 7.05 (m, 1H), 7.12 (d, 1H, *J* = 2.4 Hz), 7.24–7.30 (m, 2H), 8.15 (d, 1H, *J* = 8.8 Hz), 8.79 (br s, 1H); MS (EI) *m/e* 323 (M^+, 15), 305 (2), 238 (78), 220 (67), 254 (100). **11** was employed in the next reaction without further purification.

4-Chloro-2-(3'-thienylcarbonyl)-N-t-butylcarbonylaniline 13
The alcohol **12** (1.8 g, 5.6 mmol) was dissolved in CH_2Cl_2 (20 ml) and the solution was added into a suspension of PDC (3.14 g, 8.35 mmol) in CH_2Cl_2 (50 ml). The mixture which resulted was stirred at rt for 1 h. After ether (50 ml) had been added, the dark solution was filtered and passed through a short column of alumina. Evaporation of solvent provided a solid which was recrystallized in ether to provide **13** as a light-yellow solid (1.63 g, 91%): ^{1}H-NMR ($CDCl_3$) δ 1.30 (s, 9H), 7.40 (dd, 1H, *J* = 2.9, 5.1 Hz), 7.46–7.51 (m, 2H), 7.69 (d, 1H, *J* = 2.6 Hz), 7.88 (m, 1H), 8.61 (d, 1H, *J* = 9.0 Hz), 10.83 (br s, 1H); MS (EI) 321 (M^+, 26), 264 (56), 220 (15), 204 (100), 180 (38). The 3-thienylcarbonyl analog **13** was employed in the next reaction without further purification.

2-(N-Benzoylamino)-3-(2'-thienylcarbonyl)naphthalene 15a and bis(2'-thienyl)(3'-N-benzoylamino-2'-naphthyl)methanol 16a
The 2-phenyl-4*H*-3,1-naphtho[2,3-*d*]oxazin-4-one [14] (0.4 g, 1.5 mmol) was reacted with 2-thienyllithium (1.0 M, 2.05 ml) according to *Procedure b* to provide **15a** as light-yellow crystals and **16a**.

15a: mp 158.4–159.3°C (hexane/EtOAC); IR (KBr): 3331 (NH), 3109, 3075, 1677 (C=O), 1625, 1590, 903, 833, 740 (cm^{-1}); ^{1}H-NMR ($CDC1_3$) δ 7.21 (t, 1H, *J* = 4.5 Hz), 7.44–7.57 (m, 4H), 7.61 (t, 1H, *J* = 7.5 Hz), 7.68 (d, 1H, *J* = 5 Hz), 7.80 (d, 1H, *J* = 5 Hz), 7.83 (d, 1H, *J* = 7.5 Hz), 7.92 (d, 1H, *J* = 7.5 Hz), 8.03–8.06 (m, 2H), 8.41 (s, 1H), 9.22 (s, 1H), 11.19 (br s, 1H); MS (EI): *m/e* 357 (M^+, 8), 252 (3), 246 (7), 140 (4), 113 (4), 105 (100); anal $C_{22}H_{15}NO_2S$ (C, H, N).

16a: white solid: mp 174.8–175.5°C (hexane/EtOAc); IR (KBr): 3380 (OH), 3242 (NH), 1648 (C=O), 1548, 1341, 891, 823, 704 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 4.41 (br s, 1H), 6.79 (t, 2H, *J* = 1.0 Hz), 6.93 (t, 1H, *J* = 4.8 Hz), 7.42–7.26 (m, 5H), 7.45 (d, 2H, *J* = 1.0 Hz), 7.48 (d, 2H, *J* = 7.8 Hz), 7.62 (d, 3H, *J* = 7.0 Hz), 7.79 (d, 1H, *J* = 7.8 Hz), 8.99 (s, 1H), 10.03 (br, 1H); MS (EI): *m/e* 441 (M^+, 6), 423 (4), 318 (74), 286 (7), 111 (20), 105 (100); anal $C_{26}H_{19}NO_2S_2$ (C, H, N).

2-(N-Benzoylamino)-3-(2'-furoyl)naphthalene 15b
The 2-phenyl-4*H*-3,1-naphtho[2,3-*d*]oxazin-4-one **14** (2 g, 7.34 mmol) was reacted with furan/*n*-BuLi (9 mmol, 0°C, 10 min) according to *Procedure b* to afford **15b** (1.35 g, 54%) as a light-yellow solid: mp 171–172°C (hexane/EtOAc); IR (KBr): 3300, 3124, 2364, 1665 (C=O), 1635 (C=O), 1544, 1459, 1301, 948, 784 (cm^{-1}); ^{1}H-NMR ($CDCl_3$): δ 6.66 (dd, 1H, *J* = 1.8, 3.5 Hz), 7.27 (d, 1H, *J* = 3.5 Hz), 7.54–7.46 (m, 4H), 7.61 (t, 1H, *J* = 5.7 Hz), 7.79 (d, 1H, *J* =1.9 Hz), 7.85 (d, 1H, *J* = 8.1 Hz), 7.90 (d, 1H, *J* = 8.1 Hz), 8.06 (m, 2H), 8.51 (s, 1H), 9.24 (s, 1H), 11.38 (br s, 1H); MS (EI): *m/e* 341 (M^+,12), 286 (4), 246 (7), 236 (3), 152 (4), 105 (100); anal $C_{22}H_{15}NO_3$ (C, H, N).

2-Amino-3-(2'-thienylcarbonyl)naphthalene 17
The thienylnaphthalene **15a** (0.1 g, 0.28 mmol) was treated with 10% NaOH according to *Procedure d* to afford **17** (0.046 g, 65%) as dark-yellow crystals: mp 160.2–161.0°C (hexane/EtOAc); IR(KBr): 3472, 3367 (NH_2), 3050, 1630 (C=O), 1560, 1412, 1356, 880 (cm^{-1}); ^{1}H-NMR ($CDCl_3$) δ 5.19 (br, 2H, NH_2), 7.02 (s, 1H), 7.15–7.21 (m, 2H), 7.42 (t, 1H, *J* = 7.5 Hz), 7.56 (d, 1H, *J* = 8.3 Hz), 7.63 (d, 1H, *J* = 3.6 Hz), 7.69 (d, 1H, *J* = 8.3 Hz), 7.72 (d, 1H, *J* = 4.9 Hz), 8.19 (s, 1H); MS (EI): *m/e* 253 (M^+, 100), 252 (100), 220 (13), 169 (60), 142 (58),126 (22), 115 (87); anal $C_{15}H_{11}NOS \cdot 1/4H_2O$ (C, H, N).

2-(N-Bromoacetylamino)-3-(2'-thienylcarbonyl)naphthalene 18a
The aminoketone **17** (0.95 g, 3.8 mmol) was treated with bromoacetylbromide as described in *Procedure c* to provide **18a** (1.3 g, 92%) as a yellow solid: mp 139.5–140.1°C (hexane/EtOAC); IR (KBr) 3272, 1687, 1634, 1542, 1217, 859, 806, 750 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 4.03 (s, 2H), 7.20 (dd, 1H,

J = 4.7, 5.7 Hz), 7.48 (t, 1H, J = 1.2 Hz), 7.59 (t, 1H, J = 1, 3 Hz), 7.65 (d, 1H, J = 1, 1 Hz), 7.67 (d, 1H, J = 1.1 Hz), 7.79 (d, 1H, J = 1.1 Hz), 7.81 (d, 1H, J = 1.1 Hz), 8.35 (1H, s). 8.93 (1H, s), 10.84 (1H, s); MS (EI) *m/e* 375 (M^+, 29), 373 (M^+, 29), 253 (40), 252 (55), 196 (30), 140 (31), 111 (100); anal $C_{17}H_{12}NO_2SBr$ (C, H, N).

*2-(N-Chloroacetylamino)-3-(2'-furoyl)naphthalene **18b***
The lactone **21** (1 g, 4 mmol) was reacted with furan/*n*-BuLi (5 mmol) according to *Procedure b* to provide **18b** (0.8 g, 63%) as light-yellow crystals: mp 128–129°C (hexane/EtOAC); IR(KBr) 3255, 3127, 2986, 1680, 1643, 1552, 947, 886 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 4.21 (s, 2H), 6.65 (dd, 1H, J = 0.8, 1.5 Hz), 7.27 (d, 1H, J = 4.3 Hz), 7.48 (t, 1H, J = 7.0 Hz), 7.61 (t, 1H, J = 7.0 Hz), 7.78 (d, 1H, J = 1.5 Hz), 7.85 (d, 1H, J = 7.9 Hz), 7.88 (d, 1H, J = 7.9 Hz), 8.46 (s, 1H), 8.79 (s, 1H), 11.20 (s, 1H); MS (EI) *m/e* 313 (M^+, 72), 264 (30), 236 (42), 196 (100), 169 (31), 140 (46); anal $C_{17}H_{12}NO_3Cl$ (C, H, N).

*5-(2'-Thienyl)-1,3-dihydronaphtho[e][1,4]diazepine **19a***
The amide **18a** (1.3g, 3.5 mmol) was treated with anhydrous ammonia according to *Procedure d* to afford **19a** (0.9 g, 88%) as yellow crystals: mp 266.5–267.0°C (hexane/EtOAc); IR (KBr) 3084, 1684, 1632, 1425, 839, 762, 710 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 4.30 (br s, 2H), 7.03 (dd, 1H, J = 3.9, 4.9 Hz), 7.12 (d, 1H, J = 3.7 Hz), 7.46–7.59 (m, 4H), 7.84 (d, 1H, J = 8.5 Hz), 7.86 (s, 1H), 8.21 (s, 1H), 8.92 (s, 1H); MS (EI) *m/e* 292 (M^+, 70), 291 (38), 264 (100), 236 (20), 152 (17), 127 (36); anal $C_{17}H_{12}N_2OS$ (C, H, N).

*5-(2'-Furyl)-1,3-dihydronaphtho[e][14]diazepine **19b***
The amide **18b** (0.5 g, 1.6 mmol) was treated with anhydrous ammonia according to *Procedure d* to provide **19b** (0.24 g, 55%) as a light-yellow solid: mp 273.1–273.9°C (hexane/EtOAc); IR (KBr) 3080, 1682, 1629, 1479, 1374, 863, 745 (cm^{-1}); ^{1}H-NMR (DMSO-d_6) δ 4.12 (br, 2H) 6.65 (dd, 1H, J = 1.8, 3.3 Hz), 6.81 (d, 1H, J = 3.5 Hz), 7.48–7.62 (m, 2H), 7.65 (s, 1H), 7.90 (s, 1H), 7.92 (d, 1H, J = 9.2 Hz), 8.03 (d, 1H, J = 8.3 Hz), 8.27 (s, 1H), 10.57 (s, 1H); MS (EI) *m/e* 276 (M^+, 60), 275 (19), 248 (100), 219 (22), 165 (25), 139 (23), 127 (23); anal $C_{17}H_{12}O_2 \cdot 1/3\ H_2O$ (C, H, N).

*1-Methyl-5-(2'-thienyl)-1,3-dihydronaphtho[e][1,4]diazepine **20a***
The benzodiazepine **19a** (0.89 g, 3 mmol) was treated with NaH/CH_3I as described in *Procedure e* to furnish **20a** (0.75 g, 80%) as a yellow solid: mp 178.4–179.1°C (hexane/EtOAc); IR (KBr) 3084, 1674, 1608, 1599, 1369, 1317, 1046, 834, 701 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 3.49 (s, 3H), 3.85 (d, 1H, J = 11 Hz), 4.66 (d, 1H, J = 2.9 Hz), 7.05 (d, 1H, J = 4.3 Hz), 7.18 (d, 1H, J = 2.9 Hz), 7.71–7.47 (m, 3H), 7.81 (s, 1H), 7.87 (d, 2H, J = 8.1 Hz), 8.16 (s, 1H); MS (EI) *m/e* 306 (M^+, 93), 278 (100), 153 (25), 139 (39), 125 (36); anal $C_{18}H_{14}N_2OS \cdot 3/4H_2O$ (C, H, N).

*1-Methyl-5-(2'-furyl)-1,3-dihydronaphtho[e][1,4]diazepine **20b***
The benzodiazepine **19b** (0.1 g, 0.4 mmol) was treated with NaH/CH_3I according to *Procedure e* to afford **20b** (0.079 g, 70%) as yellow crystals: mp 145.5–146.3°C (hexane/EtOAc); IR (KBr), 3071, 1675, 1631, 1601, 1313, 825, 759 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 3.49 (s, 3H), 3.86 (d, 1H, J = 17 Hz), 4.75 (d, 1H, J = 17 Hz), 6.50 (s, 1H), 6.72 (d, 1H, J = 2.5 Hz), 7.49–7.56 (m, 2H), 7.58 (s, 1H), 7.69 (s, 1H), 7.84 (d, 2H, J = 7.5 Hz), 8.13 (s, 1H); MS (EI) *m/e* 290 (M^+, 56) 262 (82), 261 (60), 176 (52), 152 (76), 126 (83), 102 (100); anal $C_{18}H_{14}N_2O_2$ (C, H, N).

*2-Chloromethyl[2,3]naphthoxazin-4-one **22***
The 2-amino-3-naphthoic acid (2.2 g, 11.7 mmol) was treated with chloroacetyl chloride according to the procedure mentioned for **1a** to produce **22** (1.5 g, 52%) as a colorless solid: mp 151–156°C; IR (KBr) 3022, 2968, 1749 (C=O), 1628, 1457, 976, 827 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 4.44 (s, 2H), 7.61–7.72 (m, 2H), 7.79 (d, 1H, J = 7.7 Hz), 8.04 (d, 1H, J = 8.2 Hz), 8.08 (s, 1H), 8.84 (1H, S); MS (EI) *m/e* 245 (M^+, 46),196 (100),147 (14), 141 (8), 140 (69), 126 (17); anal $C_{13}H_8NO_2Cl$ (C, H, N).

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