Dopamine D_1/D_5 Receptor Antagonists with Improved Pharmacokinetics: Design, Synthesis, and Biological Evaluation of Phenol Bioisosteric Analogues of Benzazepine D_1/D_5 Antagonists

Wen-Lian Wu,* Duane A. Burnett, Richard Spring, William J. Greenlee, Michelle Smith, Leonard Favreau, Ahmad Fawzi, Hongtao Zhang, and Jean E. Lachowicz

Schering-Plough Research Institute, 2015 Galloping Hill Road, Kenilworth, New Jersey 07033

Received December 12, 2003

Benzazepines **1** and **2** (SCH 23390 and SCH 39166, respectively) are two classical benzazepine D_1/D_5 antagonists, with K_i values 1.4 and 1.2 nM, respectively. Compound **2** has been in human clinical trials for a variety of diseases, including schizophrenia, cocaine addition, and obesity. Both **1** and **2** displayed low plasma levels and poor oral bioavailability, due to rapid first-pass metabolism of the phenol moieties. Several heterocyclic systems containing an N−H hydrogen bond donor were synthesized and evaluated as phenol isosteres. The preference orientation of the hydrogen bond was established by comparison of analogues containing different NH vectors. Replacement of the phenol group of **2** with an indole ring generated the first potent D_1/D_5 antagonist **11b**. Further optimization led to the synthesis of very potent benzimidazolones **19**, **20** and benzothiazolone analogues **28**, **29**. These compounds have excellent selectivity over D_2-D_4 receptors, α_{2a} receptor, and the 5-HT transporter. Compared to **2**, these heterocyclic phenol isosteres showed much better pharmacokinetic profiles as demonstrated by rat plasma levels. In sharp contrast, similar phenolic replacements in **1** decreased the binding affinity dramatically, presumably due to a conformational change of the pendant phenyl group. However, one indazole compound **33** was identified as a potent D_1/D_5 ligand in this series.

Introduction

Dopamine is an important neurotransmitter involved in the regulation of several biological functions, including locomotor activity, emotion, cognition, and neuroendocrine secretion.[1] The dopamine receptors belong to the superfamily of G-protein-coupled receptors. To date, five subtypes of dopamine receptors have been characterized, namely D_1-D_5. Two D_1-like receptor subtypes (D_1 and D_5) couple to the G protein G_s and activate adenylate cyclase. The other receptor subtypes belong to the D_2-like subfamily (D_{2L}, D_{2S}, D_3, and D_4) and are prototypic of G-protein-coupled receptors that inhibit adenylate cyclase and activate K^+ channels.[2] Dopamine neurotransmission is intimately involved in the pathophysiology of Parkinson's disease and schizophrenia.[3] While many D_2 antagonists are in clinical use for schizophrenia, evidence suggests that D_1-selective dopamine antagonists may also have neuroleptic properties.[4]

The discovery of benzazepine **1**, the first high-affinity and selective D_1/D_5 antagonist[5] along with the partial agonist **1a** (SKF 38393)[6] represented a major breakthrough in the pharmacology of dopamine receptors. Having been used widely as a standard pharmacological tool, this prototype specific D_1/D_5 antagonist has radically changed our perspective on the functional roles of dopamine receptors. Because of the therapeutic potential of D_1 antagonists as antipsychotics, benzazepine compounds have attracted considerable interest in the past two decades. Several novel D_1 antagonists have thus been discovered, including the conformationally restricted benzazepine analogue **2** (SCH 39166),[7] fused analogues such as **1b** (NNC-756),[8] and the ring-contracted 1-benzyl tetrahydroisoquinolines **1c** and **1d** (BW-737C89, BTS-73947)[9,10] shown in Figure 1. More recently, a chemically distinct structure **1e** (LE−300) has also been disclosed.[11]

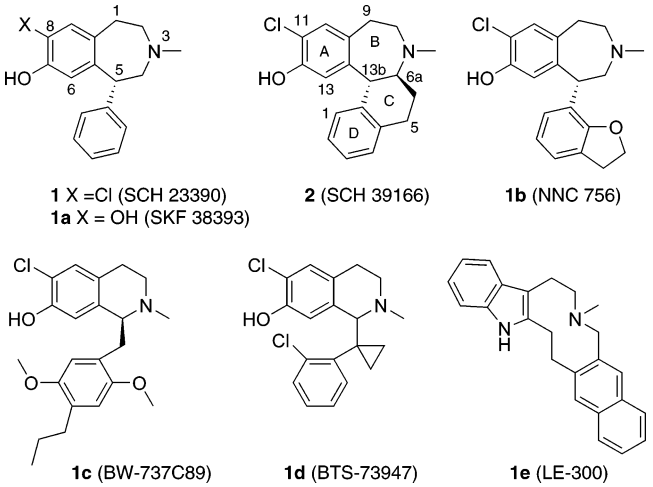


Figure 1. Representative D_1 Antagonists.

Compound **2** has undergone several clinical trials for human diseases, including schizophrenia,[12] cocaine addiction,[13] and obesity.[14] However, both **1** and **2** presented drug development issues. Benzazepine **1** was inactive in rhesus monkeys dosed orally; moreover, it had a very short duration of action. Even the longer acting analogue **2** showed low oral bioavailability (0.6%). Further pharmacokinetic evaluation has revealed that extensive O-glucuronidation of the phenol and N-dealkyl-

* To whom correspondence should be addressed. E-mail: wen-lian.wu@spcorp.com.

10.1021/jm030614p CCC: $30.25
Published on Web 01/13/2005

ation of the NMe group in vivo may contribute to the poor PK profile.[15]

As a part of our ongoing program on the synthesis of novel dopamine D_1/D_5 antagonists, we sought to improve the metabolic stability and overall PK profile of compound **2**. We reasoned that heterocyclic replacements of catechol or phenol rings would retard the metabolic inactivation due to glucuronidation and hence increase duration of action. Several examples of the isosteric replacement of one or more phenolic hydroxyl groups with heterocyclic ring systems have been reported in the literature.[16] In this paper, we describe the design, synthesis, and biological activity of various heterocyclic analogues of **1** and **2**, with the goal of improving pharmacokinetics while maintaining high D_1/D_5 affinity and selectivity over D_2-like receptors.

Design and Synthesis. This research involved an iterative design process based on observed SAR results; however, for the sake of brevity, all compound syntheses will be discussed together. The corresponding design elements and SAR will be discussed subsequently. A constant feature of the above benzazepine D_1/D_5 antagonists is a free phenolic group, which is believed to serve as a hydrogen-bond complement to one or more of three possible serines in the active site of the dopamine receptors.[17] A careful examination of the literature reveals that a free OH group is favored at the 12-position of the benzazepine ring for high affinity antagonists. Hence this requirement was considered when choosing potential phenol isosteres. Our efforts were based on an assumption that the phenol was serving as a hydrogen bond donor in its interaction with the receptor.[18,19] Furthermore, we assumed that closely related compounds would bind in an analogous fashion. Indeed, the design of fused benzazepines such as **2** was predicated on the notion that properly reducing conformational flexibility would enhance the binding affinity of the series. However, the hydrogen bond donating directionality was unclear, although some pharmacophore modeling and syntheses of related conformationally restricted analogues have been reported.[20] Because of the free rotation about the C−O bond, the O−H bond could lie anywhere on its periphery. We envisioned that a suitably arranged heterocycle with an NH group would probe its direction, and more importantly, serve as metabolically stable isostere of the phenolic group. For practical purposes, we considered only two limiting rotational conformations for the design of rigid analogues as exemplified by compound **2** in Figure 2. In both conformations A and B, the O−H bonds lie within the same plane of the phenol ring, but point in different directions. Thus, the corresponding ring systems were fused to the A ring at 11,12- and 12,13-positions to generate novel targets. The same design criteria were also applied to compound **1**.

Multigram quantities of enantiomerically pure **1** and **2** were available and served as the starting materials as well as the lead compounds for our novel targets. The synthesis of the benzotriazole analogue **8** is shown in Scheme 1. Compound **2** was hydrogenated to give the des-chloro compound **3**, which in turn was nitrated to yield compound **4** as the major isomer. The triflate of alcohol **4** was prepared and heated with benzylamine to give nitro amine compound **6**. Prolonged catalytic

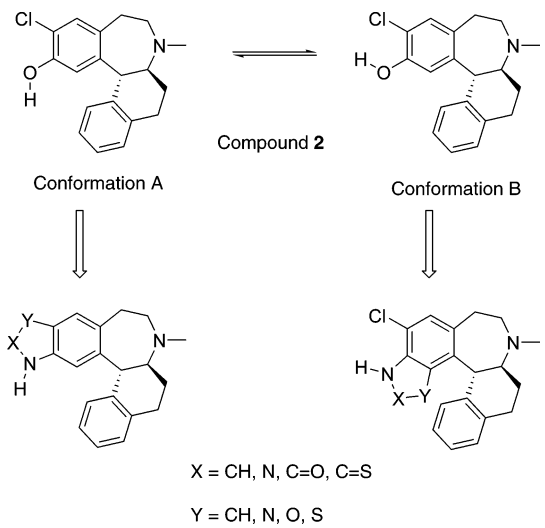


Figure 2. Conformational restriction of the OH group in **2** into isomeric frameworks.

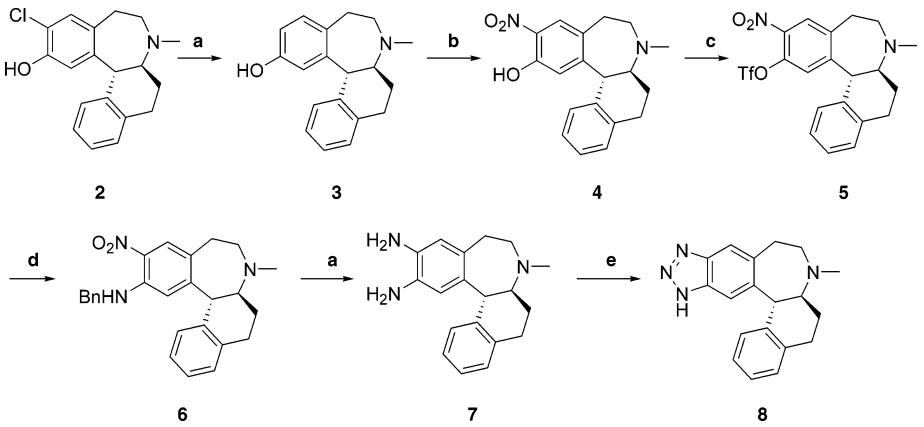
hydrogenation of **6** afforded the diamine intermediate **7** in one pot, which was subsequently treated with sodium nitrite to form compound **8** in low yield.

The synthesis of the indole **11b** also began with compound **2** and is depicted in Scheme 2. The triflate derivative **9** was prepared from **2** and reacted with allylamine under Buchwald conditions to generate compound **10**.[21] Our synthetic plan for compound **10** was to rearrange to the *C*-allyl analogue using the aza-Cope rearrangement followed by ozonylsis of the allyl group and cyclization to give indole **11a**. The aza-Cope rearrangement[22] of **10** at 215 °C in the presence of Lewis acid BF_3 unexpectedly led to the indole **11b** as the solely isolable product, presumably through an intramolecular cyclization of the initial rearrangement product.[23] Note that this route produced an analogue with an undesired additional methyl group in the region under investigation. The desired indole **11a**, without the "extra" methyl group, was not available through this route.

Compounds **16**, **18**−**21** listed in Table 1 were prepared via the syntheses outlined in Scheme 3. Nitration of compound **2** gave compound **12** in 92% yield; subsequent O-alkylation led to the ether **13**. Smiles rearrangement[24] was effected by treatment with NaOH at room temperature to afford amide **14**, which was hydrolyzed to reveal the aniline **15**. This intermediate was converted to the benzimidazole **16** by treatment with iron powder in the presence of formic acid. Alternatively, nitroaniline **15** was reduced with iron/HCl to give the stable diamine intermediate **17**. Reaction of the diamine with sodium nitrite afforded the benzotriazole **18**. While treatment of the diamine **17** with thiocarbonyl diimidazole yielded the thiobenzimidazolone **21** in good yield, exposure of the diamine to carbonyl diimidazole failed to give any desired product **19**. The benzimidazolone **19** was finally achieved by reaction of the diamine **17** with $(Boc)_2O$ catalyzed by DMAP.[25] Subsequent N-demethylation with pyridine hydrochloride produced **20.**[26]

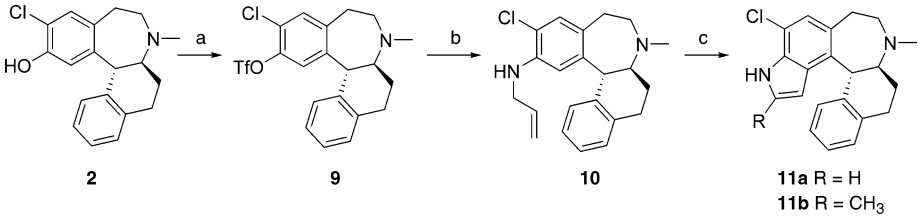
The synthesis of benzothiazolone compounds **28** and **29** also relied on a Smiles rearrangement and is depicted in Scheme 4. Phenol **2** was converted to the corresponding aniline intermediate **24** by an alkylation−rearrangement−hydrolysis sequence similar to that described for the preparation of **15**. From this aniline

Scheme 1[a]



[a] Reagents and conditions: (a) $HCOONH_4$, $Pd(OH)_2/C$, MeOH, 100%; (b) HNO_3, HCOOH, 43%; (c) $(TfO)_2O$, Et_3N, CH_2Cl_2, 92%; (d) $BnNH_2$, MeCN, 74%; (e) $NaNO_2$, HCl, 7%.

Scheme 2[a]



[a] Reagents and conditions: (a) $(TfO)_2O$, Et_3N, 60%; (b) $Pd(OAc)_2$, BINAP, allylamine, Cs_2CO_3, toluene, 13%; (c) BF_3-Et_2O, sulfolane, 215 °C, 20%.

Table 1. In Vitro Biological Data

			K_i (nM)[a,b]				K_b (nM)[a,c]
compound	D_1	D_5	D_2	D_4	5-HT	α_{2a}	D_1
1	1.4	2.8	1000		9.2	74	
2	1.2	2.0	980	5520	80	731	
8	583		3000				
11b	24.7		232				23.8
16	248		984				
18	146		1530				
19	7	4.2	1023	10000	540	72	5.4
20	16.5	2.4	3270	10000	6220	720	11.9
21	40		1040				
26	409		1390				
28	2.1	2.8	257	10000	842	268	1.4
29	6.5	1.7	661	10000	2950	14600	5.1
32	1241		10000				
33	14	30	3550	10000	137	154	
34	183		5010				
40	350		10000				
41	1790		10000				
42	1900		10000				
49	115		2890				
50	1080		3200				

[a] The standard error was 10%, and variability was less than 2-fold from assay to assay. [b] Data for inhibition of radioligand binding. [c] Data for cAMP assay in CHO−K1 cells expressing D_1 receptor, using SKF 81297 as an agonist.

compound, a slightly modified literature procedure was adopted to synthesize benzothiazolone analogues **28** and **29.**[27] Bromination of **24** under mild conditions afforded the bromo compound **25**, which was subsequently treated with potassium ethyl thiothianate to give the fused thiazol-2(3*H*)-one **26**. A two-step procedure involving alkylation, followed by hydrolysis of the thioether afforded the desired benzothiazolone **28** in good yield. As before, the corresponding benzazepine NH analogue **29** was obtained by heating **28** with pyridine hydrochloride.

The indazole analogues **33** and **34** were synthesized from compound **1**, as illustrated in Scheme 5. Compound **1** was treated with hexamethylenetetramine (HMT) under acidic conditions to give the aldehyde **30** in 32% yield.[28] The mesylate derivative of the phenol **30** was prepared and cyclized with methylhydrazine to give the indazole **32** in good yield.[29] N-Dealkylation of **32** with pyridine hydrochloride afforded a separable mixture of the desired indazole **33** and its benzazepine NH analogue **34** in a ratio of ca. 1: 1 in one pot.

The benzimidazolone analogues **40**−**42** shown in Table 2 were prepared in a similar manner as described in Scheme 3, utilizing compound **1** as the starting material (Scheme 6).

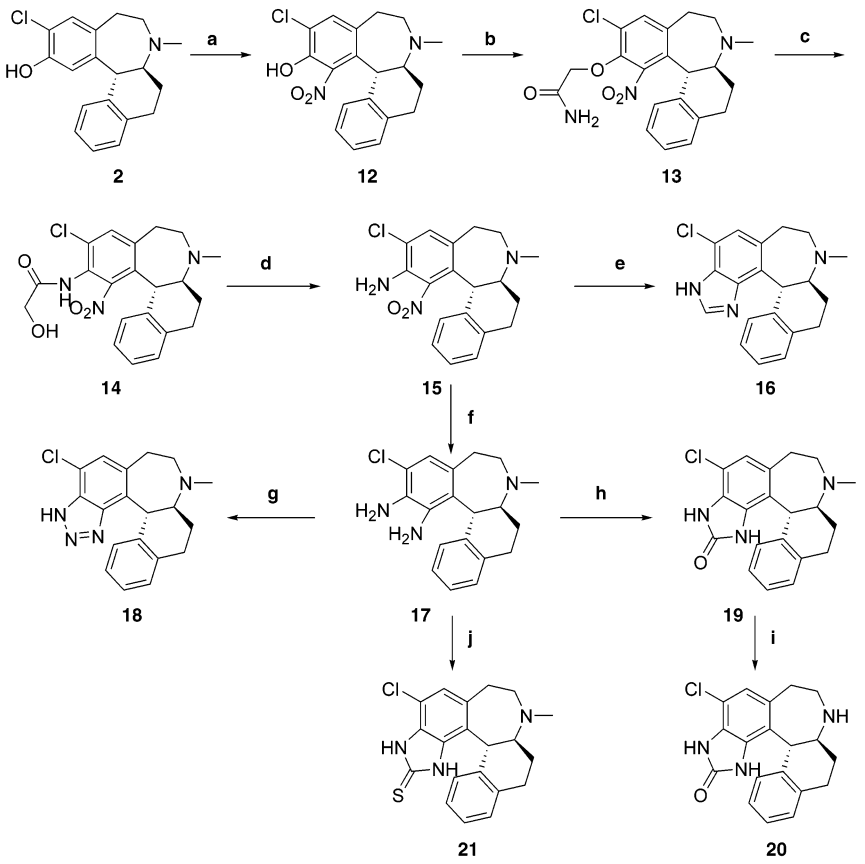
The benzothiazolone analogues **49** and **50** were prepared from compound **1** according to Scheme 7.

Results and Discussion

Our goals were to identify analogues of **1** and **2** with potent activity at D_1/D_5 and high selectivity over D_2-D_4 receptors. As an intolerable level of activity at the α_{2a} adrenergic receptor and the 5-HT transporter were observed for compound **1**, we also sought to minimize interaction with these proteins. Moreover, these novel D_1/D_5 antagonists should also possess improved in vivo pharmacokinetics as compared to compounds **1** and **2**.

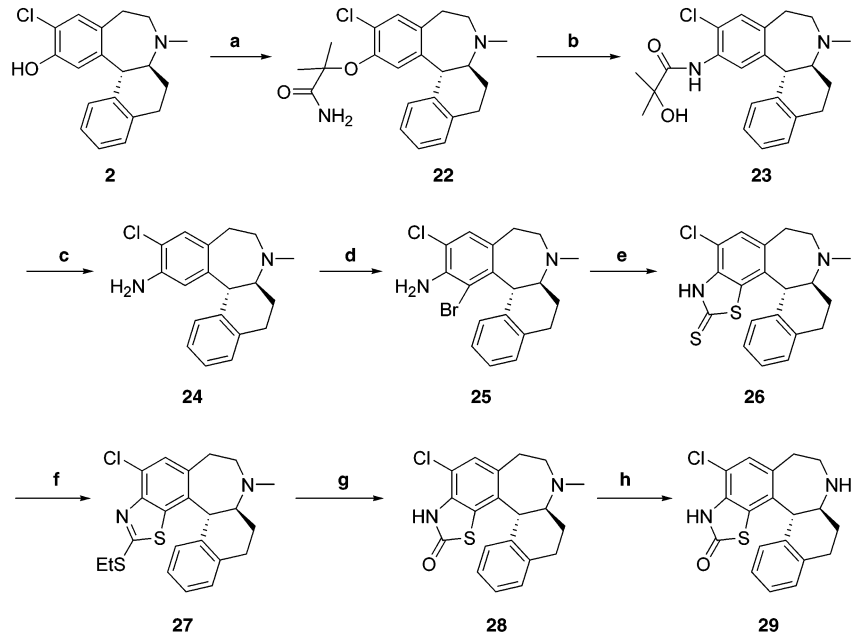
As revealed in Table 1, the benzotriazole **8**, representing a rigid analogue of conformer A (Figure 2), had weak activity for the D_1 receptor. While the triazole NH moiety is acidic enough to form a strong hydrogen bond; the poor affinity at dopamine receptors strongly suggested that conformer A was not the active binding conformer. To define the correct orientation of the hydroxyl group, we turned our attention to the heterocyclic analogues of conformation B.

Scheme 3[a]



[a] Reagents and conditions: (a) HNO_3, HCOOH, 92%; (b) $BrCH_2CONH_2$, K_2CO_3, acetone, 90%; (c) NaOH, DMF, 98%; (d) concentrated HCl, 1,4-dioxane, 89%; (e) Fe powder, HCOOH, HCl, 95%; (f) Fe powder, HCl, 96%; (g) $NaNO_2$, HCl, 84%; (h) $(Boc)_2O$, DMAP, MeCN, 69%; (i) pyridine·HCl, 225 °C, 62%; (j) thiocarbonyldiimidazole, DMAP, MeCN, 71%.

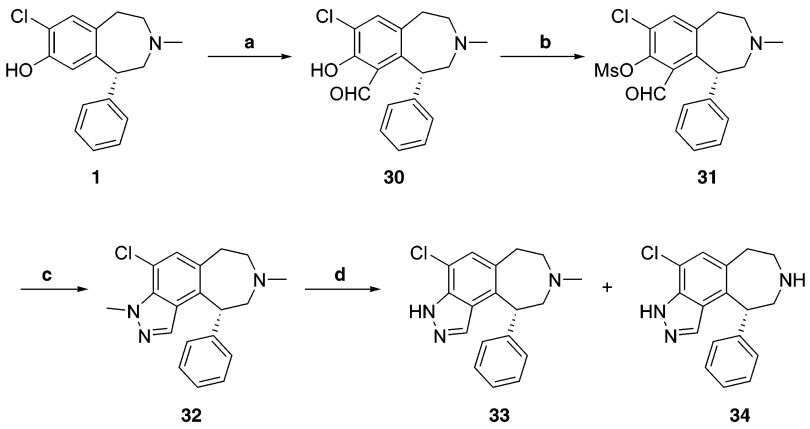
Scheme 4[a]



[a] Reagents and conditions: (a) NaH, 2-bromo-2-methylpropanamide, 1,4-dioxane; (b) NaH, DMF, 50 °C, 48% (two steps); (c) 6 N HCl, 1,4-dioxane, 100%; (d) Br_2, HCOOH, 83%; (e) EtOC(S)SK, DMF, 95%; (f) $(EtO)_2P(O)Cl$, K_2CO_3, 87%; (g) MeONa, DMF, 66%; (h) pyridine·HCl, 225 °C, 48%.

The indole ring is a classical isostere of phenol. We therefore sought to prepare analogues in which the phenol group in compound **2** was replaced with an indole moiety. As expected, the indole analogue **11b** displayed appreciable affinity for the D_1 receptor even though the hydrophobic 2-methyl group may cause unfavorable interaction with dopamine receptors. The degree of selectivity over D_2 was not high, yet it provided the first

Scheme 5[a]



[a] Reagents and conditions: (a) hexamethylenetetramine, TFA, 32%; (b) MsCl, Et_3N, 100%; (c) $MeNHNH_2$, $MeCOONH_4$, xylene, 80%; (d) pyridine·HCl, 225 °C.

Table 2. PK Profiles of Selected Compounds[a]

compound	rat PK (10 mg/kg po) AUC_{0-6h} (h μg/mL)	C_{max} (ng/mL)	T_{max} (h)	BA[b] (%)
1	0	0		0
33	0.06	15	2	
2	0.16	72	0.5	0.6
19	5.9	1300	1	87
20	6.5	1640	6	42
28	2.4	462	2	
29	28.9	5690	1	

[a] Data are from pooled samples from two mice in cassette-accelerated rapid rat protocol as described in ref 32. [b] Bioavailability data is from a 24 h full PK evaluation in rats, $n = 3$, comparing po and iv dosing AUCs.

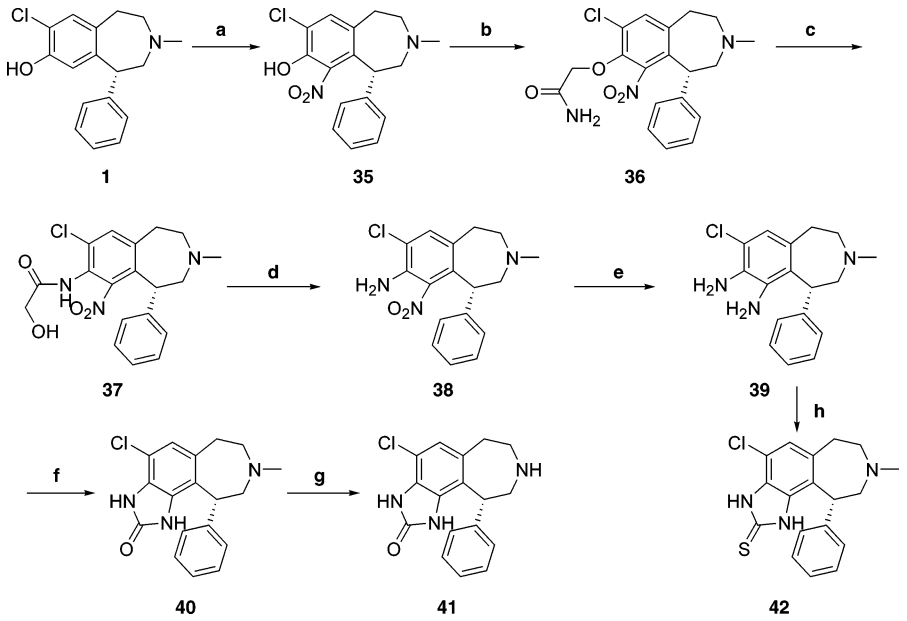
insight into the correct binding orientation of the phenol OH group. Comparison of the affinities of compounds **8** and **11b** to the D_1 receptor strongly suggested the preference of conformation B over A when binding to D_1 receptors. Therefore we set out to investigate other heterocycles bearing a similar NH directionality as in compound **11b** (Figure 2).

Thus, the benzimidazole **16** and the benzotriazole **18** were prepared. As can be seen from Table 1, their affinities at the D_1 receptor proved to be disappointing. Benzimidazole **16** had a much lower D_1 receptor affinity than the indole **11b**. The benzotriazole analogue **18** was only slightly better than **16**, possibly reflecting its stronger NH acidity. However, compared to the other benzotriazole **8** mentioned above, the affinity of **18** only improved by 3-fold despite its "correct" hydrogen bond-donating directionality. As benzimidazole and benzotriazole moieties had been shown to be of equal effectiveness as indole when used as phenolic replacements,[16k] these unexpected results could not be explained in terms of their acidities. The relative acidities of related heterocycles increase in the following order: indole (pK_a20.95)[30a] < indazole (13.86)[30b] < benzimidazole (12.75)[30b] < benzimidazolone (11.95)[30c] < benzothiazolone (9.35)[30d] < benzotriazole (8.38).[30b]

Initially, these results seemed discouraging, but a close inspection of their structures revealed useful insights. As illustrated in Figure 3, both benzimidazole **16** and benzotriazole **18** can exist in two tautomeric forms. Owing to the conformational rigidity of the tetracyclic benzazepine core, the pendant phenyl ring (D-ring, **2**) lies almost orthogonal to the A ring. In tautomer A, there is repulsion between the lone electron pair of the inner N atom and the pendant phenyl ring. In contrast, in tautomer B, the N−H points directly to the π cloud of the phenyl ring through a so-called π-facial H-bond.[31] As a result, tautomer B predominates in the equilibrium, either through a true hydrogen-bond or attenuation of the lone pair N−Ph repulsion. This tautomeric equilibrium is revealed in the NMR spectrum of isomer **16** where the NH chemical shift (6.88 ppm) is seen to be shifted upfield from the analogous proton in benzimidazole itself (8.2 ppm). These data suggest that the NH proton in this compound is significantly shielded by the aromatic ring, a result only possible from tautomer B. Unfortunately, tautomer B is expected to be a poor D_1 antagonist due to its inability to provide the crucial hydrogen-bonding to the receptor. Although tautomer A might be directionally correct and possess a suitable hydrogen bond donor, if the energy difference between A and B is significant, the overall binding of these analogues would be lessened as a result of paying this enthalpic penalty. This unfavorable equilibrium may explain the poor dopaminergic activity of compounds **16** as well as benzotriazole **18**.

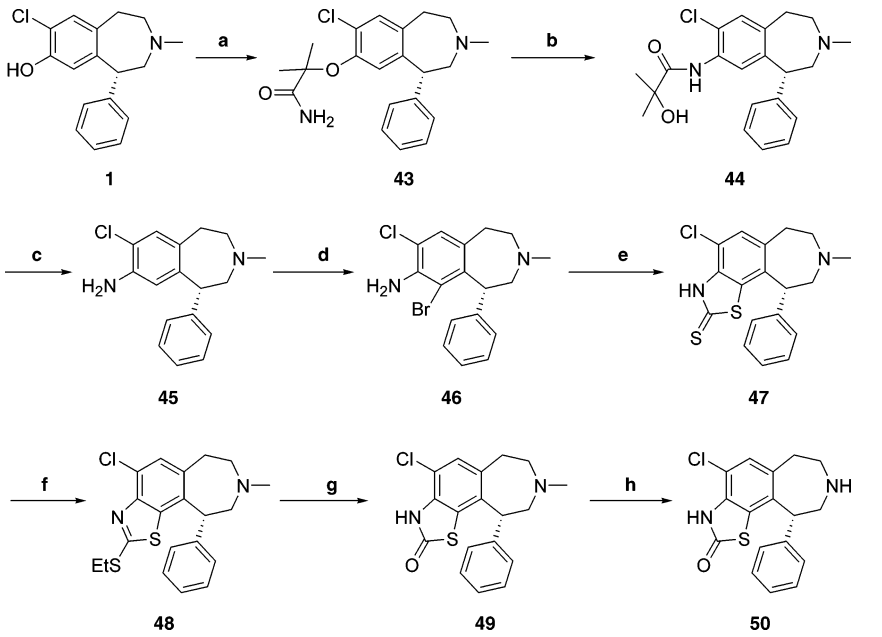
If this hypothesis were true, this result would immediately suggest our next potential heterocyclic analogue, benzimidazolone **19** (see Figure 4). We reasoned that since compound **19** had two NH groups, even with one NH interacting with the pendant phenyl ring, the other one should be able to provide hydrogen-bonding to the D_1 and D_5 dopamine receptors. Indeed, in the ^1H NMR spectrum of **19**, the two NH protons appeared at 10.4 and 5.4 ppm, respectively. This observation reflects the very different chemical and magnetic environments of the two protons. The unusual high field peak at 5.4 ppm suggests that one NH sits in the shielding region of the D-ring phenyl. The NH appearing at 10.4 ppm was still available for hydrogen-bonding to the receptors. The downfield shift of the peak revealed the acidic nature of the proton as well, further anticipating the desired activity. As expected, the benzimidazolone **19** showed single-digit nanomolar binding for dopamine D_1 and D_5 receptors. Selectivities against other dopamine receptor subtypes were also very good. These results underscore the importance of the N−H orientation. The corresponding benzazepine NH compound **20** was also potent at D_1 and D_5 receptors, although slightly weaker than **19**. Note that **20** displayed a much higher selectiv-

Scheme 6[a]



[a] Reagents and conditions: (a) HNO_3, HCOOH, 100%; (b) $BrCH_2CONH_2$, K_2CO_3, acetone, 67%; (c) NaOH, DMF, 94%; (d) 6 N HCl, 1,4-dioxane, 100%; (e) Fe powder, HCl, 100%; (f) $(Boc)_2O$, DMAP, MeCN, 75%: (g) pyridine·HCl, 225 °C, 81%; (h) thiocarbonyldiimidazole, DMAP, MeCN, 68%.

Scheme 7[a]



[a] Reagents and conditions: (a) NaH, 2-bromo-2-methylpropanamide, 1,4-dioxane; (b) NaH, DMF, 50 °C; (c) 6 N HCl, 1,4-dioxane, 100%; (d) Br_2, HCOOH, 87%; (e) EtOC(S)SK, DMF, 73%; (f) $(EtO)_2P(O)Cl$, K_2CO_3, 68%; (g) MeONa, DMF, 76%; (h) pyridine·HCl, 225 °C, 51%.

ity over 5-HT transporter compared to compound **2**. Contrary to the benzimidazolone **19**, the thiobenzimidazolone counterpart **21** was much less potent indicating limited tolerance for change at the carbonyl site.

With the knowledge that a relatively acidic NH was preferred for optimal dopaminergic receptor binding, benzothiazolone analogues **28** and **29** were examined. Because sulfur is a "soft" atom with high polarizability and low electronegativity, the benzothiazolone carbonyl group has a high-electron density and the heterocycle ring has a low electron density. As a result, this charge distribution may increase the acidity of the NH and promote binding to a complementary receptor.[16g] Indeed, the affinity-enhancing effect of sulfur atom has been reported earlier.[16g,i] As shown in Table 1, the benzothiazolone analogue **28** was three times more potent than benzimidazolone **19**, with its affinity approaching the level of compound **2**. Selectivity over other related receptors was also excellent, especially for the 5-HT transporter and the α_{2a} receptor. The corresponding benzazepine NH compound **29** maintained single digit nanomolar affinity at D_1 and D_5 receptors with even greater selectivity over other subtypes. The thiobenzothiazolone **26** was significantly less active.

Having achieved potent and selective heterocyclic phenol isostere analogues of compound **2**, we applied the similar replacements to compound **1**. The biological

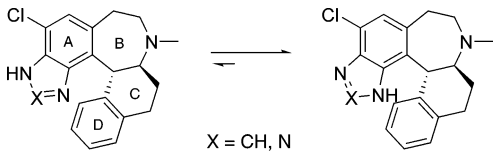


Figure 3. Tautomeric isomers of benzimidazole and benzotriazole.

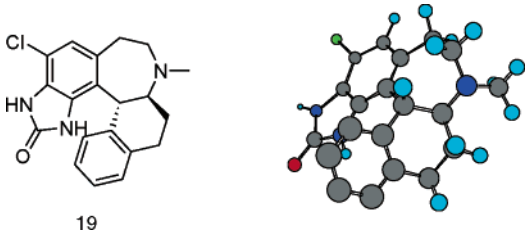


Figure 4. A three-dimensional view of compound **19** showing NH proximity for π-facial hydrogen bonding. (In Chemdraw rendering using MM2 minimization, some aryl hydrogen atoms were omitted from the ring for clarity).

binding data is exhibited in Table 1. Supporting our hypothesis concerning the importance of the hydrogen bond donating ability, compound **32**, lacking the critical NH moiety, was inactive. The indazole **33**, having this critical NH moiety showed good D_1 affinity, almost 90-fold more potent than compound N-Me analog **32**. The benzazepine NH compound **34** decreased the affinity even further. This finding was consistent with the trend observed for all benzazepine NH analogues.

In contrast to the analogues of compound **2** shown in Table 1, the benzimidazolones **41** and **42** were very weak D_1 ligands. The benzothiazolones **49** and **50** did not represent a great improvement. Owing to the rigidity of **2**, large substituents at the 13-position do not cause significant change of the pendant phenyl ring orientation, which has been known to be critical for effective binding to dopamine receptors.[6] However, as compound **1** is quite flexible in the orientation of the phenyl ring; large substituents at the 6-position (corresponding to the 13-position of **2**) disrupt the active equatorial orientation, causing the pendant phenyl to flip axial. In the compound **1**-related series, the relative activity of the indazole **33** seems to be an inexplicable exception. The binding affinity appears to correlate loosely with the hydrophilicity of the groups interacting with pendant phenyl ring (CH (**33**) > S (**49**) > NH (**41**)). This correlation most likely represents the disfavored equatorial display of the phenyl group as hydrophilicity is increased in the region. In an aqueous environment, where the hydrophilic group is undoubtedly highly solvated, any intramolecular π-facial H-bonding would not make up for overall loss of solvation. The conformational rigidity of the compound **2** series precludes conformational rearrangement favoring π-facial H-bond. This explanation, while speculative, agrees with the binding affinity order observed for the above analogues.

As shown in Table 1, key analogues **11b**, **19**, **20**, **28**, and **29** were tested in the cAMP assay and all functioned as full D_1 antagonists. The K_b values correlated well with their corresponding K_i data.

Several compounds were selected for pharmacokinetics investigation in rats.[32] The PK profiles are exhibited in Table 2.

As revealed in Table 2, the reference benzazepine **1** had a very low plasma concentration and a short duration after oral administration in rats, due to extensive glucuronidation.[15b,c] Its conformationally restricted analogue **2**, with a slightly higher plasma concentration, did not exhibit a desirable pharmacokinetic profile either. This result is not surprising because the O-glucuronidation and the N-demethylation, two major metabolic pathways associated with **1**, also inactivated **2**. In rat plasma, the concentration of glucuronide conjugate of **2** was much higher than the unconjugated parent drug. A small amount of desmethyl metabolite was also detected.[15a] First-pass metabolism, in particular glucuronidation, severely diminished the overall PK of compound **2**. Thus, phenol isosteric analogues were expected to reduce the glucuronidation and therefore increase plasma AUCs. Indeed, the benzimidazolone **19**, devoid of a phenolic group, displayed much higher plasma concentration in rats than compound **2** after oral dosing at 10 mg/kg and provided excellent oral bioavailability. Furthermore, the benzazepine NH derivative **20**, lacking both the N-Me and the phenolic group of compound **2**, exhibited even higher plasma levels and a longer duration of action. Compared to compound **19**, compound **20** with an extra hydrogen bond donor moiety (benzazepine NH) displayed lower oral bioavailability, presumably due to lower membrane permeability. Similarly, the benzothiazolone **28** showed a much higher plasma concentration than compound **2**. We were delighted to find that the corresponding benzazepine NH analogue **29** displayed an extremely high AUC in rats. In contrast, the indazole **33**, also devoid of a phenol group, did not greatly improve the PK profile compared to **1**. This unexpected result supported the notion that molecular rigidity plays an important role in enhancing the PK of drug candidates, as reported recently.[33]

Conclusion

In summary, we have applied a rational design approach to improve on the metabolic stability of D_1 dopamine antagonists **1** and **2**. To this end, several heterocyclic systems containing an N−H hydrogen bond donor have been synthesized. The preference of the hydrogen bond-donating directionality has been established. Further optimization of the hydrogen bond donating capacity of various heterocycles culminated in the identification of several potent D_1/D_5 antagonists with high selectivity over D_2−D_4, α_{2a} adrenergic receptors, and the 5-HT transporter. Of particular interest are compounds **19**, **20**, **28**, **29** in terms of their overall profiles. Owing to reduced metabolic liability compared to compound **2**, these novel D_1/D_5 antagonists exhibited excellent pharmacokinetic profiles. The principles of phenol isostere replacement demonstrated here will benefit future investigations.

Experimental Section

Mass spectra were recorded using an Applied Biosystems API-150Ex spectrometer. In general, NMR structural determinations of the compounds were made using chemical shifts and coupling constants. The ^1H and ^{13}C NMR spectra were obtained on a Varian Gemini-300 (300 MHz, ^1H; 75.5 MHz, ^{13}C) or XL-400 (400 MHz, ^1H; 100 MHz, ^{13}C). Spectrometer are reported as parts per million downfield from Me_4Si with

the number of protons, multiplicities, and coupling constants in hertz (Hz) indicated parenthetically. Compound purity was checked by TLC and LC/MS analysis using an Applied Biosystems API-100 mass spectrometer and Shimadzu SCL-10A LC column (Altech platinum C18, 3 μM, 33 mm × 7 mm). A gradient flow was used as follows: 0 min, 10% CH_3CN; 5 min, 95% CH_3CN). The purity of key compounds (**16**, **18**, **19**, **21**, **28**, and **29**) was assessed as being >95% using HPLC under two conditions. Method 1: 5-min gradient (10% to 95% acetonitrile/water containing 0.05% TFA, flow rate 1.0 mL/min) at room temperature on an ACE5 C18 column (5 μm, 50 mm × 4.6 mm). Method 2: 20-min run with 3% methanol in methylene chloride(flow rate 1.5 mL/min) on a DYNAMAX SiO_2 column (8 μm, 250 mm × 4.6 mm). The UV detection was taken at 254 nm.

In vitro and in vivo data given throughout the text for compounds in Tables 1 and 2 were collected for the hydrochloride salts. The hydrochloride salts were prepared by mixing the final compounds with 1 equiv of a 1.0 M hydrochloric acid solution in ether followed by evaporation of the solvent.

Methods and Materials. Ltk− cells stably expressing D_1 and D_2 receptors at a density of 4−7 pmol/mg protein were lysed in hypotonic buffer and centrifuged at 48 000*g*. Membrane pellets were frozen and stored at −80 °C for use in binding assays. Receptor affinities were determined by equilibrium binding experiments in which bound and free radioligand were separated by rapid filtration, and bound counts were quantified by liquid scintillation counting. For D_1 binding, the radioligand was [^{3}H] SCH 23390 (0.3 nM), and nonspecific binding was defined by addition of 10 μM unlabeled SCH 23390. For D_2 binding, the radioligand was [^{3}H]methylspiperone (0.5 nM) and nonspecific binding was defined using 10 μM (−)-sulpride. [^{3}H]-8-OH-DPAT (0.5 nM) was the radioligand for 5-HT_{1a} binding with unlabeled compound (10 μM) used to define nonspecific binding. For α_{2a} binding, [^{3}H] RX 821002 (1.5 nM) and yohimbine (50 μM) were used for labeling and nonspecific binding, respectively. Test compounds, radioligand and membrane homogenates prepared from CHO cells expressing each receptor subtype were incubated in a 200 μL volume for 1 h at room temperature prior to filtration on GF−C plates. Competition binding data was analyzed using Graphpad Prism, in which curves fit a one-site competition model with a Hill Slope equal to or approximately 1. Mean K_i values from four separate determinations are reported. The SEM was below 15% in each case.

For adenylate cyclase experiments, CHO cells stably expressing D_1 receptors at a density below 1 pmol/mg protein were harvested and used immediately. Cell suspensions (50 000 cells/assay point) were pretreated for 15 min with test compounds solubilized in DMSO so that the final DMSO concentration was 0.01%. The D_1 agonist SKF 81297 (1−1000 nM) was added in the presence of 1 mM ascorbic acid, and the reaction proceeded at room temperature for 20 min. Cells were lysed and cAMP levels were quantified using the Adenylate Cyclase Activation Flash Plate Assay (Perkin-Elmer, Boston, MA). K_b values were calculated using Schild Analysis,[34] as described by Lazareno and Birdsall.[35]

Animal Dosing, Sample Collection, and HPLC/API-MS/MS Analysis. Procedures for animal dosing and analysis of compound concentrations in plasma by LC-MS/MS have been previously published.[32] Briefly, two male Sprague−Dawley rats were dosed orally with each compound at a dose of 10 mg/kg. Blood was collected at 30 min, 1, 2, 3, 4, and 6 h postdosing, centrifuged to separate plasma, and frozen at −20 °C. Thawed plasma was treated with acetonitrile to precipitate protein and analyzed by APCI-MS/MS. Calculations were performed in an Excel spreadsheet in order to determine pharmacokinetic parameters.

6,6aS,7,8,9,13b*R*-Hexahydro-7-methyl-5*H*-benzo[*d*]naphth[2,1-*b*]azepin-12-ol (3). A mixture of 2.51 g (8 mmol) of compound **2**, 5.0 g (80 mmol) of ammonium formate and 1.25 g of $Pd(OH)_2$/C (20% w/w) in 300 mL of methanol was stirred at room temperature for 3 days. It was filtered, and the filtrate was concentrated. The residue was partitioned between 400 mL of ethyl acetate and 200 mL of saturated sodium bicarbonate. The organic layer was washed with 50 mL of H_2O and concentrated to give 2.23 g (100%) of compound **3**: ^{1}H NMR ($CDCl_3$) δ 1.63 (m, 1 H), 1.94 (m, 1 H), 2.38 (m, 1 H), 2.41 (s, 3 H), 2.56−2.84 (m, 4 H), 3.00 (m, 1 H), 3.50 (m, 1 H), 4.73 (d, J = 7 Hz, 1 H), 5.73 (d, J = 2.5 Hz, 1 H), 6.51 9dd, J = 8, 3 Hz, 1 H), 6.95−7.13 (m, 5 H). HRMS (FAB^+) *m/z*: calcd, 280.1701; found, 280.1703.

6,6aS,7,8,9,13b*R*-Hexahydro-7-methyl-11-nitro-5*H*-benzo[*d*]naphth[2,1-*b*]azepin-12-ol (4). To a solution of 2.8 g (10 mmol) of compound **3** in 10 mL of formic acid was added a solution of 1.5 mL (23 mmol) of nitric acid in 5 mL of formic acid slowly. The mixture was stirred at room-temperature overnight. It was basified with saturated sodium bicarbonate and extracted with methylene chloride. The combined organic extracts were washed with brine, and concentrated. The residue was chromatographed eluting with 1 to 10% methanol in methylene chloride to give 1.39 g (43%) of compound **4** as an yellow solid. ^{1}H NMR ($CDCl_3$) δ 1.73 (ddd, J = 3, 12, 12 Hz, 1H), 2.03 (m, 1 H), 2.52 (s, 3 H), 2.50−2.88 (m, 5 H), 3.22 (m, 1 H), 3.59 (m, 1 H), 4.81 (d, J = 7 Hz, 1 H), 6.10 (s, 1 H), 6.94 (m, 1 H), 7.21 (m, 3 H), 7.85 (s, 1 H), 10.50 (br, 1 H); ^{13}C NMR ($CDCl_3$) δ 29.70, 29.96, 32.12, 37.18, 45.74, 58.22, 66.44, 117.30, 123.83, 126.44, 126.55, 128.13, 130.59, 130.64, 134.32, 136.09, 139.39, 153.78, 159.99. HRMS (FAB^+) *m/z*: calcd, 325.1552; found, 325.1548.

6,6aS,7,8,9,13b*R*-Hexahydro-7-methyl-11-nitro-12-(trifluoromethoxy)-5*H*-benzo[*d*]naphth[2,1-*b*]azepine (5). To a solution of 0.85 g 92.6 mmol) of compound **4** and 1.1 mL (7.9 mmol) of triethylamine in 10 mL of methylene chloride was added a solution of 0.66 mL (3.95 mmol) of trifluoromethanesulfonic anhydride in 1.5 mL of methylene chloride at −15 °C. The mixture was warmed to room temperature over 1 h. It was diluted with 15 mL of methylene chloride and washed with 15 mL of saturated sodium bicarbonate. The aqueous layer was extracted with four 20 mL portions of methylene chloride. The combined organic extracts were washed with 15 mL of brine and concentrated. The residue was chromatographed eluting with 2 to 3% methanol in methylene chloride to give 1.1 g (92%) of compound **5**: ^{1}H NMR ($CDCl_3$) δ 1.73 (m, 1 H), 2.06 (m, 1 H), 2.55 (s, 3 H), 2.60−2.93 (m, 5 H), 3.24 (m, 1 H), 3.75 (m, 1 H), 4.92 (d, J = 7 Hz, 1 H), 6.29 (s, 1 H), 6.91 (d, J = 7 Hz, 1 H), 7.20 (m, 3 H), 7.95 (s, 1 H). MS (*m/z*) 457 (M^+).

6,6aS,7,8,9,13b*R*-Hexahydro-7-methyl-11-nitro-*N*-(phenylmethyl)-5*H*-benzo[*d*]naphth[2,1-*b*]azepin-12-amine (6). A mixture of 0.117 g (0.26 mmol) of compound **5** and 0.086 mL (0.78 mmol) of benzylamine in 4 mL of acetonitrile was heated to reflux for 19 h. It was diluted with 10 mL of methylene chloride and washed with 15 mL of saturated sodium bicarbonate. The aqueous layer was extracted with four 10 mL portions of methylene chloride. The combined organic extracts were washed with 10 mL of brine and concentrated. The residue was purified by preparative TLC, eluting with 3% methanol in methylene chloride to give 0.079 g (74%) of compound **6**: ^{1}H NMR ($CDCl_3$) δ 1.66 (m, 1 H), 1.95 (m, 1 H), 2.32 (m, 1 H), 2.48 (s, 3 H), 2.40−2.85 (m, 4 H), 3.20 (m, 1 H), 3.50 (m, 1 H), 3.98 (dd, J = 15, 5 Hz, 1 H), 4.19 (dd, J = 15, 6 Hz, 1 H), 4.69 (d, J = 7 Hz, 1 H), 5.73 (s, 1 H), 6.87−7.23 (m, 9 H), 7.94 (s, 1 H), 8.48 (t, J = 5 Hz, 1 H, NH). MS (*m/z*) 414 (M^+).

6,6aS,7,8,9,13b*R*-Hexahydro-7-methyl-5*H*-benzo[*d*]-naphth[2,1-*b*]azepine-11,12-diamine (7). To a solution of 0.07 g (0.17 mmol) of compound **6** in 10 mL of methanol were added 0.035 g of $Pd(OH)_2$/C (20% w/w) and 0.11 g (1.7 mmol) of ammonium formate. The mixture was stirred under reflux for 18 h. It was filtered, and the filtrate was concentrated to give 0.049 g (98%) of compound **7**: ^{1}H NMR ($CDCl_3$) δ 1.69 (m, 1 H), 2.04 (m, 1 H), 2.36 (m, 1 H), 2.52 (s, 3 H), 2.62−2.90 (m, 4 H), 3.22 (m, 1 H), 3.30 (br, 4 H, NH_2), 3.58 (m, 1 H), 4.89 (d, J = 7 Hz, 1 H), 5.70 (s, 1 H), 6.50 (s, 1 H), 7.0−7.20 (m, 4 H). HRMS (FAB+) *m/z*: calcd, 294.1970; found, 294.1974.

5,6,6aS,7,8,9,13,14b*R*-Octahydro-7-methylnaphtho[1,2-*a*][1,2,3]triazolo[4,5-*h*][3]benzazepine (8). To a solution of

0.10 g (0.34 mmol) of compound **7**, 0.11 mL of concentrated hydrochloric acid, and 0.5 mL of acetic acid in 2 mL of H_2O was added a solution of 0.04 g (0.56 mmol) of sodium nitrite in 1 mL of H_2O. The mixture was stirred at room temperature for 1 h and extracted with methylene chloride. The extracts were washed with saturated sodium bicarbonate and brine and concentrated. The residue was purified by preparative TLC, eluting with 10% methanol in methylene chloride to give 0.007 (7%) of desired product **8**: ^{1}H NMR ($CDCl_3$) δ 1.78 (m, 1 H), 2.20 (m, 1 H), 2.65 (s, 3 H), 2.60−2.98 (m, 5 H), 3.42 (m, 1 H), 3.80 (m, 1 H), 4.98 (d, J = 7 Hz, 1 H), 6.74 (s, 1 H), 7.0 (d, J = 7 Hz, 1 H), 7.14−7.20 (m, 3 H), 7.63 (s, 1 H). HRMS (FAB$^+$) *m/z*: calcd, 305.1770; found, 305.1766.

11-Chloro-6,6aS,7,8,9,13b*R*-hexahydro-7-methyl-12-(trifluoromethoxy)-5*H*-benzo[*d*]naphth[2,1-*b*]azepine (9). This compound was obtained from compound **2** (2.2 g, 7.0 mmol) by following the procedure described for compound **5**. Compound **9** (1.86 g, 60%): ^{1}H NMR ($CDCl_3$) δ 1.71 (ddd, J = 4, 13, 13 Hz, 1 H), 2.04 (m, 1 H), 2.53 (s, 3 H), 2.50−2.89 (m, 5 H), 3.22 (ddd, J = 11, 6, 2 Hz, 1 H), 3.64 (dd, J = 13, 13 Hz, 1 H), 4.80 (d, J = 11 Hz, 1 H), 6.21 (s, 1 H), 6.94 (m, 1 H), 7.15−7.21 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 29.72, 29.84, 32.74, 37.57, 44.98, 57.41, 66.36, 116.66, 119.84, 120.75, 123.52, 126.40, 128.17, 130.50, 130.64, 136.08, 139.19, 143.38, 143.64, 149.52. MS (*m/z*) 446 (M$^+$).

11-Chloro-6,6aS,7,8,9,13b*R*-hexahydro-7-methyl-*N*-(2-propenyl)-5*H*-benzo[*d*]naphth[2,1-*b*]azepin-12-amine (10). A mixture of 0.89 g (2 mmol) of compound **9**, 0.04 g (0.18 mmol) of $Pd(OAc)_2$, 0.17 g (0.27 mmol) of BINAP, 0.22 g (3.8 mmol) of allylamine, and 0.91 g of cesium carbonate in 5 mL of toluene was stirred at room temperature for 30 min. The reaction was stirred at 100 °C for 10 h, then cooled to room temperature and filtered. The filtrate was concentrated, and the residue was purified by preparative TLC, eluting with 10% methanol in methylene chloride to give 0.09 g (13%) of compound **10**: ^{1}H NMR ($CDCl_3$) δ 1.70 (ddd, J = 4, 13, 13 Hz, 1 H), 2.05 (m, 1 H), 2.36 (dd, J = 15, 5 Hz, 1 H), 2.51 (s, 3 H), 2.62−2.87 (m, 4 H), 3.19 (m, 1 H), 3.40 (m, 2 H), 3.55 (m, 1 H), 4.22 (m, 1 H), 4.73 (d, J = 7 Hz, 1 H), 4.84 (dd, J = 3, 1.5 Hz, 1 H), 4.95 (m, 1 H), 5.60−5.65 (m, 1 H), 5.68 (s, 1 H), 7.0−7.26 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 29.87, 30.03, 32.02, 37.46, 45.02, 46.27, 58.75, 66.76, 110.56, 115.35, 116.55, 125.67, 125.92, 127.69, 128.78, 130.78, 131.09, 134.63,137.67, 139.38, 141.52, 147.86. MS (*m/z*) 353 (M$^+$).

7-Chloro-1,2,2aS,3,4,5,8,10c*R*-octahydro-3,9-dimethylnaphth[2′,1′:2,3]azepino[4,5-*e*]indole (11). A mixture of 0.05 g (0.14 mmol) of compound **10** and 0.1 mL of BF_3.OEt_2 in 2 mL of sulfolane was stirred at 215 °C for 6 h. It was cooled to room temperature and quenched with 25 mL of saturated sodium bicarbonate. The aqueous solution was extracted with two 20 mL portions of ethyl acetate. The combined organic extracts were washed with 10 mL of brine and concentrated. The residue was purified by preparative TLC, eluting with 10% methanol in methylene chloride to give 0.01 g (20%) of compound **11**: ^{1}H NMR ($CDCl_3$) δ 1.71 (m, 1 H), 2.16 (s, 3 H), 2.20 (m, 1 H), 2.50 (s, 3 H), 2.60−2.90 (m, 5 H), 3.23 (m, 1 H), 3.75 (m, 1 H), 4.22 (m, 1 H), 5.01 (d, J = 7 Hz, 1 H), 6.95−7.20 (m, 5 H), 7.85 (br, 1 H). HRMS (FAB$^+$) *m/z*: calcd, 351.1628; found, 351.1631.

11-Chloro-6,6aS,7,8,9,13b*R*-hexahydro-7-methyl-13-nitro-5*H*-benzo[*d*]naphth[2,1-*b*]azepin-12-ol (12). A procedure similar to that described for compound **4** employing compound **11** (3.14 g, 10 mmol) gave compound **12** (3.32 g, 92%): MS (*m/z*) 359 (M$^+$). Due to its low solubility, this compound was not identified by ^{1}H NMR.

2-[[11-Chloro-6,6aS,7,8,9,13b*R*-hexahydro-7-methyl-13-nitro-5*H*-benzo[*d*]naphth[2,1-*b*]azepin-12-yl]oxy]acetamide (13). A mixture of 5.38 g (15 mmol) of compound **12**, 2.28 g (16.5 mmol) of bromoacetamide, and 5 g (36 mmol) of potassium carbonate in 150 mL of acetone was heated under reflux for 70 h. The solvent was evaporated, and the residue was diluted with 150 mL of H_2O and extracted with four 150 mL portions of ethyl acetate. The combined organic extracts were washed with 100 mL of brine and concentrated. The residue was chromatographed on silica gel, eluting with 1 to 4% methanol in methylene chloride to give 5.66 g (90%) of compound **13**: ^{1}H NMR ($CDCl_3$) δ 1.62 (m, 1 H), 2.26 (m, 1 H), 2.46 (s, 3 H), 2.55−2.96 (m, 5 H), 3.24 (m, 1 H), 3.63 (m, 1 H), 4.48 (AB, J = 14, 2 Hz, 2 H), 4.87 (d, J = 7 Hz, 1 H), 5.70 (br, 1 H), 6.40 (br, 1 H), 6.90 (d, J = 7 Hz, 1 H), 7.0−7.20 (m, 3 H), 7.33 (s, 1 H). MS (*m/z*) 416 (M$^+$).

***N*-[11-Chloro-6,6aS,7,8,9,13b*R*-hexahydro-7-methyl-13-nitro-5*H*-benzo[*d*]naphth[2,1-*b*]azepin-12-yl]-2-hydroxyacetamide (14).** A mixture of 0.42 g (1 mmol) of compound **13** and 0.2 g (5 mmol) of sodium hydroxide in 5 mL of DMF was stirred at room temperature under nitrogen atmosphere for 2 h. It was quenched with 50 mL of saturated sodium bicarbonate and extracted with three 50 mL portions of ethyl acetate. The combined organic extracts were washed with 30 mL of brine and concentrated to give 0.41 g (98%) of compound **14**: ^{1}H NMR ($CDCl_3$) δ 1.60 (m, 1 H), 2.35 (m, 1 H), 2.47 (s, 3 H), 2.60−2.95 (m, 4 H), 3.05 (m, 1 H), 3.25 (m, 1 H), 3.64 (m, 1 H), 4.11 (AB, J = 16 Hz, 2 H), 4.86 (d, J = 7 Hz, 1 H), 6.83 (d, J = 7 Hz, 1 H), 6.98−7.14 (m, 3 H), 7.41 (s, 1 H), 8.12 (br, 1 H). HRMS (FAB$^+$) *m/z*: calcd, 416.1377; found, 416.1365.

11-Chloro-6,6aS,7,8,9,13b*R*-hexahydro-7-methyl-13-nitro-5*H*-benzo[*d*]naphth[2,1-*b*]azepin-12-amine (15) A solution of 0.41 g (1 mmol) of compound **14** in 3 mL of concentrated hydrochloric acid and 3 mL of 1,4-dioxane was heated under reflux for 2 h. After cooling, it was quenched with 50 mL of saturated sodium bicarbonate and extracted with two portions of 50 mL of ethyl acetate. The combined organic extracts were washed with 30 mL of brine and concentrated. The residue was chromatographed on silica gel eluting with 1 to 3% methanol in methylene chloride to give 0.32 g (89%) of compound **15**: ^{1}H NMR ($CDCl_3$) δ 1.66 (ddd, J = 4, 12, 12 Hz, 1 H), 2.36 (m, 1 H), 2.47 (s, 3 H), 2.53−2.73 (m, 3 H), 2.97 (m, 1 H), 3.0−3.22 (m, 2 H), 3.48 (m, 1 H), 4.73 (d, J = 7.7 Hz, 1 H), 4.76 (br, 2 H), 6.81 (d, J = 7.7 Hz, 1 H), 6.97−7.12 (m, 3 H), 7.20 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 28.75, 29.39, 34.41, 41.86, 46.99, 57.83, 63.24, 118.17, 125.54, 126.12, 127.61, 128.63, 131.05, 134.20, 135.51, 135.79, 138.0, 139.23, 140.05. HRMS (FAB$^+$) *m/z*: calcd, 358.1322; found, 358.1325.

4-Chloro-3,6,7,8,8aS,9,10,14b*R*-octahydro-8-methylimidazole[4,5-*i*]naphtho[1,2-*a*][3]benzazepine (16). To a mixture of 0.18 g (0.5 mmol) of compound **15** and 0.5 g of iron power in 2 mL of formic acid and 2 mL of H_2O was added 2 mL of concentrate hydrochloric acid. The mixture was heated under reflux for 2 h. After cooling to room temperature, it was quenched with 80 mL of saturated sodium bicarbonate and extracted with three portions of 60 mL of ethyl acetate. The combined organic extracts were washed with 30 mL of brine and concentrated. The residue was chromatographed on silica gel eluting with 1 to 3% methanol in methylene chloride to give 0.16 g (95%) of compound **16**: ^{1}H NMR ($CDCl_3$) δ 1.70 (ddd, J = 3, 13, 13 Hz, 1 H), 2.18 (m, 1 H), 2.52 (s, 3 H), 2.66−2.89 (m, 5 H), 3.25 (m, 1 H), 3.77 (m, 1 H), 5.02 (d, J = 7 Hz, 1 H), 6.88 (br, 1 H), 7.13−7.33 (m, 5 H), 7.54 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 29.26, 29.44, 34.43, 39.49, 44.54, 58.71, 66.81, 121.46, 123.45, 126.90, 127.06, 128.35, 128.76, 131.19, 137.16, 137.77, 138.69, 139.47, 140.34. HRMS (FAB$^+$) *m/z*: calcd, 338.1424; found, 338.1423. Degree of purity: HPLC method 1, retention time of 10.5 min, >97.8%; method 2, retention of 1.95 min, 95.9%.

11-Chloro-6,6aS,7,8,9,13b*R*-hexahydro-7-methyl-5*H*-benzo[*d*]naphth[2,1-*b*]azepine-12,13-diamine (17). To a mixture of 0.6 g (1.68 mmol) of compound **15** and 1 g of iron power in 10 mL of H_2O was added 10 mL of concentrate hydrochloric acid. The mixture was heated under reflux for 1 h. After cooling to room temperature, it was quenched with saturated sodium bicarbonate and extracted with three 100 mL portions of ethyl acetate. The combined organic extracts were washed with 30 mL of brine and concentrated to give 0.56 g (96%) of compound **17**: MS (*m/z*) 328 (M$^+$). This intermediate was used in next step without further purification.

4-Chloro-3,6,7,8,8aS,9,10,14b*R*-octahydro-8-methylnaphtho[1,2-*a*]-1,2,3-triazolo[4,5-*i*][3]benzazepine (18). To a

stirred solution of 0.055 g (0.17 mmol) of compound **17** in 2 mL of concentrated hydrochloric acid was slowly added a solution of 0.014 g (0.2 mmol) of sodium nitrite in 1.2 mL of H_2O at room temperature. After stirring for 3 h, it was quenched with 30 mL of saturated sodium bicarbonate and extracted with two 40 mL portions of ethyl acetate. The combined organic extracts were washed with 20 mL of brine and concentrated. The residue was purified by preparative TLC, eluting with 10% methanol in methylene chloride to give 0.048 g (84%) of compound **18**: ^{1}H NMR ($CDCl_3$) δ 1.69 (m, 1 H), 2.11 (m, 1 H), 2.50 (s, 3 H), 2.60−2.86 (m, 5 H), 3.23 (m, 1 H), 3.74 (m, 1 H), 5.03 (d, J = 7 Hz, 1 H), 7.03−7.40 (m, 5 H). HRMS (FAB$^+$) *m/z*: calcd, 339.1376; found, 339.1382. Degree of purity: HPLC method 1, retention time of 5.0 min, >99%; method 2, retention of 1.95 min, 99.2%.

4-Chloro-3,6,7,8,8aS,9,10,14b*R*-octahydro-8-methylimidazo[4,5-*i*]naphtho[1,2-*a*][3]benzazepin-2(1*H*)-one (19). To a solution of 0.064 g (0.2 mmol) of compound **17** and 0.025 g (0.2 mmol) of DMAP in 2 mL of acetonitrile was added a solution of 0.048 g (0.22 mmol) of di-*tert*-butyl dicarbonate in 1 mL of acetonitrile. The mixture was stirred at room temperature for 1 h and concentrated. The residue was purified by preparative TLC, eluting with 10% methanol in methylene chloride to give 0.048 g (69%) of compound **19**: ^{1}H NMR ($CDCl_3$) δ 1.65 (ddd, J = 3, 13, 13 Hz, 1 H), 2.15 (m, 1 H), 2.48 (s, 3 H), 2.50−2.93 (m, 5 H), 3.22 (m, 1 H), 3.40 (m, 1 H), 4.85 (d, J = 7 Hz, 1 H), 5.40 (br, 1 H, NH), 6.86 (s, 1 H), 7.10−7.30 (m, 4 H), 10.40 (br, 1 H, NH); ^{13}C NMR ($CDCl_3$) δ 29.31, 29.37, 34.26, 39.52, 44.13, 58.96, 66.88, 111.52, 121.72, 126.45, 126.55, 126.75, 127.18, 127.37, 128.65, 130.61, 136.39, 136.42, 138.30, 154.78. HRMS (FAB$^+$) *m/z*: calcd, 354.1373; found, 354.1375. Degree of purity: HPLC method 1, retention time of 6.35 min, 97.9%; method 2, retention of 1.95 min, 97.4%.

4-Chloro-3,6,7,8,8aS,9,10,14b*R*-octahydroimidazo[4,5-*i*]naphtho[1,2-*a*][3]benzazepin-2(1*H*)-one (20). A mixture of 8.5 g of pyridine and 10 mL of concentrated hydrochloric acid was distilled at 225 °C. To this solution was added 0.14 g (0.39 mmol) of compound **19** hydrochloride salt. The mixture was stirred at 225 °C for 6 h and cooled to room temperature. The solid was dissolved in dilute ammonium hydroxide. The aqueous solution was extracted with three 100 mL portions of ethyl acetate. The combined organic extracts were washed with 80 mL of brine and concentrated. The residue was purified by preparative TLC, eluting with 10% methanol in methylene chloride to give 0.082 g (62%) of compound **20**: ^{1}H NMR ($CDCl_3$) δ 1.63 (m, 1 H), 1.96 (m, 1 H), 2.77 (m, 5 H), 3.37 (m, 2 H), 4.65 (d, J = 7 Hz, 1 H), 5.40 (br, 1 H), 6.87 (s, 1 H), 7.10−7.30 (m, 4 H), 9.50−10.0 (br, 1 H); ^{13}C NMR $CDCl_3$ δ 29.16, 32.00, 38.59, 49.20, 49.80, 60.76, 111.54, 122.01, 126.17, 126.45, 126.59, 127.05, 127.12, 129.12, 130.29, 135.49, 136.76, 137.72, 154.81. HRMS (FAB$^+$) *m/z*: calcd, 340.1217; found, 340.1224. Anal. Calcd for $C_{19}H_{18}ClN_3O\cdot HCl\cdot 2H_2O$: C, 55.35; H, 5.62; N, 10.19. Found: C, 55.25; H, 5.26; N, 9.90.

4-Chloro-3,6,7,8,8aS,9,10,14b*R*-octahydro-8-methylimidazo[4,5-*i*]naphtho[1,2-*a*][3]benzazepine-2(1*H*)-thione (21). To a solution of 0.05 g (0.15 mmol) of compound **17** and 0.02 g (0.16 mmol) of DMAP in 3 mL of acetonitrile was added a solution of 0.081 g (0.46 mmol) of thiocarbonyldiimidazole in 2 mL of acetonitrile. The mixture was stirred at room temperature for 5 h and concentrated. The residue was purified by preparative TLC, eluting with 10% methanol in methylene chloride to give 0.04 g (71%) of compound **21**: ^{1}H NMR ($CDCl_3$) δ 1.67 (m, 1 H), 2.13 (m, 1 H), 2.49 (s, 3 H), 2.55−2.85 (m, 5 H), 3.22 (m, 1 H), 3.46 (m, 1 H), 4.90 (d, J = 7 Hz, 1 H), 6.40 (br, 1 H, NH), 6.97 (s, 1 H), 7.09 (d, J = 7 Hz, 1 H), 7.20−7.40 (m, 3 H), 9.40 (br, 1 H, NH). HRMS (FAB$^+$) *m/z*: calcd, 370.1145; found, 370.1140. Degree of purity: HPLC method 1, retention time of 5.0 min, >99.0%; method 2, retention of 4.33 min, 97.6%.

2-[[11-Chloro-6,6aS,7,8,9,13b*R*-hexahydro-7-methyl-5*H*-benzo[*d*]naphth[2,1-*b*]azepin-12-yl]oxy]-2-methylpropanamide (22). To a stirred solution of 3.14 g (10 mmol) of compound **2** in 50 mL of dioxane was added 0.6 g (60%, 15 mmol) of sodium hydride. After stirring at room temperature for 1 h, 2-bromo-2-methylpropanamide (1.66 g, 10 mmol) was slowly introduced at 0 °C. The mixture was heated under reflux overnight. It was cooled to room temperature and partitioned between 50 mL of methylene chloride and 50 mL of H_2O. The aqueous layer was extracted with four 25 mL portions of methylene chloride. The combined organic extracts were washed with 100 mL of brine and concentrated to give 3.58 g of mixture of desired compound **22** and recovered **2** with a ratio of 60:40. Compound **22**: ^{1}H NMR ($CDCl_3$) δ 1.26 (s, 3 H), 1.27 (s, 3 H), 1.70 (m, 1 H), 2.05 (m, 1 H), 2.40−2.85 (m, 5 H), 2.52 (s, 3 H), 3.20 (m, 1 H), 3.58 (m, 1 H), 4.76 (d, J = 7 Hz, 1 H), 5.30 (br, 1 H, NH), 6.02 (s, 1 H), 6.20 (br, 1 H, NH), 6.95−7.20 (m, 5 H). MS (*m/z*) 399 (M$^+$).

***N*-(11-Chloro-6,6aS,7,8,9,13b*R*-hexahydro-7-methyl-5*H*-benzo[*d*]naphth[2,1-*b*]azepin-12-yl)-2-hydroxy-2-methylpropanamide (23).** To a stirred solution of 3.58 g of compound **22** containing **2** in 60 mL of DMF was added 1.08 g (60%, 27 mmol) of sodium hydride at 0 °C. The mixture was stirred at 50 °C overnight. It was cooled to room temperature and partitioned between 100 mL of water and 100 mL of ether. The aqueous layer was extracted with 50 mL of ether and five 50 mL portions of ethyl acetate. The combined organic extracts were washed with brine and concentrated. The residue was chromatographed over silica gel eluting with 2 to 3% methanol in methylene chloride to give 1.91 g (48% in two steps) of compound **23**: ^{1}H NMR ($CDCl_3$) δ 1.44 (s, 6 H), 1.72 (m, 1 H), 2.04 (m, 1 H), 2.46 (m, 1 H), 2.52 (s, 3 H), 2.70−2.90 (m, 4 H), 3.22 (m, 1 H), 3.42 (m, 1 H), 4.79 (d, J = 7 Hz, 1 H), 6.98 (m, 1 H), 7.15−7.30 (m, 5 H), 8.91 (br, 1 H). HRMS (FAB$^+$) *m/z*: calcd, 399.1831; found, 399.1839.

11-Chloro-6,6aS,7,8,9,13b*R*-hexahydro-7-methyl-5*H*-benzo[*d*]naphth[2,1-*b*]azepin-12-amine (24). Compound **23** (2.07 g, 5.2 mmol) was hydrolyzed by the procedure described for compound **15** to give compound **24** (1.66 g, 100%): ^{1}H NMR ($CDCl_3$) δ 1.68 (ddd, J = 4, 13, 13 Hz, 1 H), 2.02 (m, 1 H), 2.38 (m, 1 H), 2.50 (s, 3 H), 2.62−2.85 (m, 4 H), 3.17 (m, 1 H), 3.54 (m, 1 H), 3.72 (br, 2 H, NH_2), 4.70 (d, J = 7 Hz, 1 H), 5.71 (s, 1 H), 6.98−7.17 (m, 5 H). HRMS (FAB$^+$) *m/z*: calcd, 313.1472; found, 313.1467.

13-Bromo-11-chloro-6,6aS,7,8,9,13b*R*-hexahydro-7-methyl-5*H*-benzo[*d*]naphtho[2,1-*b*]azepin-12-amine (25). To a stirred solution of 3.13 g (10 mmol) of compound **24** in 40 mL of formic acid was added 13 mL of 1 M bromine in formic acid slowly at 0 °C. The mixture was stirred at 0−5 °C for 1.5 h and concentrated. The residue was diluted with 100 mL of saturated sodium bicarbonate and extracted with four 120 mL portions of ethyl acetate. The combined organic extracts were washed with brine and concentrated. The residue was chromatographed eluting with 1 to 2% methanol in methylene chloride to give 3.23 g (83%) of compound **25**: ^{1}H NMR ($CDCl_3$) major atropisomer δ 2.0−2.20 (m, 2 H), 2.38 (m, 1 H), 2.37 (s, 3 H), 2.90−3.20 (m, 6 H), 4.38 (d, J = 10 Hz, 1 H), 4.52 (br, 2 H, NH_2), 6.48 (d, J = 8 Hz, 1 H), 6.95−7.20 (m, 4 H); minor atropisomer δ1.70 (m, 1 H), 2.39−2.44 (m, 2 H), 2.42 (s, 3 H), 2.60 (m, 1 H), 2.70 (m, 1 H), 2.82 (m, 2 H), 3.0−3.2 (m, 1 H), 3.58 (m, 1 H), 4.41 (br, 2 H, NH_2), 4.87 (d, J = 8 Hz, 1 H), 6.82 (d, J = 7 Hz, 1 H), 7.0−7.20 (m, 4 H). HRMS (FAB$^+$) *m/z*: calcd, 391.0577; found, 391.0566.

4-Chloro-3,6,7,8,8aS,9,10,14b*R*-octahydro-8-methyl-2*H*-naphtho[1,2-*a*]thiazolo[4,5-*i*][3]benzazepine-2-thione (26). A mixture of 0.098 g (0.25 mmol) of compound **25** and 0.08 g (0.5 mmol) potassium ethylxanthate in 2 mL of DMF was heated at 160 °C for 16 h. It was cooled, quenched with 60 mL of saturated sodium bicarbonate, and extracted with three 50 mL portions of 50 mL of ethyl acetate. The combined organic extracts were washed brine and concentrated to give 0.092 g (95%) of crude compound **26**: ^{1}H NMR ($CDCl_3$) δ 1.66 (m, 1 H), 2.22 (m, 1 H), 2.49 (s, 3 H), 2.50−2.80 (m, 5 H), 3.0−3.25 (m, 1 H), 3.70 (m, 1 H), 4.95 (d, J = 7 Hz, 1 H), 6.84 (d, J = 8 Hz, 1 H), 7.05−7.23 (m, 4 H). HRMS (FAB$^+$) *m/z*: calcd, 387.0756; found, 387.0758.

4-Chloro-2-(ethylthio)-7,8,8aS,9,10,14b*R*-hexahydro-6*H*-naphtho[1,2-*a*]thiazolo[4,5-*i*][3]benzazepine (27). A mixture of 0.079 g (0.2 mmol) of compound **26**, 0.05 g (0.3

mmol) of diethyl chlorophosphate, and 0.07 g (0.5 mmol) of potassium carbonate in acetone was heated under reflux for 15 h. It was concentrated, and the residue was diluted with 30 mL of water and extracted with four 40 mL portions of ethyl acetate. The combined organic extracts were washed with brine and concentrated. The residue was purified by preparative TLC, eluting with 8% methanol in methylene chloride plus 1% NH_4OH to give 0.074 g (87%) of compound **27**: ^{1}H NMR ($CDCl_3$) δ 1.37 (t, J = 7.3 Hz, 3 H), 1.66 (m, 1 H), 2.10 (m, 1 H), 2.47 (s, 3 H), 2.60−2.81 (m, 5 H), 3.14−3.26 (m, 3 H), 3.75 (m, 1 H), 5.01 (d, J = 7 Hz, 1 H), 6.95 (d, J = 8 Hz, 1 H), 7.08−7.27 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 14.56, 27.71, 29.31, 29.46, 34.15, 39.72, 45.93, 58.79, 66.64, 122.75, 126.72, 127.11, 127.24, 128.13, 132.02, 134.00, 135.10, 138.55, 140.80, 149.56, 169.08.

4-Chloro-3,6,7,8,8aS,9,10,14b*R*-octahydro-8-methyl-2*H*-naphtho[1,2-*a*]thiazolo[4,5-*i*][3]benzazepin-2-one (28). A mixture of 0.017 g (0.04 mmol) of compound **27** and 0.02 g (0.4 mmol) of sodium methoxide in 1 mL of DMF was stirred at room temperature for 64 h. It was quenched with 25 mL of water and extracted with three 25 mL portions of ethyl acetate. The combined organic extracts were washed with brine and concentrated. The residue was purified by preparative TLC, eluting with 8% methanol in methylene chloride plus 1% NH_4OH to give 0.010 g (66%) of compound **28**: ^{1}H NMR ($CDCl_3$) δ 1.64 (m, 1 H), 2.13 (m, 1 H), 2.46 (s, 3 H), 2.53−2.80 (m, 5 H), 3.21 (m, 1H), 3.66 (m, 1 H), 4.93 (d, J = 7 Hz, 1 H), 6.97 (d, J = 7 Hz, 1 H), 7.15 (s, 1 H), 7.22−7.26 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 29.33, 29.37, 34.26, 39.72, 45.63, 58.92, 66.62, 113.02, 122.70, 126.21, 126.97, 127.53, 128.23, 131.64, 132.05, 134.56, 137.88, 139.59, 140.74, 172.13. HRMS (FAB$^+$) *m/z*: calcd, 371.0985; found, 371.0979. Degree of purity: HPLC method 1, retention time of 5.4 min, 95.8%; method 2, retention of 1.95 min, 98.0%.

4-Chloro-3,6,7,8,8aS,9,10,14b*R*-octahydro-2*H*-naphtho-[1,2-*a*]thiazolo[4,5-*i*][3]benzazepin-2-one (29). This compound was prepared from **28** (0.037 g, 0.1 mmol) according to the procedure described for compound **20** (0.017 g, 48%): ^{1}H NMR ($CDCl_3$) δ 1.60 (m, 1 H), 1.96 (m, 1 H), 2.73−2.80 (m, 5 H), 3.36−3.48 (m, 2 H), 4.73 (d, J = 7 Hz, 1 H), 6.97 (d, J = 8 Hz, 1 H), 7.09 (s, 1 H), 7.10−7.23 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 29.26, 32.11, 38.62, 49.20, 51.46, 60.58, 113.00, 122.82, 126.51, 126.88, 127.42, 128.68, 131.56, 132.06, 133.96, 138.18, 139.31, 140.01, 171.66. HRMS (FAB$^+$) *m/z*: calcd, 357.0828; found, 357.0832. Degree of purity: HPLC method 1, retention time of 8.2 min, 97.6%; method 2, retention of 1.95 min, 96.3%.

8-Chloro-2,3,4,5-tetrahydro-7-hydroxy-3-methyl-5(*R*)-phenyl-1*H*-3-benzazepine-6-carboxaldehyde (30). A mixture of 2.88 g (10 mmol) of compound **1** and 1.4 g (10 mmol) of hexamethylenetetramine in 60 mL of TFA was heated under reflux for 42 h. The solvent was evaporated, and the residue was quenched with 200 mL of saturated sodium bicarbonate. It was extracted with three 150 mL portions of ethyl acetate. The combined organic extracts were washed with brine (80 mL) and concentrated. The residue was chromatographed on silica gel eluting with 0.5 to 3% methanol in methylene chloride to give 1.02 g (32%) of compound **30**: ^{1}H NMR ($CDCl_3$) d 2.39 (s, 3 H), 2.37−2.56 (m, 2 H), 2.74−2.93 (m, 3 H), 3.50 (dd, J = 13, 6.6 Hz, 1 H), 5.10 (dd, J = 6.6, 4 Hz, 1 H), 7.07 (m, 2 H), 7.20−7.32 (m, 3 H), 7.44 (s, 1 H), 10.20 (s, 1 H). HRMS (FAB$^+$) *m/z*: calcd, 316.1104; found, 316.1105,.

8-Chloro-2,3,4,5-tetrahydro-3-methyl-7-[(methylsulfonyl)oxy]-5(*R*)-phenyl-1*H*-3-benzazepine-6-carboxaldehyde (31). To a stirred solution of 1.0 g (3.2 mmol) of compound **30**, 0.63 g (6.3 mmol) of triethylamine, and 0.01 g of DMAP in 20 mL of methylene chloride was added 0.44 g (3.8 mmol) of methanesulfonyl chloride at 0 °C. The mixture was warmed to room temperature and stirred for 18 h. It was diluted with 200 mL of ethyl acetate and washed with 80 mL of saturated sodium bicarbonate and 50 mL of brine. The organic layer was concentrated to give 1.26 g (100%) of crude product **31**: ^{1}H NMR ($CDCl_3$) δ 2.20 (m, 1 H), 2.36 (s, 3 H), 2.53−2.60 (m, 2 H), 2.84−2.91 (m, 2 H), 3.42 (s, 3 H), 3.60 (m, 1 H), 5.38 (m, 1 H), 7.05 (m, 2 H), 7.17−7.28 (m, 3 H), 7.43 (s, 1 H), 10.39 (s, 1 H). MS (*m/z*) 394 (M$^+$).

4-Chloro-3,6,7,8,9,10-hexahydro-3,8-dimethyl-10(*R*)-phenylazepino[4,5-*e*]indazole (32). A mixture of 0.8 g (2 mmol) of compound **31**, 0.19 g (4 mmol) of methylhydrazine, and 0.39 g (5 mmol) of ammonium acetate in 60 mL of *m*-xylene was stirred at 135 °C for 15 min and at 150 °C for 3 days with azeotropic removal of water using a Dean−Stark apparatus. The solvent was evaporated, and the residue was diluted with 150 mL of saturated sodium bicarbonate. It was extracted with three 100 mL portions of ethyl acetate. The combined organic extracts were washed with 80 mL of brine and concentrated. The residue was chromatographed on silica gel, eluting with 1 to 2% methanol in methylene chloride to give 0.53 g (80%) of compound **32**: ^{1}H NMR ($CDCl_3$) δ 2.32−2.40 (m, 1 H), 2.39 (s, 3 H), 2.69−3.06 (m, 4 H), 3.54 (dd, J = 13, 6 Hz, 1 H), 4.37 (s, 3 H), 4.75 (m, 1 H), 7.10−7.30 (m, 6 H), 7.69 (s, 1 H). HRMS (FAB$^+$) *m/z*: calcd, 326.1420; found, 326.1426.

4-Chloro-3,6,7,8,9,10-hexahydro-8-methyl-10(*R*)-phenylazepino[4,5-e]indazole (33) and 4-Chloro-3,6,7,8,9,10-hexahydro-10(*R*)-phenylazepino[4,5-*e*]indazole (34). Both compound **33** and compound **34** were obtained in one pot from compound **32** (0.33 g, 1 mmol) by following the procedure described for compound **20**. Compound **33** (0.083 g, 27%): ^{1}H NMR ($CDCl_3$) δ 2.44 (s, 3 H), 2.60 (m, 1 H), 2.80 (m, 2 H), 2.93 (dd, J = 13, 3 Hz, 1 H), 3.07 (m, 1 H), 3.44 (dd, J = 13, 7 Hz, 1 H), 4.83 (dd, J = 7, 3 Hz, 1 H), 7.14−7.28 (m, 5 H), 7.64 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 34.84, 46.85, 47.79, 57.14, 60.33, 113.04, 125.93, 126.23, 127.68, 128.33, 128.65, 133.62, 134.02, 134.24, 136.97, 141.40. HRMS (FAB$^+$) *m/z*: calcd, 312.1268; found, 312.1278.

Compound **34** (0.067 g, 21%): ^{1}H NMR ($CDCl_3$) δ 2.75−2.89 (m, 2 H), 3.05 (m, 1 H), 3.22 (m, 1 H), 3.40 (dd, J = 14, 2 Hz, 1 H), 3.86 (dd, J = 14, 5 Hz, 1 H), 4.76 (m, 1 H), 7.10−7.30 (m, 5 H), 7.88 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 39.08, 47.90, 49.27, 51.52, 113.01, 126.29, 126.59, 127.60, 128.69, 129.27, 133.39, 134.31, 134.93, 136.67, 139.77. HRMS (FAB$^+$) *m/z*: calcd, 298.1111; found, 298.1108.

8-Chloro-2,3,4,5-tetrahydro-3-methyl-6-nitro-5(*R*)-phenyl-1*H*-3-benzazepin-7-ol (35). This compound was prepared from compound **1** (8.63 g, 30 mmol) by the procedure described for compound **4.** Compound **35** (10.2 g, 100%): ^{1}H NMR ($CDCl_3$) δ 2.10 (m, 1 H), 2.30 (s, 3 H), 2.60−2.90 (m, 4 H), 3.50 (br, 1 H), 4.10 (br, 1 H), 6.95−7.22 (m, 6 H). HRMS (FAB$^+$) *m/z*: calcd, 333.1006; found, 333.1014.

2-[[8-Chloro-2,3,4,5-tetrahydro-3-methyl-6-nitro-5(*R*)-phenyl-1*H*-3-benzazepin-7-yl]oxy]acetamide (36). This compound was synthesized from compound **35** (5.0 g, 15 mmol) by a similar procedure described for compound **13**. Compound **36** (3.89 g, 67%): ^{1}H NMR ($CDCl_3$) δ 2.20 (m, 1 H), 2.37 (s, 3 H), 2.60 (m, 2 H), 2.95 (m, 2 H), 3.60 (m, 1 H), 4.18 (br, 1 H), 4.60 (s, 2 H), 5.95 (br, 1 H, NH), 6.50 (br, 1 H, NH), 7.07 (d, J = 7.4, Hz, 2 H), 7.20−7.35 (m, 4 H). HRMS (FAB$^+$) *m/z*: calcd, 390.1221; found, 390.1205.

***N*-[8-Chloro-2,3,4,5-tetrahydro-3-methyl-6-nitro-5(*R*)-phenyl-1*H*-3-benzazepin-7-yl]-2-hydroxyacetamide (37).** This compound was prepared from compound **36** (1.8 g, 4.6 mmol) by a similar procedure described for compound **14**. Compound **37** (1.7 g, 94%): ^{1}H NMR (CD_3OD) δ 2.20 m, 1 H), 2.32 (s, 3 H), 2.60 (m, 1 H), 2.75 (m, 1 H), 2.88 (m, 2 H), 3.75 (m, 1 H), 4.13 (s, 2 H), 4.22 (m, 1 H), 4.90 (br, 1 H), 7.10−7.30 (m, 5 H), 7.58 (s, 1 H). HRMS (FAB$^+$) *m/z*: calcd, 390.1221; found, 390.1216.

8-Chloro-2,3,4,5-tetrahydro-3-methyl-6-nitro-5(*R*)-phenyl-1*H*-3-benzazepin-7-amine (38). This compound was obtained from compound **37** (1.5 g, 3.85 mmol) according to the procedure described for compound **15**. Compound **38** (1.3 g, 100%): ^{1}H NMR ($CDCl_3$) δ 2.04 (m, 1 H), 2.41 (s, 3 H), 2.80−3.0 (m, 2 H), 3.60−3.80 (m, 3 H), 4.40 (m, 1 H), 4.76 (br, 2 H), 7.05−7.35 (m, 6 H). HRMS (FAB$^+$) *m/z*: calcd, 332.1166; found, 332.1165.

8-Chloro-2,3,4,5-tetrahydro-3-methyl-5(*R*)-phenyl-1*H*-3-benzazepine-6,7-diamine (39). This compound was pre-

pared from compound **38** (0.5 g, 1.5 mmol) by the procedure described for compound **17**. Compound **39** (0.49 g, 100%): ^{1}H NMR ($CDCl_3$) δ 2.37 (s, 3 H), 2.58 (m, 2 H), 2.76−3.0 (m, 3 H), 3.30−3.70 (br, 4 H), 3.78 (m, 1 H), 4.40 (m, 1 H), 6.67 (s, 1 H), 7.15−7.33 (m, 5 H). MS (*m/z*) 302 (M^+).

4-Chloro-3,6,7,8,9,10-hexahydro-8-methyl-10(*R*)-phenylimidazo[4,5-*g*][3]benzazepin-2(1*H*)-one (40). This compound was synthesized from compound **39** (0.44 g, 1.45 mmol) by the procedure described for compound **19**. Compound **40** (0.36 g, 75%): ^{1}H NMR ($CDCl_3$) δ 2.46 (m, 1 H), 2.56 (s, 3 H), 2.66 (m, 1 H), 2.93−3.35 (m, 3 H), 3.79 (br, 1 H), 5.24 (br, 1 H), 6.67 (s, 1 H), 7.10−7.30 (m, 5 H), 10.5 (br, 1 H, NH), 12.0 (br, 1 H, NH). HRMS (FAB^+) *m/z*: calcd, 328.1217; found, 328.1213.

4-Chloro-3,6,7,8,9,10-hexahydro-10(*R*)-phenylimidazo-[4,5-*g*][3]benzazepin-2(1*H*)-one (41). This compound was prepared from compound **40** (0.13 g, 0.29 mmol) by following the procedure described for compound **20**. Compound **41** (0.08 g, 81%): ^{1}H NMR (CD_3OD) δ 2.63 (m, 2 H), 2.93−3.20 (m, 3 H), 3.80 (m, 1 H), 4.55 (m, 1 H), 4.90 (br, 2 H, NH), 6.91 (s, 1 H), 7.07−7.35 (m, 5 H); ^{13}C NMR (CD_3OD) δ 39.82, 46.99, 68.88, 52.01, 113.10, 123.29, 123.95, 126.95, 127.34, 128.46, 129.73, 131.70, 138.00, 140.16. HRMS (FAB^+) *m/z*: calcd, 314.1060; found, 314.1064.

4-Chloro-3,6,7,8,9,10-hexahydro-8-methyl-10(*R*)-phenylimidazo[4,5-*g*][3]benzazepine-2(1*H*)-thione (42). This compound was prepared from compound **39** (0.04 g, 0.13 mmol) by the procedure described for compound **21.** Compound **42** (0.031 g, 68%): ^{1}H NMR ($CDCl_3$) δ 2.45 (m, 1 H), 2.67 (s, 3 H), 2.40−3.05 (m, 4 H), 3.38 (br, 1 H), 4.05 (br, 1 H), 5.71 (br, 1 H), 6.86 (s, 1 H), 7.97 (d, J = 7 Hz, 2 H), 7.10−7.30 (m, 3 H), 12 (br, 1 H). HRMS (FAB^+) *m/z*: calcd, 344.0988; found, 344.0984.

2-[[8-Chloro-2,3,4,5-tetrahydro-3-methyl-5(*R*)-phenyl-1*H*-3-benzazepin-7-yl]oxy]-2-methylpropanamide (43). This compound was prepared from compound **1** by the procedure described for compound **22**. Compound **43**: ^{1}H NMR ($CDCl_3$) δ 1.31 (s, 6 H), 2.34 (s, 3 H), 2.65−3.20 (m, 6 H), 4.25 (d, J = 9 Hz, 1 H), 5.90 (br, 1 H), 6.30 (s, 1 H), 6.95−7.40 (m, 6 H). MS (*m/z*) 373 (M^+).

N-[8-chloro-2,3,4,5-tetrahydro-3-methyl-5(*R*)-phenyl-1*H*-3-benzazepin-7-yl]-2-hydroxy-2-methylpropanamide (44). This compound was prepared from compound **43** by the procedure described for compound **23**. Compound **44**: ^{1}H NMR ($CDCl_3$) δ 1.49 (s, 3 H), 1.50 (s, 3 H), 2.38 (s, 3 H), 2.40−3.20 (m, 6 H), 4.34 (m, 1 H), 7.10−7.40 (m, 7 H), 9.11 (br, 1 H, NH). MS (*m/z*) 373 (M^+).

8-Chloro-2,3,4,5-tetrahydro-3-methyl-5(*R*)-phenyl-1*H*-3-benzazepin-7-amine (45). This compound was prepared from compound **44** by the procedure described for compound **15**. Compound **45**: ^{1}H NMR ($CDCl_3$) δ 2.33 (m, 1 H), 2.37 (s, 3 H), 2.67−3.10 (m, 5 H), 3.78 (br, 2 H), 4.23 (d, J = 8 Hz, 1 H), 6.05 (s, 1 H), 7.02 (s, 1 H), 7.16−7.37 (m, 5 H). MS (*m/z*) 287 (M^+).

6-Bromo-8-chloro-2,3,4,5-tetrahydro-3-methyl-5(*R*)-phenyl-1*H*-3-benzazepin-7-amine (46). This compound was prepared from compound **45** (1.12 g, 3.9 mmol) by the procedure described for compound **15.** Compound **46** (1.24 g, 87%): ^{1}H NMR ($CDCl_3$) δ 2.19 (m, 1 H), 2.35 (s, 3 H), 2.43 (m, 1 H), 2.60−2.90 (m, 3 H), 3.50−3.80 (m, 1 H), 4.54 (br, 2 H, NH_2), 5.01 (m, 1 H), 7.02 (s, 1 H), 7.0−7.35 (m, 5 H). MS (*m/z*) 365 (M^+).

4-Chloro-3,6,7,8,9,10-hexahydro-8-methyl-10(*R*)-phenyl-2*H*-thiazolo[5,4-*g*][3]benzazepin-2-thione (47). This compound was prepared from compound **46** (0.80 g, 2.19 mmol) by the procedure described for compound **25.** Compound **47** (0.58 g, 73%): ^{1}H NMR ($CDCl_3$) δ 2.20 (m, 1 H), 2.40 (s, 3 H), 2.70−3.20 (m, 4 H), 3.38 (m, 1 H), 4.40 (m, 1 H), 7.10−7.30 (m, 6 H). MS (*m/z*) 361 (M^+).

4-Chloro-2-(ethylthio)-7,8,9,10-tetrahydro-8-methyl-10(*R*)-phenyl-6*H*-thiazolo[5,4-*g*][3]benzazepine (48). This compound was prepared from compound **47** (0.58 g, 1.6 mmol) by the procedure described for compound **26**. Compound **48** (0.42 g, 68%): ^{1}H NMR ($CDCl_3$) δ 1.47 (t, J = 7 Hz, 3 H), 2.38 (s, 3 H), 2.45 (m, 1 H), 2.71−2.84 (m, 3 H), 3.04 (m, 1 H), 3.32 (q, J = 7 Hz, 2 H), 3.46 (m, 1 H), 4.36 (m, 1 H), 7.11 (d, J = 7 Hz, 2 H), 7.20−7.30 (m, 4 H). MS (*m/z*) 389 (M^+).

4-Chloro-3,6,7,8,9,10-hexahydro-8-methyl-10(*R*)-phenyl-2*H*-thiazolo[5,4-*g*][3]benzazepin-2-one (49). This compound was synthesized from compound **48** (0.36 g, 0.94 mmol) by the procedure described for compound **28**. Compound **49** (0.25 g, 76%): ^{1}H NMR ($CDCl_3$) δ 2.40 (s, 3 H), 2.46−2.65 (m, 2 H), 2.78−3.02 (m, 3 H), 3.40 (m, 1 H), 4.22 (m, 1 H), 7.08 (s, 1 H), 7.10 (d, J = 7 Hz, 1 H), 7.20−7.30 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 34.84, 47.55, 49.58, 57.11, 59.86, 113.90, 126.63, 127.44, 127.50, 128.48, 131.14, 134.80, 136.30, 139.28, 170.26. HRMS (FAB^+) *m/z*: calcd, 345.0828; found, 345.0831.

4-Chloro-3,6,7,8,9,10-hexahydro-10(*R*)-phenyl-2*H*-thiazolo[5,4-*g*][3]benzazepin-2-one (50). This compound was prepared from compound **49** (0.16 g, 0.46 mmol) by the procedure described for compound **20.** Compound **50** (0.08 g, 51%): ^{1}H NMR ($CDCl_3$) δ 2.63 (dd, J = 15, 3 Hz, 1 H), 2.76−2.96 (m, 2 H), 3.16 (m, 1 H), 3.32 (dd, J = 15, 3 Hz, 1 H), 3.79 (dd, J = 15, 6 Hz, 1 H), 4.13 (m, 1 H), 7.07 (d, J = 8 Hz, 2 H), 7.10 (s, 1 H), 7.22−7.34 (m, 3 H). HRMS (FAB^+) *m/z*: calcd, 331.0672; found, 331.0675.

Acknowledgment. The authors gratefully acknowledge the assistance of Lia Kwee Isaac and April Smith-Torhan for binding assays, Lisa Broske for animal dosing, and Dr. Sam Wainhaus and Neeta Juvekar for mass spectrometric analysis. We thank Dr. Birendra Pramanik's group and Dr. Tse-Ming Chan's group for analytical support, and Drs. Jesse Wong and Jianshe Kong for scale-up of key intermediate **24.** We also thank Robert Budich for the ACS nomenclature of all the compounds.

Note Added after ASAP Publication

The units for C_{max} in column 3 of Table 2 are incorrect in the version posted ASAP January 13, 2005. The unit μM is replaced by ng/mL in the corrected version posted January 20, 2005.

References

(1) Claudi, F.; Stefano, A. D.; Napolitani, F.; Cingolani, G. M.; Giorgioni, G.; Fontenla, J. A.; Montenegro, G. Y.; Rivas, M. E.; Rosa, E.; Michelotto, B.; Orlando, G.; Brunetti, L. Binding and preliminary valuation of 5-hydroxy- and 10-hydroxy-2,3, 12, 12a-tetrahydro-1H-[1]benzoxepino[2,3,4-ij]isoquinolines as dopamine receptor ligands. *J. Med. Chem.* **2000**, *43*, 599−608.

(2) Emilien, G.; Durlach, C.; Aveaux, D.; Maloteaux, J.-M. Dopamine D_3 agonists. *Expert Opin. Ther. Pat.* **2001**, *11*, 1713−1728.

(3) Neve, K. A.; Neve, R. L. Eds. The Dopamine Receptors. Humana Press: Totowa, NJ, 1997.

(4) Andersen, H.; Nielsen, B. Novel approaches to development of antipsychotics. *Drug News Perspect.* **1991**, *4*, 150−157.

(5) Iorio, L. C.; Barnett, A.; Leitz, F. H.; Houser, V. P.; Korduba, C. A. SCH 23390, a potential benzazepine antipsychotic with unique interactions on dopamineric systems. *Pharmacology* **1983**, *226*, 462−468.

(6) (a) Pendlton, R. G.; Samler, L.; Kaiser, C.; Ridley, P. T. Studies on renal dopamine receptors with a new agonist. *Eur. J. Pharmacol*. **1978**, *51*, 19−28. (b) Settler, P. G.; Saru, H. M.; Zirkle, C. L.; Saunders, H. L. The central effects of a novel dopamine agonist. *Eur. J. Pharmacol*. **1978**, *50*, 419−430.

(7) Berger, J. G.; Chang, W. K.; Clader, J. W.; Hou, D.; Chipkin, R. E.; Mcphail, A. T. Synthesis and receptor affinities of some conformationally restricted analogues of the dopamine D_1 selectiveligand (5*R*)-8-chloro-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1*H*-3-benzazepine-7-ol. *J. Med. Chem.* **1989**, *32*, 1913−1921.

(8) Andersen, P. H.; Gronvald, F. C.; Hohlweg, R.; Hansen, L. B.; Guddal, E.; Braestrup, C.; Nielsen, E. B. NNC-112, NNC-687, and NNC-756, new selective and highly potent dopamine D1 receptor antagonists. *Eur. J. Pharmacol.* **1992**, *219*, 45−52.

(9) Riddall, D. R.; A comparison of the selectivities of SCH 23390 with BW737C89 for D_1, D_2 and 5-HT_2 binding sites both in vitro and in vivo. *Euro. J. Pharmacol.* **1992**, *210*, 279−284.

(10) Kozlik, A.; Sargent, B. J.; Needham, P. L. Substituted tetrahydroisoquinoline dopamine receptor inhibitors. Patent WO 9313073, 1993.

(11) Witt, T.; Hock, F. J.; lehmann, J. 7-Methyl-6,7,8,9,14,15-hexahydro-5*H*-benz[*d*]indolo[2,3-*g*]azecine: a new heterocyclic system and a new lead compound for dopamine receptor antagonists. *J. Med. Chem.* **2000**, *43*, 2079−2081.

(12) Barnett, A.; McQuade, R. D.; Tedford, C. Highlights of D_1 dopamine receptor antagonist research. *Neurochem. Int.* 1992, *20 (Suppl)*, 119S−122S. (b) Schtzberg, A. F.; Haddad, P.; Kaplan, E. M.; Lejoyeux, M.; Rosenbaum, J. F.; Young, A. H.; Zajecka, J. Serotonin reuptake inhibitor discontinuation syndrome: a hypothetical definition. *J. Clin. Psychiatry* **1997**, *58 (Suppl 7)*, 5−10.

(13) (a) Haney, M.; Ward, A. S.; Foltin, R. W.; Fischman, M. W. Effects of SCH 39166, a selective dopamine D_1 antagonist, on smoked cocaine self-administration by humans. *Psychopharmacology* **2001**, *155*, 330−337. (b) Nann-Vernptica, E.; Donny, E. C.; Bigelow, G, E.; Walsh, S. L. Repeated administration of the $D_{1/5}$ antagonist SCH 39166 fails to attenuate the subjective effects of cocaine. *Psychopharmacology* **2001**, *155*, 338−347.

(14) Coffin, V. L. Use of dopamine D_1/D_5 antagonists for treating obsessive compulsive disorders, somatoform disorders, dissociative disorders, eating disorders, impulse control disorders, and autism. Patent WO 19990301, 1999.

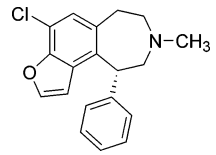
(15) (a) Tedford, C. E.; Coffin, V. L.; Ruperto, V.; Cohen, M.; McQuade, R. D.; Johnson, R.; Kim, H.-K.; Lin, C.-C. determination of plasma and brain concentrations of SCH 39166 and their correlation to conditioned avoidance behavior in rats. *Psychophamacology* **1993**, *113*, 199−204. (b) Tedford, C. E.; Ruperto, V. B.; Coffin, V. L.; Cohen, M.; Libonati, M.; Barnett, A. SCH 39166, a novel dopamine D_1 receptor antagonist: in vitro investigation of its glucuronidation and potential species differences. *Drug Dev. Res*. **1992**, *26*, 389−403. (c) Tedford, C. E.; Ruperto, V. B.; Barnett, A. Characterization of a rat liver glucuronosyltransferase that glucuronidates the selective D_1 antagonist, SCH 23390 and other benzazepines. *Drug Metab. Dispos*. **1990**, *19*, 1152−1159.

(16) (a) Doll, M. K.-H.; Nichols, D. E.; Kilts, J. D.; Prioleau, C.; Lawler, C. P.; lewis, M. M.; mailman, R. B. Synthesis and dopamineric properties of benzo-fused analogues of quinpirole and quinelorane. *J. Med. Chem*. **1999**, *42*, 935−940. (b) Asselin, A. A.; Humber, L. G.; Voith, K.; Matcalf, G. Drug design via pharmacophore identification. Dopamineric activity of 3H-benz[*e*]indol-8-amines and their mode of interaction with the dopamine receptor. *J. Med. Chem.* **1986**, *29*, 648−654. (c) Bach, N. J.; Kornfeld, E. C.; Jones, N. D.; Chaney, M. O.; Dorman, D. E.; paschal, J. W.; Clemens, J. A.; Smalstig, E. B. Bicyclic and tricyclic ergoline partial structures. Rigid 3-(2-aminoethyl)pyrrol and 3- and 4-(2-aminoethyl)pyrazoles as dopamine agonists. *J. Med. Chem.* **1980**, *23*, 481−491. (d) Schneider, C. S.; Mierau, J. Dopamine autoreceptor agonists: resolution and pharmacological activity of 2,6-diaminotetrahydrobenzothiazole and an aminothiazole analogue of apomorphine. *J. Med. Chem.* **1987**, *30*, 494−498. (e) Cannon, J. G.; Demopoulos, B. J.; Long, J. P.; Plynn, J. P.; Sharabi, F. M. Porposed dopaminergic pharmacophore of lergotrile, pergolide, and related ergot alkaloid derivatives. *J. Med. Chem*. **1981**, *24*, 238−239. (f) Glass, S. A.; Corbin, A. E.; Pugsley, T. A.; Heffner, T. G.; Wiss, L. D. Synthesis and dopaminergic activity of pyridine analogues of 5-hydroxy-2-(di-*n*-propylamino)tetralin. *J. Med. Chem.* **1995**, *38*, 3132−3137. (g) Weistock, J.; Gaitanopoulos, Stringer, O. D.; Franz, R. G.; Hieble, J. P. Kinter, L. B.; Mann, W. A.; Flaim, K. E.; Gessner, G. Synthesis and evaluation of noncatechol D-1 and D-2 dopamine receptor agonists: benzimidazol-2one, benzoxazol-2-one, and the highly potent benzothiazol-2-one 7-ethylamines. *J. Med. Chem.* **1987**, *30*, 1166−1176. (h) Denyer, C. V.; Bunyan, H.; Loakes, D. M.; Tucker, J.; Gillam, J. Synthesis of a hexahydro-2H-imidazole[4,5-g]isoquinolin-2-one derivative as an isostere of catecholamine-based selective dopamine D_1 antagonists. *Tetrahedron* **1995**, *51*, 5057−5066. (i) Singh, B.; Bacon, E. R.; Shaughnessy, R.; Fritz, R. K.; Lesher, G. Y.; Kumar, V.; Dority, J. A.; Reuman, M.; Kuo, G.-H.; Eissenstat, M. A.; Pagani, E. D.; Bode, D. C.; Bentley, R. G.; Connell, M. J.; Hamel, L. T.; Silver, P. J. Novel cAMP PDE III inhibitors: imidazo[4,5-*b*]pyridine-2(3*H*)-ones and thiazolo[4,5-*b*]pyridine-2(3*H*)-ones and their analogues. *J. Med. Chem.* **1994**, *37*, 248−254. (j) Bosch, J.; Roca, T.; Perez, C. G.; Montanari, S. Synthesis and dopaminergic activity of heterocyclic analogues of 5,6-dihydroxy-2-aminotetralins. *Bioorg. Med. Chem. Lett*. **2000**, *10*, 563−566. (k) Wright, J. L.; Gregory, T. F.; Kesten, S. R.; Boxer, P. A.; Serpa, K. A.; Meltzer, L. T.; Wise, L. D. Subtype-selective *N*-methyl-D-aspartate receptor antagonists: synthesis and biological evalution of 1-(heteroarylalkynyl)-4-benzylpiperidines. *J. Med. Chem.* **2000**, *43*, 3408−3419. (l) Mewshaw, R. E. Zhao, R. L.; Shi, X. J.; Marquis, K.; Brennan, J. A.; Mazandarani, H.; Coupet, J.; Andree, T. H. New generation dopaminergic agents. Part 8: heterocyclic bioisosteres that exploit the 7-OH-2-(Aminomethyl)chroman D_2 template. *Bioorg. Med. Chem. Lett*. **2002**, *12*, 271−274. (m) For a general review, see: Patani, G. A., LaVoie, E. J. Bioisosterism: a rational approach in drug design. *Chem. Rev.* **1996**, *96*, 3147−3176.

(17) Strange, P. G. The binding of agonists and antagonists to dopamine receptors. *Biochem. Soc. Trans.* **1996**, *24*, 188−192.

(18) (a) Shah, J. H.; Izenwasser, S.; Geter-Douglass, B.; Witkin, J. M.; Newman, A. H. (±)−(N−Alkylamino)benzazepine analogues: novel dopamine D_1 receptor antagonists. *J. Med. Chem*. **1995**, *38*, 4284−4293. (b) Shah, J. H.; Kline, R. H.; Geter-Douglass, B.; Izenwasser, S.; Witkin, J. M.; Newman, A. H. (±)-3-[4′-(*N*,*N*-Dimethylamino)cinnamyl]benzazepine analogues: novel dopamine D_1 receptor antagonist. *J. Med. Chem*. **1996**, *39*, 3423−3428. (c) In house data unpublished.

(19) Compound **i** below is closely related to our active analogue series. In this benzofuran, the oxygen can only act as a hydrogen bond acceptor and is oriented similarly to possible hydrogen bonding directionality seen with our "conformation B" structures. Lacking the hydrogen bond donating ability reduced the activity of this species revealed by a D_1 K_i = 910 nM. Subsequent comparison to the affinities of indazole compounds **32** and **33** echo these observations.



i

(20) (a) Negash, K.; Nichols, D. E.; Watts, V. J.; Mailman, R. B. Further definition of the D_1 dopamine receptor pharmacophore: synthesis of *trans*-6,6a,7,8,9,13b-hexahydro-5*H*-benzo[*d*]naphth[2,1-*b*]azepines as rigid analogues of β-phenyldopamine. *J. Med. Chem*. **1997**, *40*, 2140−2147. (b) Pettersson, I.; Liljefors, T.; Bogeso, K. Conformational analysis and structure−activity relationships of selective dopamine D-1 receptor agonists and antagonists of the benzazepine series. *J. Med. Chem*. **1990**, *33*, 2197−2204. (c) Minor, D. L.; Wyrick, S. D.; Charifson, P. S.; Watts, V. J.; Nichols, D. E.; Mailman, R. B. Synthesis and molecular modeling of 1-phenyl-1,2,3,4-tetrahydroisoquinolines and related 5,6,8,9-tetrahydro-13b*H*-dibenzo[*a*,*h*]quinolines as D_1 dopamine antagonists. *J. Med. Chem*. **1994**, *79*, 4317−4328. (d) Hoffman, B.; Cho, S. J.; Zheng. W. F.; Wyrick, S.; Nichols, D. E.; Mailman, R. B.; Tropsha, A. Quantitative structure−activity relationship modeling of dopamine D_1 antagonists using comparative molecular field analysis, genetic algorithms-partial least-squares, and K nearest neighbor methods. *J. Med. Chem*. **1999**, *42*, 3217−3226.

(21) Ahman, J.; Buchwald, S. L. An improved method for the palladium-catalyzed amination of aryl triflates. *Tetrahedron Lett*. **1997**, *38*, 6363−6366.

(22) Anderson, W. K.; Lai, G. Boron trifluoride-diethyl ether complex catalysed aromatic amino-Claisen rearrangements. *Synthesis* **1995**, 1287−1290.

(23) Beholz, L. G.; Stille, J. R. Lewis acid-promoted 3-aza-Cope rearrangement of *N*-alkyl-*N*-allyanilines. *J. Org. Chem.* **1993**, *58*, 5095−5100.

(24) (a) Bayles, R. Johnson, M. C.; Maisey, R. F.; Turner, R. W. The Smiles rearrangement of 2-aryloxy-2-methylpropanamides. Synthesis of N-aryl-2-hydroxy-2-methylprapanamides. *Synthesis* **1977**, 31−33. (b) Bayles, R. Johnson, M. C.; Maisey, R. F.; Turner, R. W. A Smiles rearrangement involving non-activated aromatic systems: the facile conversion of phenols to anilines. *Synthesis* **1977**, 33−34.

(25) Knolker, H.-J.; Brazmeier, T.; Synthesis of chiral oxazolidin-2-ones and imidazolidin-2-ones via DMAP-catalyzed isocyanation of amines with di-*tert*-butyl dicarbonate. *Tetrahedron Lett.* **1998**, 39, 9407−9410.

(26) DeWald, H. A. The synthesis of 4-(o-fluorophenyl)6,8-dihydro-3,8-dimethylpyrazolo[3,4-e]diazepin-7(1H)one, a metabolite of zolazepam. *J. Heterocycl. Chem.* **1974**, *11*, 1061−1062.

(27) Singh, B.; Pennock, P. O.; Lesher, G. Y.; Bacon, E. P.; Page, D. F. An efficient and novel synthesis of fused thiazol-2(3H)-ones. *Heterocycles* **1993**, *36*, 133−144.

(28) Suzuki, Y.; Takahashi, H. Formylation of phenols with electron-withdrawing groups in strong acids. Synthesis of substituted salicylaldehydes. *Chem. Pharm. Bull*. **1983**, *31*, 1751−1753.

(29) Caron, S.; Vazquez, E. A versatile and efficient synthesis of substituted 1H-Indazoles. *Synthesis* **1999**, 588−592.

(30) (a) Bordwell, F. G.; Drucker, G. E.; Fried, H. E. Acidities of carbon and nitrogen acids: the aromaticity of the cyclopentadienyl anion. *J. Org. Chem*. **1981**, *46*, 632−635. (b) Catalan, J. Claramunt, R. M.; Elguero, J.; Laynez, J.; Menendez, M.; Anvia, F.; Quian, J. H.; Taagepera, M.; Taft, R. W. Basicity and acidity of azoles: the annelation effect in azoles. *J. Am. Chem. Soc.* **1988**, *110*, 4105−4111. (c) Brown, D. J. Some 2-substituted linear naphthiminazoles. *J. Chem. Soc*. **1958**, 1774−1777. (d) Antonova, A.; Simov, D. Ionization constants of 5- and 6-substituted benzothiazolones. *Monatsh. Chem*. **1976**, *107*, 1487−1491.

(31) Desiraju, G. R.; Steiner, T. *The weak hydrogen bond in structural chemistry and biology*; Oxford University Press: New York, 1999.
(32) Korfmacher, W. A.; Cox, K. A.; Ng, K. J.; Veals, J.; Hsien, Y.; Wainhaus, S.; Broske, L.; Prelusky, D.; Nomeir, A.; White, R. E. Cassette-accelerated rapid rat screen: a systematic procedure for the doing and liquid chromatography/atmospheris pressure ionization tandem mass spectrometric analysis of new chemical entities as part of new drug discovery. *Rapid Commun. Mass. Spectrom*. **2001**, *15*, 335−340.
(33) Veber, D. F.; Johnson, S. R.; Cheng, H.-Y.; Smith, B. R.; Ward, K. W.; Kopple, K. D. Molecular properties that influence the oral bioavailability of drug candidates. *J. Med. Chem.* **2002**, *45*, 2615−2623.
(34) Schild, H. O., Drug antagonism and pA2. *Pharmacol. Rev*. **1957**, *9*, 242−246.
(35) Lazareno, S. and Birdsall, N. J. M., Estimation of competitive antagonist affinity from functional inhibition curves using the Gaddum, Schild and Cheng-Prusoff equations. *Br. J. Pharmacol.* **1993**, *109*, 1110−1119.

JM030614P