Design, Synthesis, and Evaluation of 3,4-Dihydro-2*H*-[1,4]diazepino[6,7,1-*hi*]indol-1-ones as Inhibitors of Poly(ADP-Ribose) Polymerase

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Received October 10, 2003

The design, synthesis, and biological evaluation of potent inhibitors of poly(ADP-ribose) polymerase-1 (PARP-1) are reported. A novel series of 3,4-dihydro-2*H*-[1,4]diazepino[6,7,1-*hi*]-indol-1-ones were designed using a combination of protein structure-based drug design, molecular modeling, and structure−activity relationships (SAR). These novel submicromolar inhibitors possess a tricyclic ring system conformationally restricting the benzamide in the preferred cis orientation. The compounds were designed to optimize space-filling and atomic interactions within the NAD^+ binding site of PARP-1. Previously described and newly adapted methods were applied to syntheses of these tricyclic inhibitors. Various modifications were made to the diazepinoindolones at the 6- and 7-positions in order to study this region of the active site and optimize noncovalent interactions. The electron density of derivative **28** bound to chicken PARP-1 revealed that the oxime makes a tight hydrogen bond with the catalytic γ-carboxylate of glutamic acid (Glu) 988 in accordance with our original designs and models. Most of the compounds have been evaluated for inhibition of human PARP-1. Selected inhibitors were also tested for the ability to potentiate the cytotoxic effect of the DNA-damaging agent Topotecan.

Introduction

Poly(ADP-ribose) polymerases (PARPs), nuclear enzymes found in almost all eukaryotic cells, catalyze the transfer of ADP-ribose units from nicotinamide adenine dinucleotide (NAD^+) to nuclear acceptor proteins and are responsible for the formation of protein-bound linear and branched homo-ADP-ribose polymers.[1−8] The activation of PARP and the formation of poly(ADP-ribose) are the result of DNA strand breaks induced from exposure to certain chemotherapeutics, ionizing radiation, oxygen free radicals, or nitric oxide.[9,10] The acceptor proteins of poly(ADP-ribose), including histones, topoisomerases, DNA and RNA polymerases, DNA ligases, and metal-dependent endonucleases, are involved in maintaining DNA integrity.[7,11−14]

The cellular ADP-ribose transfer process may "indirectly" contribute to the resistance that often develops to various types of cancer therapies through its role in repairing DNA strand breaks caused by radiotherapy or chemotherapy. Consequently, inhibition of PARP-1 (EC 2.4.2.30), the most abundant form of the PARPs, may retard intracellular DNA repair and thereby enhance and prolong the antitumor effects of certain anticancer therapies. In vitro and in vivo data show that many PARP inhibitors potentiate the effects of ionizing radiation or cytotoxic agents and, therefore, may serve as effective adjunct cancer chemotherapeutics.[15−20]

PARP-1 has also been implicated in several other disease states. In addition to anticancer therapies, inhibitors may have utility against myocardial infarction, neurotoxicity consequent to stroke, head trauma, neurodegenerative diseases, insulin-dependent diabetes mellitus, and arthritis and inflammation.[10,21−25]

Many PARP inhibitors, designed as nicotinamide mimics, have been reported. Representative examples are shown in Figure 1. 3-Aminobenzamide, **I**, has been widely used in numerous studies; however, this simple compound lacks the potency and efficacy required to make it therapeutically useful.[26,27] Second-generation nicotinamide-based molecules made use of tetrahydroisoquinolin-2-one to restrict the amide in its cis conformation. PD128763, **II**, was shown to be approximately 50-fold more active than 3-aminobenzamide; however, development of this compound was discontinued.[15,28] Other constricted carboxamide-like examples include imides such as **III**[27] and quinazolinones such as **IV**.[17] More recently, a class of potent benzimidazole PARP inhibitors, **V**, was developed at the University of Newcastle.[29] The requisite cis amide geometry is locked in place through an eloquent design of an intramolecular hydrogen bond between the $-NH_2$ and the lone pair electrons of N-3.

Our group has recently reported three novel classes of tricyclic PARP-1 inhibitors, shown in Figure 2.[20,30,31]

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10.1021/jm030513r CCC: $27.50
Published on Web 09/29/2004

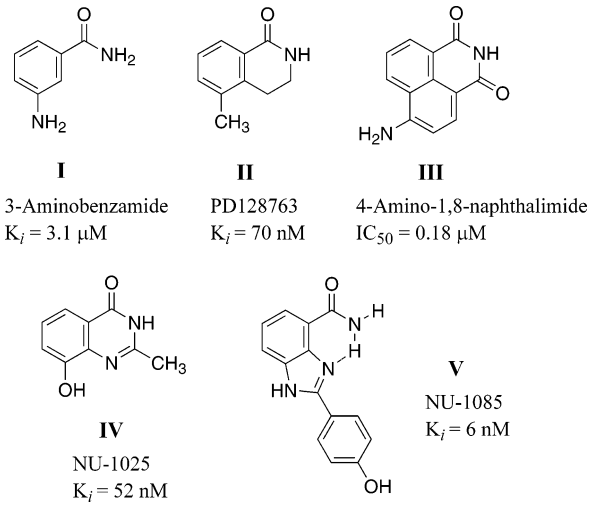


Figure 1.

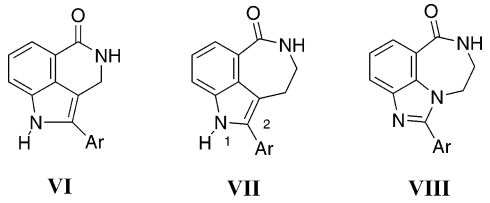


Figure 2.

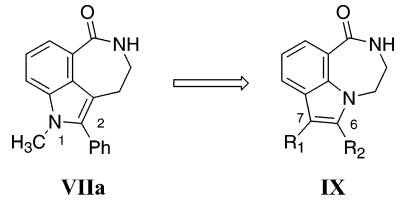


Figure 3.

The conception of these unique tricyclic inhibitors was based on the combination of reported information and protein−ligand structure-based design. As a continuation of our research, we have expanded this series to include 3,4-dihydro-2*H*-[1,4]diazepino[6,7,1-*hi*]indol-1-ones.

Molecular Design

In preceding publications, our group has described the design and syntheses of tricyclic PARP-1 inhibitors.[30,31] Incorporation of the seven-membered ring in **VII** and **VIII** not only locks the critical amide in the required cis geometry but also better disrupts the planarity of the tricyclic core, thereby filling more hydrophobic space while conceivably enhancing the overall physical properties of the molecule. Close examination of cocrystal structures of chicken PARP-1 complexed with inhibitors of type **V** or **VII** revealed a region adjacent to *N*-1 accessible for further modification.[29,30] It was previously shown that *N*-1 methylation of 2-phenyl-1,3,4,5-tetrahydroazepino[5,4,3-*cd*]indol-6-one (**VIIa**) is well-tolerated and not detrimental to binding.[30] We envisaged the tricyclic 3,4-dihydro-2*H*-[1,4]diazepino[6,7,1-*hi*]indol-1-one **IX** (Figure 3) to be an attractive alternative scaffold since synthetic modifications at C-7 would allow us to readily probe this scantily explored region of the active site.

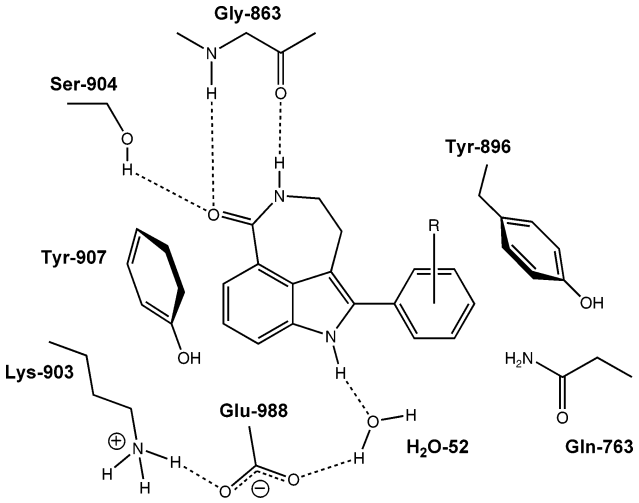


Figure 4.

Models of structure **IX** in the PARP-1 active site also show C-7 to be in close proximity to the catalytically relevant γ-carboxylic acid of Glu-988. Glu-988 functions in the polymerization reaction by forming a crucial hydrogen bond with the 2′-hydroxyl of the growing poly(ADP-ribose) chain, thus activating this hydroxyl for nucleophilic attack of carbon in the nicotinamide−ribose bond of the donor NAD^+ molecule.[32−34] In addition to activation, the hydrogen bond to the donor ribose hydroxyl stabilizes an oxocarbenium-like transition state.[34−36]

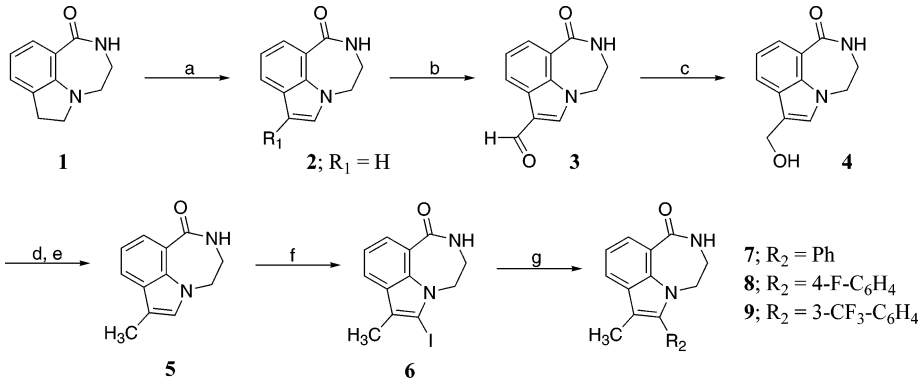
From crystallographic data, a water molecule is often observed situated between the nitrogen atom of the inhibitor and the γ-carboxylate of Glu-988, forming hydrogen bonds that "bridge" the ligand to the enzyme.[30,31] Figure 4 illustrates a schematic depiction of crystallographically observed atomic interactions between inhibitors of type **VII** and the active site residues of chicken PARP-1.[30]

We became very interested in the design of inhibitors that would possibly interact directly with Glu-988. Other research groups have also explored this region of the active site. Through crystallographic studies, Ruf et al. provided evidence that the 4-amino group of **III** forms a hydrogen bond with the γ-carboxylate of Glu-988.[37] Watson et al. designed electrophilic benzamide and isoquinolinone derivatives in an attempt to test whether Glu-988 would act as a nucleophile to form a covalent bond in a mechanism-based fashion.[38]

Our initial molecular modeling and design indicated that H_2O-52 could be displaced by other hydrogen bond donors, in particular the NOH of an *E*-carboxaldehyde oxime. A number of C-7-substituted diazepinoindolones were designed and prepared in order to determine whether direct interactions to Glu-988 would enhance inhibition of PARP-1 and to test the limitations of H_2O-52 displacement or reorientation.

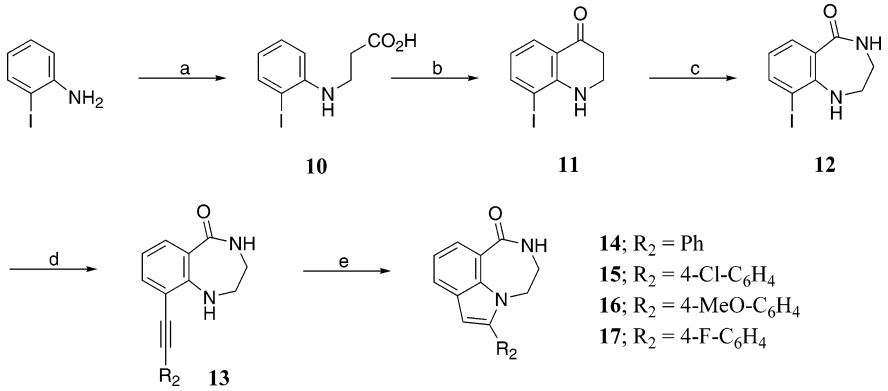
From our previous studies, we also learned that aryl groups at C-2 of tricylic compounds **VII** and **VIII** were advantageous to binding.[30,31] Aryl rings occupy hydrophobic space in this region of the active site, predominantly interacting with the side chains of Tyr-889 and Tyr-896. Capitalizing on the structure−activity relationship (SAR) information learned from the published series, several 6-substituted diazepinoindolones were

Scheme 1. Synthesis of 7-Methyl-3,4-dihydro-2*H*-[1,4]diazepino[6,7,1-*hi*]indol-1-ones (Method A)[a]



[a] Conditions and reagents: (a) DDQ, Ph-H. (b) ex $POCl_3$, DMF. (c) $NaBH_4$, EtOH. (d) AcOAc, pyr, DMAP. (e) 10% Pd/C, H_2, AcOH, MeOH. (f) I_2, $(CF_3CO_2)_2IC_6H_5$, CH_2Cl_2. (g) R_2-$B(OH)_2$, catalytic $(Ph_3P)_4Pd$, LiCl, Na_2CO_3, DMF, H_2O.

Scheme 2. Synthesis of 6-Substituted 3,4-Dihydro-2*H*-[1,4]diazepino[6,7,1-*hi*]indol-1-ones (Method B)[a]



[a] Conditions and reagents: (a) β-Propiolactone, CH_3CN, reflux. (b) P_2O_5, CH_3SO_3H, room temperature−65 °C. (c) NaN_3, CH_3SO_3H. (d) R_2−≡−H, catalytic $(Ph_3P)_4Pd$, CuI, Et_2NH, DMF. (e) Catalytic $PdCl_2$, CH_3CN, 60−70 °C.

therefore prepared and tested. The *meta*- and *para*-substituted *N*-alkylaminomethyl and *N*,*N*-dialkylaminomethyl phenyl analogues were designed with the primary intent to improve the aqueous solubility of the compounds. These substituents were previously exploited in tricyclic series **VI**−**VIII**.[30,31] The aminomethylene groups are generally well-accommodated in the enzyme active site. Molecular modeling of these functional groups and crystallographic data for a related inhibitor[31] suggest that the positively charged amino group participates in favorable electrostatic interactions to the side chains of Gln-763,[39] Asp-766, and Tyr-896.

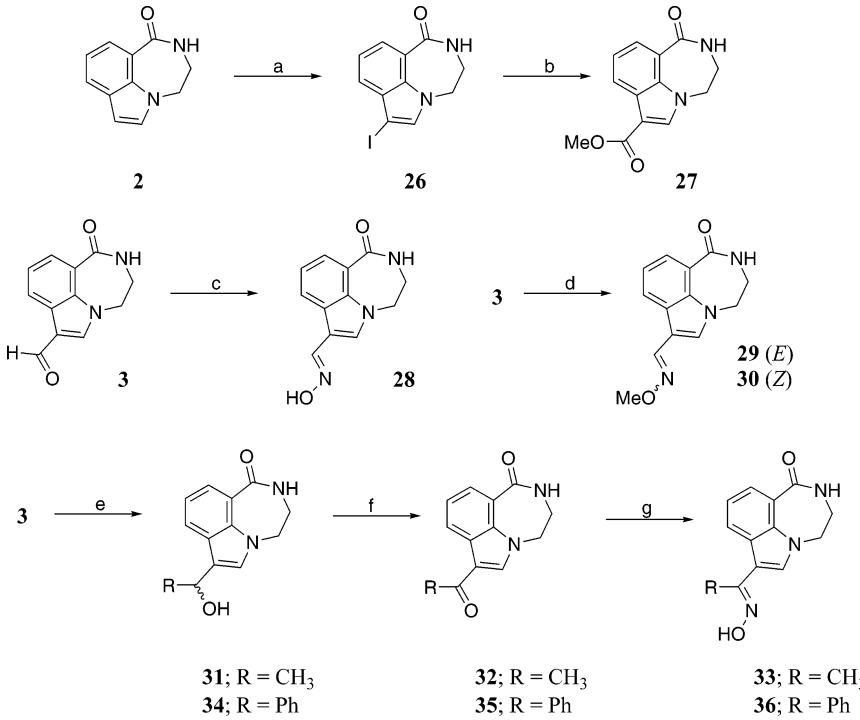
Finally, we were curious to learn whether 6,7-disubstituted derivatives would have additive effects on PARP inhibition. The 3,4-dihydro-2*H*-[1,4]diazepino-[6,7,1-*hi*]indol-1-one tricycle is an ideal ring system that readily allowed us to concurrently access both active site regions of interest via disubstitutions at the 6- and 7-positions.

Chemistry

We initially considered the unsubstituted 3,4-dihydro-2*H*-[1,4]diazepino[6,7,1-*hi*]indol-1-one **2** to be a versatile intermediate. It was synthesized from **1** using reported procedures.[40] Formylation or iodination via electrophilic aromatic substitution of **2** at C-7 allowed for the preparation of several derivatives as shown in Schemes 1 and 3. Scheme 1 (method A) depicts the syntheses of key intermediates **2** and **3** and further describes the preparation of 7-methyl-3,4-dihydro-2*H*-[1,4]diazepino-[6,7,1-*hi*]indol-1-one **5** by the catalytic deoxygenation of the acetate of **4**. Iodide **6**, generated in moderate yield from **5**, was used as a common intermediate in Suzuki type[41] palladium-catalyzed coupling of arylboronic acids to prepare the 6-aryl-7-methyl analogues **7**−**9** listed in Table 3.

Achieving monosubstitution at C-6 and disubstitution at C-6 and C-7 with greater diversity turned out not to be very convenient using **2** as a starting material. Because of synthetic limitations, an alternative synthesis of 3,4-dihydro-2*H*-[1,4]diazepino[6,7,1-*hi*]indol-1-ones was investigated as outlined in Scheme 2 (method B). Our new strategy relied on indole ring formation in the final step of the construction of the tricyclic core. Starting from 2-iodoaniline, compound **10** was prepared following a literature procedure.[42] In the same report, however, the authors were unsuccessful in their attempts to convert **10** to 8-iodo-tetrahydro-quinolin-4-one **11** using polyphosphoric acid and only observed position scrambling of iodine and dehalogenation during cyclization.[42] We were able to circumvent this problem and thus transform **10** to **11** in good yields when Eaton's reagent (P_2O_5/CH_3SO_3H)[43] was used. Ring expansion under Schmidt[44] reaction conditions gave iodo-diazepinone **12** in very good yield. Intermediate **12** was then subjected to tandem palladium-catalyzed acetylene coupling and indole cyclization to afford the tricyclic lactams **14**−**19**.[45,46] This new route also proved to be a more efficient method to prepare compound **2**. The 6-

Scheme 3. Synthetic Modifications to the 7-Position of 3,4-Dihydro-2*H*-[1,4]diazepino[6,7,1-*hi*]indol-1-ones[a]



[a] Conditions and reagents: (a) I_2, DMF, KOH. (b) CO, Et_3N, catalytic $(Ph_3P)_2PdCl_2$, DMF, MeOH. (c) $NH_2OH{\cdot}HCl$, H_2O, NaOH, EtOH. (d) $NH_2OMe{-}HCl$, pyr., EtOH. (e) RLi, THF. (f) *o*-Iodooxybenzoic acid, DMSO. (g) $NH_2OH{\cdot}HCl$, pyr.

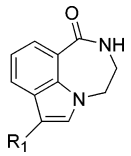
substituted 3,4-dihydro-2*H*-[1,4]diazepino[6,7,1-*hi*]indol-1-ones prepared are listed in Table 2.

The syntheses of 7-substituted derivatives via the highly versatile 7-formyl or 7-iodo intermediates **3** and **26**, respectively, are described in Scheme 3. Intermediate **3** was directly converted to oximes **28**−**30**, while a three-step sequence was used to synthesize keto-oximes **33** and **36**. Table 1 lists all 7-substituted diazopinoindolones synthesized.

Next, we focused our efforts on the synthesis of 6,7-disubstituted 3,4-dihydro-2*H*-[1,4]diazepino[6,7,1-*hi*]-indol-1-ones. Schemes 4 and 5 describe the synthesis of 6,7-disubstituted compounds with functional groups at the C-7 other than methyl and capable of displacing or hydrogen bonding to H_2O-52. As shown in Scheme 4, oximes **38** and **40** were readily prepared from aldehydes **37** and **39**, respectively. Oxime **40** was dehydrated with thiocarbonyldiimidazole to give nitrile **41**, a common intermediate used to prepare amide **42** and thioamide **43**. The methyl thiouronium salt **44** was readily prepared from **43** and further converted to *N*-hydroxyamidine **45** with hydroxylamine or *N*-aminoamidine **46** with hydrazine. Scheme 5 describes the synthesis of 7-acetyl-diazepinoindolone **48** from the corresponding iodide **47**. Acetyl **48** is used to prepare keto-oxime **49** and pyrrazole **51**. The data for the 6,7-disubstituted 3,4-dihydro-2*H*-[1,4]diazepino[6,7,1-*hi*]indol-1-ones prepared are listed in Table 3.

The last sets of compounds, *meta*- and *para*-arylaminomethylene derivatives **20**−**25**, were derived under reductive amination conditions of the appropriate aldehyde. As exemplified in Scheme 6, the *meta*-dimethylaminomethylene analogue **20** was prepared using method C. This route was developed and chosen over method B since it provided a more convenient and higher yielding synthesis of the penultimate aldehydes from common intermediate **53** and commercially available iodobenzaldehydes.

Table 1. 7-Substituted 3,4-Dihydro-2*H*-[1,4]diazepino[6,7,1-*hi*]indol-1-ones

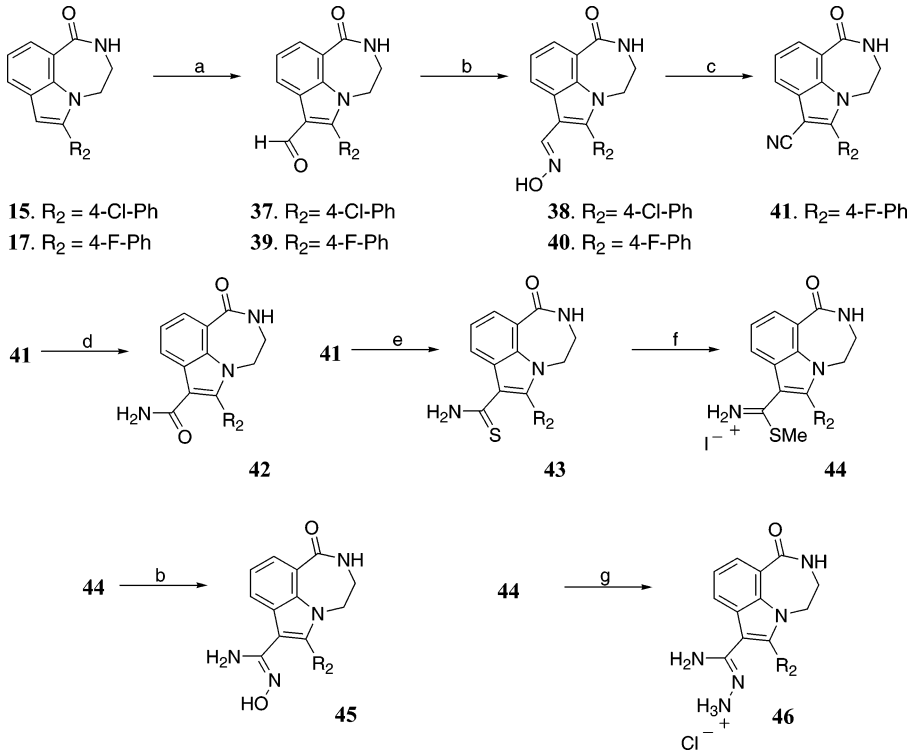


no.	R_1	mp (°C)	formula[a]	K_i (nM)[b,c]
2	H	165−167	$C_{11}H_{10}N_2O{\cdot}0.05H_2O$	105
3	CHO	238−240	$C_{12}H_{10}N_2O_2{\cdot}0.1H_2O$	176
4	CH_2OH	180−182	$C_{12}H_{12}N_2O_2{\cdot}0.20H_2O$	79
5	CH_3	135−137	$C_{12}H_{12}N_2O$	122
26	I	188−190	$C_{11}H_9N_2OI$[a]	304
27	$COOCH_3$	259−261	$C_{13}H_{12}N_2O_3{\cdot}0.25H_2O$	900
28	CH=NOH	262−264	$C_{12}H_{11}N_3O_2$	9.4
29	(*E*)-CH=NOMe	173−175	$C_{13}H_{13}N_3O_2{\cdot}0.25H_2O$	809
30	(*Z*)-CH=NOMe	210−212	$C_{13}H_{13}N_3O_2{\cdot}0.1H_2O$[a]	121
31	$CH(OH)CH_3$	295−297	$C_{13}H_{14}N_2O_2$	692
32	$COCH_3$	285−287	$C_{13}H_{12}N_2O_2$	606
33	$C(CH_3)$=NOH	238−240	$C_{13}H_{13}N_3O_2$	39
34	$C(OH)C_6H_5$	178−180	$C_{18}H_{16}N_2O_2{\cdot}0.25H_2O$	380
35	COC_6H_5	229−230	$C_{18}H_{14}N_2O_2$	337
36	(*E*) and (*Z*)-$C(C_6H_5)$=NOH	263−265	$C_{18}H_{15}N_3O_2{\cdot}0.1H_2O$	38

[a] Compounds were analyzed for C, H, and N; the results are in agreement to within ±0.4% of the theoretical values except for **26**: C, calcd, 42.33; found, 42.81. Compound **30**: analysis passed only with 0.1EtOAc. [b] Human PARP-1 enzyme inhibition; values are an average of at least two independent experiments; % error ≤ ±20%. [c] See Experimental Section for conditions.

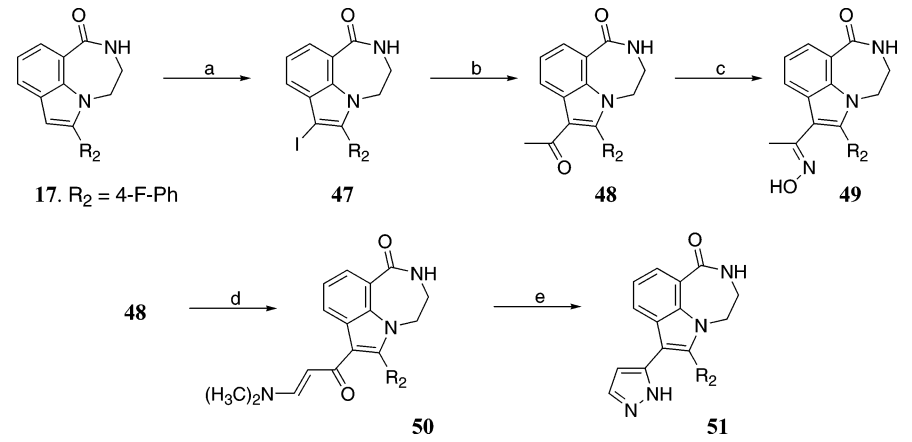
Enzyme Inhibition and Crystallographic Analysis. Data for the synthesized diazepinoindolinones are reported in Tables 1−3. Enzyme inhibition constants were determined using a previously reported method as described in the Experimental Section.[30,31,33] Oxime

Scheme 4. Synthesis of 6,7-Disubstituted 3,4-Dihydro-2*H*-[1,4]diazepino[6,7,1-*hi*]indol-1-ones[a]



[a] Conditions and reagents: (a) ex $POCl_3$, DMF. (b) $NH_2OH{\cdot}HCl$, pyr. (c) Thiocarbonyldiimidazole, THF. (d) 85% H_3PO_4, 90−100 °C. (e) H_2S, pyr., Et_3N, 0 °C. (f) CH_3I, THF. (g) NH_2NH_2, CH_3CN, then HCl/MeOH.

Scheme 5. Synthesis of 6,7-Disubstituted 3,4-Dihydro-2*H*-[1,4]diazepino[6,7,1-*hi*]indol-1-ones[a]



[a] Conditions and reagents: (a) I_2, DMF, KOH. (b) $H_2C{=}C(OEt)SnBu_3$, $(Ph_3P)_4Pd$, 2,6-di-^{t}Bu-4-Me-phenol, 1,4-dioxane, DMF. (c) $NH_2OH{\cdot}HCl$, pyr. (d) $(CH_3)_2NCH(OCH_3)_2$, DMF, 110−120 °C. (e) $NH_2NH_2{\cdot}H_2O$, THF.

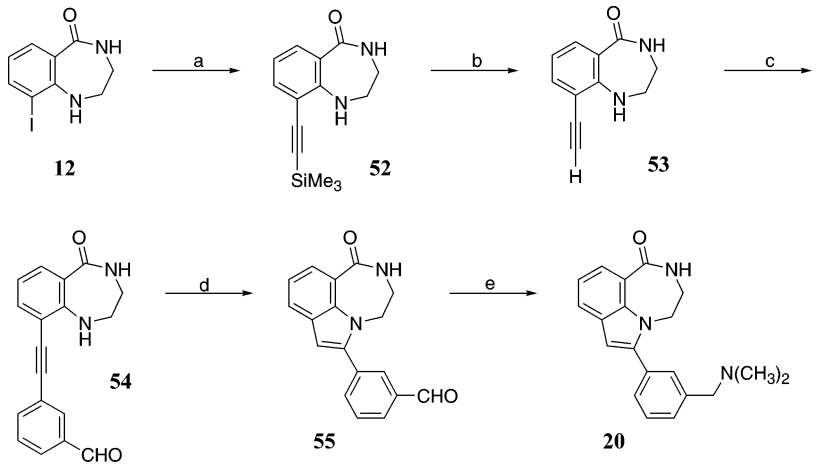
derivatives were the best enzyme inhibitors of all of the C-7 monosubstituted diazapinoindolinones (Table 1). The simplest trans-oxime, compound **28**, a 9.8 nM inhibitor of PARP-1, was the most potent derivative in this series with a K_i value 11 times lower than the parent compound **2**.

Compound **28** was cocrystallized with the C-terminal catalytic domain of chicken PARP-1 protein, and a 2.8 Å structure was solved (Figures 5 and 6). As anticipated from previous studies, the tricyclic core is wedged between the side chains of Tyr-896 and Tyr-907, while three key hydrogen bonds between the ligand amide and the protein are made.[30,31] The C-1 lactam carbonyl forms two hydrogen bonds, one to the side chain hydroxyl of Ser-904 and the other to the backbone amide of Gly-863. The N-2 lactam NH hydrogen bonds to the backbone carbonyl of Gly-863. The three-dimensional structure also confirmed our modeling. The *E*-oxime displaced a water molecule, and the −OH formed a very tight H-bond to the catalytic γ-carboxylic acid of Glu-988.

The important role this interaction has on binding was confirmed by the loss of affinity upon *O*-methylation of the oxime group. The corresponding *trans*-*O*-methyl analogue **29** has a K_i value 86 times greater than **2**, whereas the *cis*-*O*-methyl oxime **30** has a K_i about 13 times higher. Models of either **29** or **30** into the crystallographic complex of **28** and PARP-1 suggest that neither compound can be situated in the active site as well as **28**, especially since the *O*-methyl group prevents a direct interaction to Glu-988.

Oximes **33** and **36**, derived from methyl ketone **32** and phenyl ketone **35**, respectively, have K_i values four times

Scheme 6. Synthesis of 6-[3-(CH_2NMe_2)phenyl]-3,4-dihydro-2*H*-[1,4]diazepino[6,7,1-*hi*]indol-1-ones (Method C)[a]



[a] Conditions and reagents: (a) Trimethylsilylacetylene, catalytic $(Ph_3P)_4Pd$, CuI, Et_2NH, DMF. (b) Catalytic K_2CO_3, MeOH. (c) 4-Iodobenzaldehyde, catalytic $(Ph_3P)_4Pd$, CuI, Et_2NH, DMF. (d) $PdCl_2$, CH_3CN, 70−80 °C. (e) $HN(CH_3)_2$, MeOH, $NaBH_3CN$, HCl, H_2O.

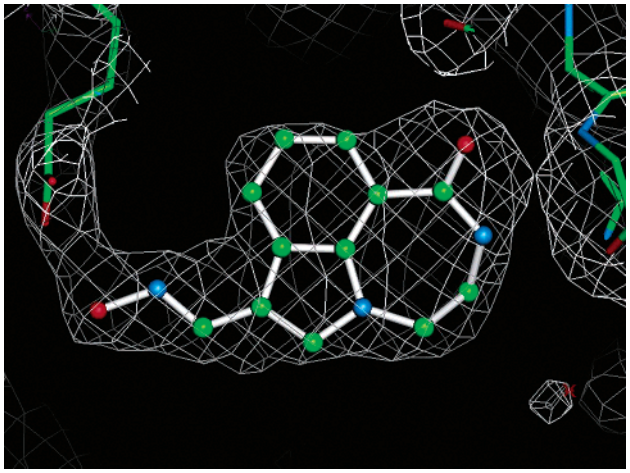


Figure 5. Electron density for compound **28** bound to chicken PARP-1. The initial 2.8 Å 2Fo-Fc electron density contoured at 1σ and phased with the PARP-1 protein and solvent model from a previous cocrystal structure.[29]

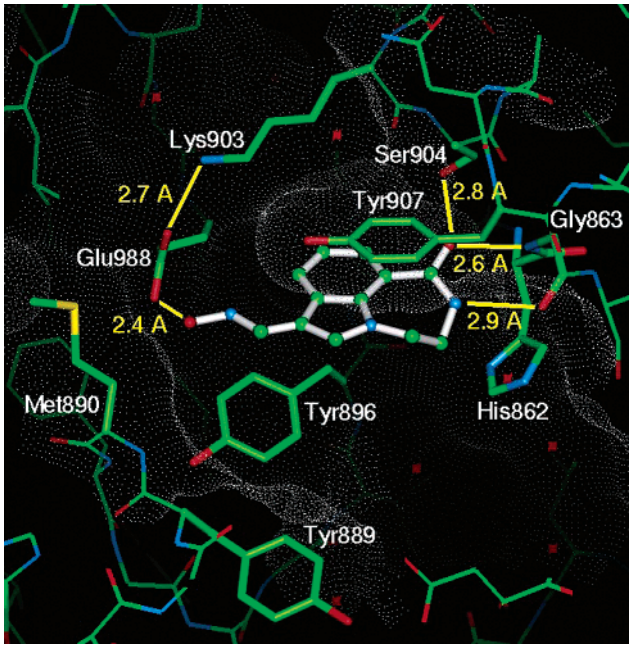


Figure 6. X-ray structure complex of **28** and chicken PARP-1 highlighting key protein residues and hydrogen bonds. Ordered water molecules are represented as red crosses, and the solvent-exposed surface of the PARP-1 active site is drawn with white dots.

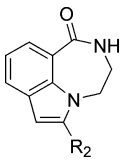
greater than **28**. Models of both compounds into the cocrystal structure suggest that there is inadequate space in the active site to accommodate either the methyl or the phenyl substituents, forcing the tricyclic ring to shift, thereby perturbing the optimal binding orientation observed with **28**. Hydroxymethyl derivative **4** was the only compound other than the oximes with a K_i value less than parent compound **2**.

Next, we focused our attention on C-6 monosubstituted diazepinoindolinones. As expected, the addition of various aryl groups at C-6 markedly enhances PARP-1 inhibition. Previous studies also established that potency could be enhanced with *meta*- or *para*-aminomethylene groups while improving aqueous solubility.[30,31] In general, *para*-aminomethylene derivatives **23**−**25** were indeed three of the most potent enzyme inhibitors prepared. The inhibition data for the C-6 monosubstituted diazepinoindolinones are listed in Table 2.

Examples of 6,7-disubstituted diazepinoindolones are shown in Table 3. Compound **7**, 7-methyl-6-phenyl-3,4-dihydro-2*H*-[1,4]diazepino[6,7,1-*hi*]indol-1-one, is closely related structurally to *N*-1-methyl-2-phenyl-1,3,4,5-tetrahydroazepino[5,4,3-*cd*]indol-6-one (**VIIa**), a 7 nM inhibitor of PARP-1 reported by Canan Koch et al.[30] However, when comparing their inhibitory activities against PARP-1, **7** has a K_i value of 41 nM, approximately six times higher than **VIIa**. Modeling results imply that the reduction in potency may be due, at least in part, to the loss of a weak hydrogen bond to Tyr-907 (CH_3N- - -H−O) and a less favorable electrostatic interaction with the aromatic ring of Tyr-907.

We postulated that a 6,7-disubstituted diazepinoindolone combining the carboxaldeoxime of **28** and the 4-fluorophenyl of **17** might provide a significant boost in activity against PARP-1. Analogue **40** is a 6.0 nM inhibitor of PARP-1, only marginally better than either **28** or **17**. Of interest is the 6,7-disubstituted diazepinoindolone analogue **49**, a combination of the methyl ketoxime of **33** and the 4-fluorophenyl of **17**. Compound **49**, a 9.1 nM enzyme inhibitor, has a K_i about four times less than **33**, but when compared to **17**, **28**, or **40**, the

Table 2. 6-Substituted 3,4-Dihydro-2*H*-[1,4]diazepino[6,7,1-*hi*]indol-1-ones



	R_2	mp (°C)	formula[a]	K_i (nM)[b,c]
14	C_6H_5	165−167	$C_{17}H_{14}N_2O\cdot0.1H_2O$	14.3
15	4-Cl-C_6H_4	238−240	$C_{17}H_{13}N_2OCl$	11
16	4-MeO-C_6H_4	188−190	$C_{18}H_{16}N_2O_2\cdot0.1H_2O$	8.2
17	4-F-C_6H_4	198−200	$C_{17}H_{13}N_2OF$	11
18	$(CH_2)_2C_6H_4$	188−190	$C_{19}H_{18}N_2O$	27
19	2-pyridyl	185−187	$C_{16}H_{13}N_3O\cdot0.8H_2O$	68
20	3-[$CH_2N(CH_3)_2$]-C_6H_4	98−100	$C_{20}H_{21}N_3O\cdot0.25H_2O$	9.1
21	3-[CH_2NHCH_3]-C_6H_4	128−130	$C_{19}H_{19}N_3O\cdot0.6H_2O$	6.9
22	3-[CH_2N-pyrrolyl]-C_6H_4	158−160	$C_{22}H_{23}N_3O\cdot0.4H_2O$	12.5
23	4-[$CH_2N(CH_3)_2$]-C_6H_4	140−142	$C_{20}H_{21}N_3O\cdot0.3H_2O$	6.4
24	4-[CH_2NHCH_3]-C_6H_4	178−180	$C_{19}H_{19}N_3O\cdot0.1H_2O$	3.8
25	4-[CH_2N-pyrrolyl]-C_6H_4	146−148	$C_{22}H_{23}N_3O\cdot0.25H_2O$	6.8
55	3-CHO-C_6H_4	192−194	$C_{18}H_{14}N_2O_2\cdot0.25H_2O$	ND

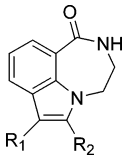
[a] Compounds were analyzed for C, H, and N; the results are in agreement to within ±0.4% of the theoretical values. [b] Human PARP-1 enzyme inhibition; values are an average of at least two independent experiments; % error ≤ ±20%. [c] See Experimental Section for conditions.

K_i values are relatively equal. Other 6-aryl-diazepinoindolones with various functional groups at the 7-position capable of forming H-bonds directly to Glu-988, or via the mobile bridging water molecule, were investigated. None of these, including amide **42**, *N*-hydroxyamidine **45**, and *N*-aminoamidine **46**, showed enhanced binding to PARP-1 when compared to oximes **38**, **40**, and **49** or to the simpler 6-aryl- or 7-carboxaldeoxime monosubstituted diazepinoindolones.

In Vitro Cellular Growth Inhibition; Enhancement of Topotecan (TP) Cytotoxicity. To evaluate their possible use as resistance-modifying agents, selected 3,4-dihydro-2*H*-[1,4]diazepino[6,7,1-*hi*]indol-1-one PARP-1 inhibitors were evaluated for potentiation of topoisomerase I inhibitor TP cytotoxicity against human lung carcinoma A549 cells. Alone, diazepinoindolone PARP-1 inhibitors did not inhibit A549 cell growth at 400 nM, the standard concentration selected to investigate the potentiation of TP. This concentration is well below the IC_{50} values of those compounds tested, except for compound **40**, where the single agent IC_{50} was less than twice the standard concentration used in the potentiation assay. The potentiation factor is reported as a PF_{50}. PARP-1 inhibitors with a PF_{50} value >1 increase the growth inhibitory effects of TP to that degree, while inhibitors with values = 1 have no effect.[30,31] As learned from previous studies, a correlation between the K_i and the PF_{50} value does not exist; however, low nanomolar inhibition of PARP-1 is undoubtedly required for potentiation. Of the inhibitors tested, compound **23** provided the best enhancement, reducing the IC_{50} of TP by a factor of 1.9. The data are listed in Table 4.

In summary, 3,4-dihydro-2*H*-[1,4]diazepino[6,7,1-*hi*]-indol-1-ones (**IX**), a third generation of novel 5,6,7-tricyclic PARP-1 inhibitors with structural homology to the 3,4,5,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indol-6-ones (**VII**) and 8,9-dihydro-7*H*-2,7,9*a*-triaza-benzo[*cd*]azulen-6-ones (**VIII**), were designed with the aid of protein structure-based drug design, molecular modeling, and SAR. An efficient synthesis was developed to prepare various C-7-substituted molecules that allowed us to study additional intermolecular interactions within the catalytic site, particularly with Glu-988. The C-7 carboxaldeoxime derivatives are some of the most potent PARP-1 inhibitors reported to date. The cocrystal structure of compound **28** bound to the PARP-1 validated our design process. The combination of an oxime

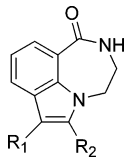
Table 3. 6,7-Disubstituted 3,4-Dihydro-2*H*-[1,4]diazepino[6,7,1-*hi*]indol-1-ones



no.	R_1	R_2	mp (°C)	formula[a]	K_i (nM)[b,c]
7	CH_3	C_6H_5	278−280	$C_{18}H_{16}N_2O\cdot0.4H_2O$	41
8	CH_3	4-F-C_6H_4	270−272	$C_{18}H_{15}N_2OF\cdot0.1H_2O$	22
9	CH_3	3-CF_3-C_6H_4	258−260	$C_{19}H_{15}N_2OF_3$[d]	79
37	CHO	4-Cl-C_6H_4	278−279	$C_{18}H_{13}N_2O_2Cl\cdot0.25H_2O$	43
38	CH=NOH	4-Cl-C_6H_4	249−251	$C_{18}H_{14}N_3O_2Cl$[a]	7.5
39	CHO	4-F-C_6H_4	268−270	$C_{18}H_{13}N_2O_2F$[e]	ND
40	CH=NOH	4-F-C_6H_4	277−279	$C_{18}H_{14}N_3O2F\cdot0.3H_2O$[a]	6
41	CN	4-F-C_6H_4	248−250	$C_{18}H_{12}N_3OF\cdot0.1H_2O$	54
42	$CONH_2$	4-F-C_6H_4	287−289	$C_{18}H_{14}N_3O_2F\cdot0.5H_2O$	200
43	$CSNH_2$	4-F-C_6H_4	238−240	$C_{18}H_{14}N_3OSF\cdot0.4H_2O$	219
45	$CH{=}NOHNH_2$	4-F-C_6H_4	257−259	$C_{18}H_{15}N_4O_2F\cdot0.5H_2O$	87
46	$CH{=}NHNHNH_2$	4-F-C_6H_4	272−274	$C_{18}H_{16}N_5OF\cdot1H_2O$[a]	57
47	I	4-F-C_6H_4	283−285	$C_{17}H_{12}NOIF$	ND
48	$COCH_3$	4-F-C_6H_4	275−276	$C_{19}H_{15}N_2O_2F$[f]	306
49	$C(CH_3){=}NOH$	4-F-C_6H_4	248−250	$C_{19}H_{16}N_3O_2F\cdot0.1H_2O$	9.1
51	2-pyrazolyl	4-F-C_6H_4	173−175	$C_{20}H_{15}N_4OF$[a]	249

[a] Compounds were analyzed for C, H, and N; the results are in agreement to within ±0.4% of the theoretical values except for **38**: analysis passed only with $0.75CH_2Cl_2$. Compound **40**: N, calcd, 12.78; found, 12.32. Compound **46**: analysis passed only with 4.5HCl. Compound **51**: analysis passed only with 1.0MeOH. [b] Human PARP-1 enzyme inhibition; values are an average of at least two independent experiments; % error ≤ ±20%. [c] See Experimental Section for method. [d] 90% pure by HPLC. [e] 99% pure by HPLC. [f] 98% pure by HPLC.

Table 4. Potentiation of TP-Induced Growth Inhibition by 6,7-Disubstituted 3,4-Dihydro-2*H*-[1,4]diazepino[6,7,1-*hi*]indol-1-ones in A549 Cells



no.	R_1	R_2	K_i (nM)[a]	IC_{50} (alone) (nM)[b]	IC_{50} (+TP) (nM)[c]	PF_{50}[d]
8	CH_3	4-F-C_6H_4	22	6000	21.8	1.1
15	H	4-Cl-C_6H_4	11	3000	13.3	1.8
17	H	4-F-C_6H_4	11	8000	13.3	1.8
20	H	3-[$CH_2N(CH_3)_2$]C_6H_4	9.1	11000	15.0	1.6
23	H	4-[$CH_2N(CH_3)_2$]C_6H_4	6.4	7000	12.6	1.9
28	CH=NOH	H	9.4	8000	18.5	1.3
40	CH=NOH	4-F-C_6H_5	6	<800	20.0	1.2
TP				24		

[a] Human PARP-1 enzyme inhibition; values are an average of at least two independent experiments; % error ≤ ±20%. [b] Cytotoxicity of single agent. [c] Cytotoxicity of TP plus 0.4 μM corresponding PARP-1 inhibitor. [d] PF_{50} = (IC_{50} of TP)/(IC_{50} of TP + 0.4 μM PARP-1 inhibitor). [a−d] See Experimental Section for methods.

at C-6 and an aryl group at C-7 did not produce a substantial increase in PARP-1 binding potency or in vitro potentiation of TP cytotoxicity. Further crystallographic studies may help lead to the design of an improved class of 3,4-dihydro-2*H*-[1,4]diazepino[6,7,1-*hi*]indol-1-one PARP-1 inhibitors with better cytotoxic potentiation.

Experimental Section

Proton magnetic resonance spectra (NMR) were determined using a Bruker Avance 300DPX or 500DRX spectrometer operating at a field strength of 300 and 500 MHz, respectively. Chemical shifts are reported in parts per million (δ) with references set such that in $CDCl_3$ the $CHCl_3$ is at 7.26 ppm, in acetone-d_6 the acetone is at 2.02 ppm, and in DMSO-d_6 the DMSO is at 2.49 ppm. Standard and peak multiplicities are designated as follows: s, singlet; doublet; dd, doublet of doublets; t, triplet; q, quartet; br s, broad singlet; and m; multiplet. Mass spectra were determined at the University of California, Riverside, or Scripps Research Institute, San Diego, CA, Mass Spectrometry Facilities. Infrared absorption (IR) spectra were taken on a MIDAC Corp. FTIR or a Perkin-Elmer 1600 series FTIR spectrometer. Elemental microanalyses were performed by Atlantic Microlab Inc. (Norcoss, GA) and gave results for the elements stated with ±0.4% of the theoretical values. Analytical HPLC was performed using a Hewlett-Packard (HP) Series 1100 Quaternary system, equipped with a HP 1100 variable wavelength detector set at 254 nm; sensitivity, 0.02−50 AUFS. A Pheomenex Prodigy 5 ODS (3) column (250 mm × 4.6 mm; 5 μm) was used. Typically, a gradient mobile phase starting with 90% H_2O with 0.1% TFA, 10% CH_3CN with 0.1% TFA up to 20 min (min), then 35% H_2O with 0.1% TFA, 65% CH_3CN with 0.1% TFA up to 25 min, then 10% H_2O with 0.1% TFA, 90% CH_3CN with 0.1% TFA thereafter was used. Flow rate = 1 mL/min. Preparative HPLC was performed using Gilson model 806 Manometric module, equipped with a Gilson 811c dynamic mixer, two Gilson model 306 pumps, a Gilson 215 liquid handler, and a Gilson model 119 UV/visible detector set at 2145 or 220 and 254 nm; sensitivity, 0.02−50 AUFS. A Metasil AQ C18 column (250 mm × 212 mm; 10 μm) was used. Typically, a gradient mobile phase starting with 90% H_2O with 0.1% TFA, 10% CH_3CN with 0.1% TFA up to 2 min, then reaching 35% H_2O with 0.1% TFA, 65% CH_3CN with 0.1% TFA after 22 min or 90% 0.1M NH_4OAc, 10% CH_3CN up to 2 min, then reaching 100% CH_3CN after 22 min, was used. Flow rate = 25 mL/min. Flash column chromatography was performed using silica gel 60 (Merck Art 9385). Thin layer chromatographs were performed on precoated sheets of silica 60 F_{254} (Merck Art 5719). Melting points were determined on a Mel-Temp apparatus and are uncorrected. All commercial solvents were reagent grade or better and used as supplied. All reactions were performed in septum-sealed flasks under a slight positive pressure of argon, unless otherwise noted.

PARP Enzyme Inhibition Assay. The PARP enzyme-inhibiting activities of the compounds were assayed as described by Simonin et al.[47] and Marsischky et al.[33] with minor modifications as follows. Samples (50 μL) containing 20 nM purified PARP protein, 10 μg/mL DNAse I-activated calf thymus DNA (sigma), 500 μM NAD^+, 0.5 μCi [^{32}P]NAD^+, 2% DMSO, and various concentrations of test compounds were incubated in sample buffer [50 mM Tris, pH 8.0, 10 mM $MgCl_2$, and 1 mM tris(carboxyethyl)phosphine HCl] at 25 °C for 4 min. Under these conditions, the reaction rate was linear up to 10 min. The reaction was stopped by the addition of an equal volume of ice-cold 40% trichloroacetic acid. The samples were then incubated on ice for 15 min, transferred to a Bio-Dot microfiltration apparatus (Biorad), and filtered through Whatman GF/C glass-fiber filter paper. Filters were washed three times with 150 μL of wash buffer (5% trichloroacetic acid and 1% inorganic pyrophosphate) and dried. [^{32}P]ADP-ribose incorporation into the acid insoluble material was quantified using a PhosphorImager (Molecular Dynamics) and ImageQuant software. Inhibition constants (K_i) were calculated by nonlinear regression analyses using the velocity equation for competitive inhibition.[48] In the case of tight-binding inhibitors, 5 nM enzyme was used and the reaction was incubated at 25 °C for 15 min. K_i values for tight-binding inhibitors were calculated using the equation described by Sculley et al.[49]

Potentiation of TP Growth Inhibition Assay. A549 cells (ATCC, Rockville, MD) were seeded into 96 well cell culture plates (Falcon brand, Fisher Scientific, Pittsburgh, PA) 16−24 h before experimental manipulation. The cells were then treated with a test compound (or a combination of test compounds where indicated) each at a concentration of 0.4 μM for either 3 or 5 days. At the end of treatments, the relative cell number was determined by either MTT assay or SRB assay. For the MTT assay, 0.2 μg/μL of MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] (Sigma Chemical Co., St. Louis, MO) was added to each well of a plate, and the plate was incubated in a cell culture incubator for 4 h. Metabolized MTT in each well was solubilized in 159 μL of DMSO (Sigma Chemical Co.) with shaking and quantified with a Wallac 1420 Victor plate reader (EG&G Wallad, Gaithersburg, MD) at 540 nm. For the SRB assay, the cells were fixed with 10% trichloroacetic acid (Sigma Chemical Co.) for an hour at 4 °C. After they were extensively washed, fixed cells were stained for 30 min with 0.4% sulforhodamine B (SRB, Sigma Chemical Co.) in 1% acetic acid (Sigma Chemical Co.). Unbound SRB was washed away with 1% acetic acid. Then, the cultures were air-dried, and bound dye was solubilized with 10 mM unbuffered Tris base (Sigma Chemical Co.) with shaking. The bound dye was measured photometrically with the Wallac Victor plate reader at 515 nm. The ratio of the OD (optical density) value of a compound-treated culture to the OD value of a mock-treated culture, expressed in percentage, was used to quantify the cytotoxicity of a compound. The concentration at which a compound causes 50% cytotoxicity is referred to as IC_{50}. To quantify the potentiation of the cytotoxicity of TP by test compounds, a dimensionless parameter PF_{50} is used and defined as the ratio of the IC_{50} of TP alone to the IC_{50} of TP in combination with a test compound.

Crystallographic Methods. Purified protein and cocrystals for the C-terminal catalytic domain of chicken PARP-1 were obtained using procedures similar to those previously described. In this study, 100 mM Tris, pH 8.5, 16−32% PEG-600, and 8% isopropyl alcohol were used as a precipitant. X-ray diffraction data were collected with a MAR345 image plate to

2.8 Å resolution. The space group is $P2_12_12_1$, with $a = 59.31$ Å, $b = 63.80$ Å, and $c = 96.93$ Å. The 19100 observations were scaled and merged into 8942 unique reflections using DENZO and SCALEPACK. The overall *R*-merge was 6.0%, the ratio $I/\sigma(I)$ was 14.2, and the data were 94% complete. Corresponding values for the high-resolution data shell (2.9−2.8 Å) were 16.4, 4.7, and 91.3%, respectively. The structure of **28** bound to chicken PARP-1 was solved and refined using these data, the program CNX,[50] and the 2.2 Å protein and solvent model.[29] The conventional and free *R*-factors for the refined model are 16.5 and 24%. The rms deviations between model and ideal bond distances, bond angles, dihedral angels, and improper angels are 0.007 Å, 1.3°, 22.7°, and 0.8°.

Computational Methods. Molecular modeling of inhibitors with a chimeric human PARP-1 model was performed with Macromodel version 5.5.[51] The model was created from the X-ray structure of compound **28** complexed with chicken PARP-1; however, residue 763 was changed from a glutamine to a glutamate. A Monte Carlo conformational search of the Glu-763 side chain was performed using the Amber* force field.

Method A. 3,4,6,7-Tetrahydro-2*H*-[1,4]diazepino[6,7,1-*hi*]indol-1-one (1).[40] ^{1}H NMR (DMSO-d_6): δ 2.92 (t, 2H, J = 7.5 Hz), 3.29−3.31 (m, 4H), 3.47 (t, 2H, J = 7.5 Hz), 6.49 (t. 1H, J = 7.5 Hz), 7.04 (d, 1H, J = 7.5 Hz), 7.49 (d, 1H J = 7.5 Hz), 7.86 (br s, 1H). HRMS calcd for $C_{11}H_{12}N_2O$ (M^+), 188.0950; found (M^+), 188.0957. Anal. ($C_{11}H_{12}N_20$) C, H, N.

3,4-Dihydro-2*H*-[1,4]diazepino[6,7,1-*hi*]indol-1-one (2).[40] mp 165−167 °C. ^{1}H NMR (DMSO-d_6): δ 3.52−3.56 (m, 2H), 4.31−4.36 (m, 2H), 6.53 (d, 1H J = 3.0 Hz), 7.11 (t, 1H J = 6.0 Hz), 7.38 (d, 1H, J = 3.0 Hz), 7.70 (d, 1H, J = 6.0 Hz), 7.80 (d, 1H, J = 6.0 Hz), 8.30 (br s, 1H). LRMS (M^+) 186. Anal. ($C_{11}H_{10}N_2O\cdot 0.05H_2O$) C, H, N.

1-Oxo-1,2,3,4-tetrahydro[1,4]diazepino[6,7,1-*hi*]indole-7-carbaldehyde (3). $POCl_3$ (16.37 g, 106.76 mmol) was slowly added to DMF (225 mL) at 0 °C. The mixture was stirred for 15 min and then was treated with a solution of **2** (1.46 g, 7.85 mmol) in DMF (10 mL). The reaction mixture was warmed to room temperature and stirred for 17 h. After all of the solvent was removed, the residue was taken up in H_2O, made basic (pH 12) using 20% aqueous NaOH, and extracted with EtOAc several times. The organic layer was dried over anhydrous $MgSO_4$ and concentrated to give a pale yellow solid, which was used without further purification; mp 238−240 °C. ^{1}H NMR (DMSO-d_6): δ 3.58−3.61 (m, 2H), 4.48 (br s, 2H), 7.37 (t, 1H, J = 7.5 Hz), 7.97 (d, 1H, J = 7.5 Hz), 8.33−8.35 (m, 2H), 8.43−8.45 (m, 1H), 9.95 (s, 1H). HRMS calcd for $C_{12}H_{10}N_2O_2$ (M^+), 214.0742; found (M^+), 214.0737. Anal. ($C_{12}H_{10}$ $N_2O_2\cdot 0.1H_2O$) C, H, N.

7-Hydroxymethyl-3,4-dihydro-2*H*-[1,4]diazepino[6,7,1-*hi*]indol-1-one (4). Sodium borohydride (0.018 g, 0.466 mmol) was added to a suspension of **3** (0.050 g, 0.233 mmol) in 15 mL EtOH. The reaction mixture was refluxed for 1.5 h and cooled, and the solvent was evaporated. The residue was partitioned between 1% aqueous NaOH and EtOAc. The organic extract was dried over anhydrous $MgSO_4$ and evaporated to give a pale yellow solid (88%); mp 180−182 °C. ^{1}H NMR (DMSO-d_6): δ 3.52−3.55 (m, 2H), 4.31 (br s, 2H), 4.63 (d, 2H, J = 5 Hz), 4.84 (t, 1H, J = 5 Hz), 7.12 (t, 1H, J = 7.5 Hz), 7.29 (s, 1H), 7.80−7.83 (m, 2H), 8.24−8.26 (m, 1H). HRMS calcd for $C_{12}H_{12}N_2O_2$ (M^+), 216.0899; found (M^+), 216.0908; Anal. ($C_{12}H_{12}N_2O_2\cdot 0.2H_2O$) C, H, N.

Acetic Acid 1-Oxo-1,2,3,4-tetrahydro[1,4]diazepino-[6,7,1-*hi*]indol-7-ylmethyl Ester (4a). 4-(Dimethylamino)-pyridine (0.057 g, 0.466 mmol) was added to a solution of the alcohol **4** (1.007 g, 4.66 mmol) in a mixture of acetic anhydride (1.1 mL, 11.65 mmol) and pyridine (25 mL). The mixture was stirred for 15 h at room temperature, and then, the solvent evaporated. The residue was purified by flash silica gel chromatography eluting with a gradient of 0−3% MeOH in $CHCl_3$ to give 0.925 g (77%) of the acetate. ^{1}H NMR (DMSO-d_6): δ 2.0 (s, 3H), 3.42−3.44 (br s, 2H), 4.23−4.25 (br s, 2H), 5.30 (s, 2H), 9.10 (t, 1H, J = 7.5 Hz), 7.50 (s, 1H), 7.75 (d, 1H, J = 7.5 Hz), 7.85 (d, 1H, J = 7.5 Hz), 8.30 (m, 1H).

7-Methyl-3,4-dihydro-2*H*-[1,4]diazepino[6,7,1-*hi*]indol-1-one (5). Acetate **4a** (0.508 g, 1.97 mmol) was dissolved in MeOH (70 mL) and glacial acetic acid (30 mL). Pd/C (10%) (0.076 g) was added, and the suspension was stirred under an atmosphere of H_2 for 4.5 h at room temperature. The black suspension was filtered, and the filtrate was concentrated to give a white solid, which was purified by flash silica gel chromatography eluting with a gradient of 0−1% MeOH in $CHCl_3$ to give 0.296 g (75%) of the product; mp 135−137 °C. ^{1}H NMR (DMSO-d_6): δ 2.52 (s, 3H), 3.51−3.54 (m, 2H), 4.27−4.28 (m, 2H), 7.11 (t, 1H, J = 7.5 Hz), 7.15 (s, 1H), 7.69 (d, 1H, J = 7.5 Hz), 7.81 (d, 1H, J = 7.5 Hz), 8.22−8.24 (m, 1H). HRMS calcd for $C_{12}H_{12}N_2O$ (M^+), 200.0950; found (M^+), 200.0955. Anal. ($C_{12}H_{12}N_2O$) C, H, N.

6-Iodo-7-methyl-3,4-dihydro-2*H*-[1,4]diazepino[6,7,1-*hi*]indol-1-one (6). To a solution of **5** (0.030 g, 0.150 mmol) in CH_2Cl_2 (5 mL) was added iodine (0.038 g, 0.150 mmol) and bistrifluoroacetoxyiodobenzene (0.077 g, 0.180 mmol). The reaction mixture was stirred at room temperature for 5 min, diluted with CH_2Cl_2, and washed with 10% $Na_2S_2O_3$. The organic layer was dried over anhydrous $MgSO_4$ and concentrated. The residue was purified by flash silica gel chromatography eluting with a gradient of 0−1% MeOH in $CHCl_3$ to give 0.026 g (53%) of the desired product. ^{1}H NMR (DMSO-d_6): δ 2.20 (s, 3H), 3.33−3.35 (br s, 2H), 4.32−4.35 (br s, 2H), 7.10 (t, 1H, J = 7.5 Hz), 7.60 (d, 1H, J = 7.5 Hz), 7.80 (d, 1H, J = 7.5 Hz), 8.30 (br s, 1H).

7-Methyl-6-phenyl-3,4-dihydro-2*H*-[1,4]diazepino[6,7,1-*hi*]indol-1-one (7). To a solution of the iodide **6** (0.024 g, 0.736 mmol) in DMF (3 mL) was added phenylboronic acid (0.010 g, 0.0810 mmol), Na_2CO_3 (0.020 g, 0.184 mmol) dissolved in minimum H_2O, LiCl (0.010 g, 0.221 mmol), and tetrakistriphenylphosphine palladium (5.0 mg, 0.0037 mmol) at room temperature. The reaction mixture was stirred at 80−90 °C for 19 h, and then, the solvent evaporated. The residue was taken up in H_2O and extracted with EtOAc several times. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated to give a brown solid. The crude mixture was purified by flash silica gel chromatography eluting with a gradient of 0−1% MeOH in $CHCl_3$ to give 0.014 g (70%) of the product; mp 278−280 °C. ^{1}H NMR (DMSO-d_6): δ 2.23 (s, 3H), 3.46 (br s, 2H), 4.13 (br s, 2H), 7.17 (t, 1H, J = 7.5 Hz), 7.45−7.56 (m, 5H), 7.76 (d, 1H, J = 7.5 Hz), 7.84 (d, 1H, J = 7.5 Hz), 8.29−8.31 (m, 1H). LRMS (M^+) 276. Anal. ($C_{18}H_{16}N_2O\cdot$ 0.4 H_2O) C, H, N.

Compounds **8** and **9** were prepared from **6** using method A.

6-(4-Fluoro-phenyl)-7-methyl-3,4-dihydro-2*H*-[1,4]diazepino[6,7,1-*hi*]indol-1-one (8). White solid (73%); mp 270−272 °C. ^{1}H NMR (DMSO-d_6): δ 2.77 (s, 3H), 3.74 (br s, 2H), 3.39−4.37 (m, 2H), 7.45 (t, 1H, J = 7.5 Hz), 7.63−7.67 (m, 2H), 7.81−7.83 (m, 2H), 8.04 (d, 1H, J = 7.5 Hz), 8.12 (d, 1H, J = 7.5 Hz), 8.57−8.59 (m, 1H). HRMS calcd for $C_{18}H_{15}N_2OF$ (M^+), 294.1168; found (M^+), 294.1175. Anal. ($C_{18}H_{15}N_2OF\cdot 0.1H_2O$) C, H, N.

7-Methyl-6-(3-trifluoromethyl-phenyl)-3,4-dihydro-2*H*-[1,4]diazepino[6,7,1-*hi*]indol-1-one (9). White solid (81%); mp 258−260 °C. ^{1}H NMR (DMSO-d_6): δ 2.25 (s, 3H), 3.44−3.48 (m, 2H), 4.13−4.16 (m, 2H), 7.19 (t, 1H, J = 7.5 Hz), 7.77−7.88 (m, 6H), 8.32−8.36 (m, 1H). HRMS calcd for $C_{19}H_{15}N_2OF_3$ (M^+), 344.136; found (M^+), 344.1136. Anal. HPLC R_t = 14.9 min. Purification done using preparative HPLC. A gradient mobile phase, starting with 90% 0.1 M NH_4OAc, 10% CH_3CN up to 2 min, then reaching 100% CH_3CN after 22 min, was used. R_t = 17.59 min.

Method B. 8-Iodo-2,3-dihydro-1*H*-quinolin-4-one (11). A mixture of the acid 3-(2-iodo-phenylamino)propionaldehyde carboxylic acid **10**[42] (0.103 g, 0.354 mmol) in 7% P_2O_5:CH_3SO_3H (Eaton's reagent)[43] (2 mL) was heated at 60−70 °C for 3 h. Ice-cold water was added to the reaction mixture, made basic (pH 12) with 50 wt % NaOH, and extracted with EtOAc several times. The combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated to give 0.070 g (72%) of the product as orange oil. The product was used without further purification. ^{1}H NMR ($CDCl_3$): δ 2.71 (t, 2H, J = 6.0 Hz), 3.65

(t, 2H, J = 6.0 Hz), 4.86 (br s, 1H), 6.50 (t, 1H, J = 9.0 Hz), 7.79 (d, 1H, J = 9.0 Hz), 7.85 (d, 1H, J = 9.0 Hz). LRMS (M + H) 272.

9-Iodo-1,2,3,4-tetrahydro-benzo[*e*][1,4]diazepin-5-one (12). To a solution of **11** (3.47 g, 0.0127 mmol) in CH_3SO_3H (50 mL) was added NaN_3 (1.074 g, 0.0165 mmol) slowly at room temperature. The reaction mixture was stirred at room temperature for 0.5 h. Upon consumption of starting material by TLC, ice-cold water was added to the reaction mixture and made basic (pH 13) using 50 wt % NaOH whereupon the product (3.05 g, 83%) precipitates. The solids were filtered, washed with water, and dried; mp 182−184 °C. ^{1}H NMR (DMSO-d_6): δ 3.25−3.27 (m, 2H), 3.48 (br s, 2H), 5.43 (br s, 1H), 6.41 (t, 1H, J = 6.0 Hz), 7.73 (d, 1H, J = 6.0 Hz), 7.80 (d, 1H, J = 6.0 Hz), 8.15 (br s, 1H). LRMS (M^+) 288.

9-Phenylethynyl-1,2,3,4-tetrahydro-benzo[*e*][1,4]diazepin-5-one (13a). A mixture of **12** (0.144 g, 0.5 mmol), phenylacetylene (0.055 mL, 0.5 mmol), tetrakistriphenylphosphine palladium chloride (6 mg, 0.005 mmol), CuI (2 mg, 0.01 mmol) in diethylamine (4 mL), and DMF (2 mL) was stirred at room temperature for 2 h. The solvent was evaporated to dryness, and the residue was taken in water and extracted with EtOAc. The organic extract was dried over anhydrous $MgSO_4$ and concentrated. The crude mixture was purified by flash silica gel chromatography eluting with a gradient of 0−3% MeOH in $CHCl_3$ to give 0.102 g (78%) of the desired product. ^{1}H NMR (DMSO-d_6): δ 3.27−3.29 (m, 2H), 3.53−3.56 (m, 2H), 6.26 (t, 1H, J = 6.0 Hz), 6.61 (t, 1H, J = 6.0 Hz), 7.40−7.47 (m, 4H), 7.62−7.65 (m, 2H), 7.80 (d, 1H, J = 6.0 Hz), 8.13 (t, 1H, J = 6.0 Hz). LRMS (M^+) 262. IR (KBr) 3400, 3190, 3051, 1641, 1589, 1518, 1446, 1250, 756, 690 cm^{-1}.

6-Phenyl-3,4-dihydro-2*H*-[1,4]diazepino[6,7,1-*hi*]indol-1-one (14). To a clear solution of **13a** (0.08 g, 0.305 mmol) in CH_3CN (10 mL) was added $PdCl_2$ (3.0 mg, 0.0153 mmol) at room temperature. The reaction mixture was heated at 70−80 °C for 3.5 h. Upon consumption of starting material (TLC), the solvent was evaporated and the crude residue was purified by flash silica gel chromatography eluting with a gradient of 0−3% MeOH in $CHCl_3$ to give 0.058 g (73%) of the desired product; mp 165−167 °C. ^{1}H NMR (DMSO-d_6): δ 3.46−3.51 (m, 2H), 4.31−4.33 (m, 2H), 6.71 (s, 1H), 7.17 (t, 1H, J = 9.0 Hz), 7.42−7.55 (m, 3H), 7.60−7.63 (m, 2H), 7.78 (d, 1H, J = 9.0 Hz), 7.82 (d, 1H, J = 9.0 Hz), 8.38 (t, 1H, J = 6.0 Hz). HRMS calcd for $C_{17}H_{14}N_2O$ (M^+), 262.1106; found (M^+), 262.1109. Anal. ($C_{17}H_{14}N_2O\cdot0.1H_2O$) C, H, N.

Compounds **15**−**18** were made using method B.

6-(4-Chloro-phenyl)-3,4-dihydro-2*H*-[1,4]diazepino[6,7,1-hi]indol-1-one (15). Pale yellow solid (69%); mp 238−240 °C. ^{1}H NMR (DMSO-d_6): δ 3.47−3.50 (m, 2H), 4.29−4.32 (m, 2H), 6.74 (s, 1H), 7.18 (t, 1H, J = 9.0 Hz), 7.58 (d, 2H, 9.0 Hz), 7.65 (d, 2H, J = 9.0 Hz), 7.80 (d, 2H, J = 9.0 Hz), 7.83 (d, 2H, J = 9.0 Hz), 8.39 (t, 1H, J = 4.5 Hz). HRMS calcd for $C_{17}H_{13}N_2OCl$ (M^+), 296.0716; found (M^+), 296.0715. Anal. ($C_{17}H_{13}N_2OCl$) C, H, N.

6-(4-Methoxy-phenyl)-3,4-dihydro-2*H*-[1,4]diazepino-[6,7,1-*hi*]indol-1-one (16). Pale yellow solid (84%); mp 188−190 °C. ^{1}H NMR (DMSO-d_6): δ 3.48−3.50 (m, 2H), 4.27−4.30 (m, 2H), 6.60 (s, 1H), 7.07 (d, 2H, J = 9.0 Hz), 7.15 (t, 1H, J = 6.0 Hz), 7.54 (d, 2H, J = 9.0 Hz), 7.75 (d, 1H, J = 6.0 HZ), 7.79 (d, 1H, J = 6.0 Hz), 8.36 (t, 1H, J = 6.0 Hz). HRMS calcd for $C_{18}H_{16}N_2O_2$ (M^+), 292.1212; found (M^+), 292.1218. Anal. ($C_{18}H_{16}N_2O_2\cdot0.1H_2O$) C, H, N.

6-(4-Fluoro-phenyl)-3,4-dihydro-2*H*-[1,4]diazepino[6,7,1-*hi*]indol-1-one (17). Pale yellow solid (79%); mp 198−200 °C. ^{1}H NMR (DMSO-d_6): δ 3.48−3.50 (m, 2H), 4.28−4.30 (m, 2H), 6.70 (s, 1H), 7.15 (t, 1H, J = 6.0 Hz), 7.33−7.39 (m, 2H), 7.65 (d, 1H, J = 6.0 Hz), 7.68 (d, 1H, J = 6.0 Hz), 7.78 (d, 1H, J = 6.0 Hz), 7.82 (d, 1H, J = 6.0 Hz), 8.38 (t, 1H, J = 6.0 Hz). HRMS calcd for $C_{17}H_{13}N_2OF$ (M^+), 280.1012; found (M^+), 280.1002. Anal. ($C_{17}H_{13}N_2OF$) C, H, N.

6-Phenethyl-3,4-dihydro-2*H*-[1,4]diazepino[6,7,1-*hi*]-indol-1-one (18). Pale yellow solid (70%); mp 188−190 °C. ^{1}H NMR (DMSO-d_6): δ 2.96−3.06 (m, 4H), 3.49−3.50 (m, 2H), 4.21 (br s, 2H), 6.37 (s, 1H), 7.07 (t, 1H, J = 6.0 Hz), 7.18−7.29 (m, 5H), 7.65 (d, 1H, J = 6.0 HZ), 7.74 (d, 1H, J = 6.0 Hz), 8.26 (t, 1H, J = 6.0 Hz). HRMS calcd for $C_{19}H_{18}N_2O$ (M^+), 290.1419; found (M^+), 290.1421. Anal. ($C_{19}H_{18}N_2O$) C, H, N.

6-Pyridin-2-yl-3,4-dihydro-2*H*-[1,4]diazepino[6,7,1-*hi*]-indol-1-one (19). To a solution of 9-pyridin-2-ylethynyl-1,2,3,4-tetrahydro-benzo[*e*][1,4]diazepin-5-one (0.050 g, 0.190 mmol) in DMF (6 mL) were added CuI (0.003 g, 0.012 mmol) and $PdCl_2$ (5.0 mg, 0.029 mmol) at room temperature. The reaction mixture was heated at 80−85 °C for 4 h. Upon completion, the solvent was evaporated to dryness. The crude residue was purified by flash silica gel chromatography eluting with a gradient of 0−3% MeOH in $CHCl_3$ to give 0.010 g (20%) of the product. ^{1}H NMR (DMSO-d_6): δ 3.38−3.55 (m, 2H), 4.64 (br s, 2H), 7.06 (s, 1H), 7.19 (t, 1H, J = 9.0 Hz), 7.37−7.41 (m, 1H), 7.82−7.96 (m, 4H), 8.38 (t, 1H, J = 6.0 Hz), 8.70 (d, 1H, J = 3.0 Hz). HRMS calcd for $C_{16}H_{13}N_3O$ (M^+), 263.1059; found (M^+), 263.1062. Anal. ($C_{16}H_{13}N_3O\cdot0.8\ H_2O$) C, H, N.

Method C. 9-Trimethylsilanylethynyl-1,2,3,4-tetrahydro-benzo[*e*][1,4]diazepin-5-one (52). A mixture of **12** (1.0 g, 3.47 mmol), TMS acetylene (5.0 mL, 34.70 mmol), tetrakistriphenylphosphine palladium chloride (0.040 g, 0.0347 mmol), CuI (0.013 g, 0.0694 mmol) in diethylamine (10 mL), and DMF (10 mL) was stirred at room temperature for 5 h. The solvent was evaporated, and the residue was taken up in H_2O and extracted with EtOAc several times. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated. The crude mixture was purified by flash silica gel chromatography eluting with a gradient of 0−5% MeOH in $CHCl_3$ to give 0.733 g (82%) of a brown solid; mp 180−182 °C. ^{1}H NMR (DMSO-d_6): δ 0.25 (s, 9H), 3.25−3.33 (m, 2H), 3.51−3.55 (m, 2H), 5.90 (br s, 1H), 6.57 (t, 1H, J = 6.0 Hz), 7.35 (d, 1H, J = 6.0 Hz), 7.78 (d, 1H, J = 6.0 Hz), 8.13 (t, 1H, J = 6.0 Hz). LRMS (M^+) 258.

9-Ethynyl-1,2,3,4-tetrahydro-benzo[*e*][1,4]diazepin-5-one (53). A mixture of **52** (0.712 g, 2.76 mmol) and K_2CO_3 (0.038 g, 0.276 mmol) in MeOH (35 mL) was stirred at room temperature for 2.5 h. The solvent was evaporated, and the residue taken up in H_2O and extracted with EtOAc several times. The combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated to give 0.504 g (98%) of a brown solid. The solid was used without further purification; mp 146−148 °C. ^{1}H NMR (DMSO-d_6): δ 3.15−3.23 (m, 2H), 3.48−3.52 (m, 2H), 4.50 (s, 1H), 6.13 (br s, 1H), 6.57 (t, 1H, J = 9.0 Hz), 7.37 (d, 1H, J = 9.0 Hz), 7.79 (d, 1H, J = 9.0 Hz), 8.10 (t, 1H, J = 6.0 Hz). LRMS (M^+) 186.

3-(5-Oxo-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepin-9-ylethynyl)benzaldehyde (54). Using the procedure described for the preparation of **13**, 3-iodobenzaldehyde and **53** were used to synthesize **54** in 62% yield as a yellow solid; mp 176−178 °C. ^{1}H NMR (DMSO-d_6): δ 3.30−3.33 (m, 2H), 3.54−3.57 (m, 2H), 6.40 (br s, 1H), 6.63 (t, 1H, J = 6.0 Hz), 7.49 (d, 1H, J = 6.0 Hz), 7.66 (t, 1H, J = 9.0 Hz), 7.83 (d, 1H, J = 6.0 Hz), 7.90−7.97 (m, 2H), 8.15 (br s, 1H), 8.31 (s, 1H), 10.03 (s, 1H). LRMS (M^++ H) 291.

3-(1-Oxo-1,2,3,4-tetrahydro[1,4]diazepino[6,7,1-*hi*]indol-6-yl)benzaldehyde (55). Using the procedure described for the preparation of **14**, compound **54** was converted to **55** in 66% yield as a pale yellow solid; mp 192−194 °C. ^{1}H NMR (DMSO-d_6): δ 3.49−3.51 (m, 2H), 4.33−4.36 (m, 2H), 6.83 (s, 1H), 7.19 (t, 1H, J = 6.0 Hz), 7.75 (t, 1H, J = 9.0 Hz), 7.80−7.86 (m, 2H), 7.96 (d, 2H, J = 6.0 Hz), 8.15 (s, 1H), 8.41 (t, 1H, J = 6.0 Hz), 10.11 (s, 1H). LRMS (M^+) 290.

6-(3-Dimethylaminomethyl-phenyl)-3,4-dihydro-2*H*-[1,4]diazepino[6,7,1-*hi*]indol-1-one (20). Dimethylamine (2 M) in methanol (16.34 mmol, 8.2 mL) was added to a suspension of **55** (1.90 mmol, 0.55 g) in MeOH (110 mL) at room temperature. The reaction mixture was heated to reflux until the suspended solids went into solution. The reaction mixture was cooled to room temperature, and a solution of $NaCNBH_3$ (2.09 mmol, 0.131 g) and $ZnCl_2$ (1.05 mmol, 0.143 g) in MeOH (55 mL) was slowly added. The pH of the reaction was adjusted to 3−4 using 2 M methanolic HCl. The reaction mixture was stirred at room temperature for 2.5 h. Upon completion (TLC), concentrated HCl was added (pH 1) and the solvent was

removed in vacuo. The residue was diluted with H_2O, made basic (pH 12−14) with 50% aqueous NaOH, and extracted with EtOAc several times. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated. The crude mixture was purified by flash silica gel chromatography eluting with a gradient of 0−7% MeOH in $CHCl_3$ followed by 3−7% MeOH/NH_3 in $CHCl_3$ to give 0.527 g (87%) of a white solid; mp 98−100 °C. ^{1}H NMR (DMSO-d_6): δ 2.18 (s, 6H), 3.47 (br s, 4H), 4.30−4.32 (m, 2H), 6.70 (s, 1H), 7.17 (t, 1H, J = 6.0 Hz), 7.35−7.37 (m, 1H), 7.43−7.50 (m, 3H), 7.78 (d, 1H, J = 6.0 Hz), 7.81 (d, 1H, J = 6.0 Hz), 8.38 (t, 1H, J = 6.0 Hz). HRMS calcd for $C_{20}H_{21}N_3O$ (M^+), 319.1685; found (M^+), 319.1682; Anal. ($C_{20}H_{21}N_3O\cdot$ 0.25 H_2O) C, H, N.

Compounds **21**−**25** were made using method C.

6-(3-Methylaminomethyl-phenyl)-3,4-dihydro-2*H*-[1,4]-diazepino[6,7,1-*hi*]indol-1-one (21). Pale yellow solid (94%); mp 128−130 °C. ^{1}H NMR (DMSO-d_6): δ 2.29 (s, 3H), 3.48 (br s, 2H), 3.71 (s, 2H), 4.30−4.33 (m, 2H), 6.69 (s, 1H), 7.17 (t, 1H, J = 9.0 Hz), 7.38−7.39 (m, 1H), 7.44−7.46 (m, 2H), 7.54 (s, 1H), 7.80 (t, 2H, J = 9.0 Hz), 8.39 (t, 1H, J = 6.0 Hz). HRMS calcd for $C_{19}H_{19}N_3O$ (M^+), 305.3828; found (M^+), 305.1520. Anal. ($C_{19}H_{19}N_3O\cdot$0.6 H_2O) C, H, N.

6-(3-Pyrrolidin-1-ylmethyl-phenyl)-3,4-dihydro-2*H*-[1,4]-diazepino[6,7,1-*hi*]indol-1-one (22). Pale yellow solid (92%); mp 158−160 °C. ^{1}H NMR (DMSO-d_6): δ 1.71 (br s, 4H), 2.49 (br s, 4H), 3.49 (br s, 2H), 3.68 (br s, 2H), 4.30−4.33 (m, 2H), 6.70 (s, 1H), 7.17 (t, 1H, J = 9.0 Hz), 7.38−7.52 (m, 4H), 7.79 (d, 1H, J = 9.0 Hz), 7.82 (d, 1H, J = 9.0 Hz), 8.38 (t, 1H, J = 6.0 Hz). HRMS calcd for $C_{22}H_{23}N_3O$ (M^+), 345.1841; found (M^+), 345.1848. Anal. ($C_{22}H_{23}N_3O\cdot$0.4 H_2O) C, H, N.

6-(4-Dimethylaminomethyl-phenyl)-3,4-dihydro-2*H*-[1,4]diazepino[6,7,1-*hi*]indol-1-one (23). Pale yellow solid (86%); mp 140−142 °C. ^{1}H NMR (DMSO-d_6): δ 2.18 (s, 6H), 3.45 (s, 2H), 3.47−3.50 (m, 2H), 4.32 (m, 2H), 6.69 (s, 1H), 7.16 (t, 1H, J = 10.0 Hz), 7.42 (d, 2H, J = 10 Hz), 7.56 (d, 2H, J = 10 Hz), 7.77 (d, 1H, J = 10 Hz), 7.81 (d, 1H, J = 10.0 Hz), 8.36 (t, 1H, J = 5.0 Hz). HRMS calcd for $C_{20}H_{21}N_3O$ (M^+), 319.1685; found (M^+), 319.1678. Anal. ($C_{20}H_{21}N_3O\cdot$0.3 H_2O) C, H, N.

6-(4-Methylaminomethyl-phenyl)-3,4-dihydro-2*H*-[1,4]-diazepino[6,7,1-*hi*]indol-1-one (24). Pale yellow solid (71%); mp 178−180 °C. ^{1}H NMR (DMSO-d_6): δ 2.29 (s, 3H), 3.48 (br s, 2H), 3.70 (s, 2H), 4.30−4.33 (m, 2H), 6.68 (s, 1H), 7.16 (t, 1H, J = 9.0 Hz), 7.45 (d, 2H, J = 9.0 Hz), 7.55 (d, 2H, J = 9.0 Hz), 7.77 (d, 1H, J = 9.0 Hz), 7.80 (d, 1H, J = 9.0 Hz), 8.38 (t, 1H, J = 6.0 Hz). HRMS calcd for $C_{19}H_{19}N_3O$ (M^+), 305.3828; found (M^+), 305.1536. Anal. ($C_{19}H_{19}N_3O\cdot$0.1H_2O) C, H, N.

6-(4-Pyrrolidin-1-ylmethyl-phenyl)-3,4-dihydro-2*H*-[1,4]-diazepino[6,7,1-*hi*]indol-1-one (25). Pale yellow solid (76%); mp 146−148 °C. ^{1}H NMR (DMSO-d_6): δ 1.71 (br s, 4H), 2.49 (br s, 4H), 3.48 (br s, 2H), 3.64 (br s, 2H), 4.30−4.33 (m, 2H), 6.69 (s, 1H), 7.16 (t, 1H, J = 9.0 Hz), 7.43 (d, 2H, J = 9.0 Hz), 7.55 (d, 2H, J = 9.0 Hz), 7.77 (d, 1H, J = 9.0 Hz), 7.80 (d, 1H, J = 9.0 Hz), 8.38 (t, 1H, J = 6.0 Hz). HRMS calcd for $C_{22}H_{23}N_3O$ (M^+), 345.1841; found (M^+), 345.1835. Anal. ($C_{22}H_{23}N_3O\cdot$0.25 H_2O) C, H, N.

7-Iodo-3,4-dihydro-2*H*-[1,4]diazepino[6,7,1-*hi*]indol-1-one (26). To a pale yellow solution **2** (0.051 g, 0.274 mmol) in 5 mL of DMF were added KOH (0.058 g, 1.03 mmol) and iodine (0.139 g, 0.548 mmol) at room temperature. The reaction mixture was stirred at room temperature overnight. The solvent was removed in vacuo, and the residue was taken up in EtOAc and washed with 0.1% sodium bisulfite, H_2O, and brine. The organic layer was dried over anhydrous $MgSO_4$ and concentrated to give 0.078 g (92%) of a pale yellow solid, which was used without further purification; mp 188−190 °C. ^{1}H NMR (DMSO-d_6): δ 3.56−3.59 (m, 2H), 4.40 (m, 2H), 7.26 (t, 1H, J = 7.5 Hz), 7.52 (d, 1H, J = 7.5 Hz), 7.67 (s, 1H), 7.93 (d, 1H, J = 7.5 Hz), 8.37 (t, 1H, J = 5.3 Hz). HRMS calcd for $C_{11}H_9N_2OI$ (M^+), 311.9761; found (M^+), 311.9776. Anal. calcd for $C_{11}H_9N_2O_2I$: % C, 42.33; % H, 2.91; % N, 8.98. Found: % C, 42.81; % H, 2.98; % N, 8.85.

1-Oxo-1,2,3,4-tetrahydro[1,4]diazepino[6,7,1-*hi*]indole-7-carboxylic Acid Methyl Ester (27). Triethylamine (0.11 mL, 0.747 mmol) was added to a mixture of **26** (0.074 g, 0.37 mmol) and bistriphenylphosphine palladium chloride (8.4 mg, 0.012 mmol) in 8 mL of MeOH and 3 mL of DMF at room temperature. The reaction mixture was heated at 50−55 °C for 18 h under a CO atmosphere (balloon). The solvent was removed under vacuo, and the residue was taken up in EtOAc and washed with water. The organic layer was dried over anhydrous $MgSO_4$ and concentrated to give a yellow solid, which was purified by flash silica gel chromatography eluting with a gradient of 0−3% MeOH in $CHCl_3$ to give 0.025 g of the methyl ester; mp 259−261 °C. ^{1}H NMR (DMSO-d_6): δ 3.34−3.60 (m, 2H), 3.83 (s, 3H), 4.46 (br s, 2H), 7.36 (t, 1H, J = 7.5 Hz), 7.95 (d, 1H, J = 7.5 Hz), 8.23 (s, 1H), 8.27 (d, 1H, J = 7.5 Hz), 8.40−8.50 (m 1H). HRMS calcd for $C_{13}H_{12}N_2O_3$ (M^+), 244.0848; found (M^+), 244.0850. Anal. ($C_{13}H_{12}N_2O_3\cdot$0.25 H_2O) C, H, N.

1-Oxo-1,2,3,4-tetrahydro[1,4]diazepino[6,7,1-*hi*]indole-7-carbaldehyde Oxime (28). To a mixture of **3** (0.050 g, 0.233 mmol) in EtOH (5 mL) and H_2O (0.5 mL) were added $NH_2OH\cdot$HCl (0.041 g, 0.583 mmol) and NaOH (0.024 g, 0.583 mmol) at room temperature. The reaction mixture was heated at 80−85 °C for 2 days. The resulting suspension was filtered, and the white solid (0.047 g) was washed with water and dried; mp 262−264 °C. ^{1}H NMR (DMSO-d_6): δ 3.56 (br s, 2H), 4.36 (br s, 2H), 7.23 (t, 1H, J = 7.5 Hz), 7.68 (s, 1H), 7.90 (d, 1H, J = 7.5 Hz), 8.21 (d, 1H, J = 7.5 Hz), 8.26 (s, 1H), 8.33−8.35 (m, 1H), 10.66 (s, 1H). HRMS calcd for $C_{12}H_{11}N_3O_2$ (M^+), 229.0851; found (M^+), 229.0843. Anal. ($C_{12}H_{11}N_3O_2$) C, H, N.

1-Oxo-1,2,3,4-tetrahydro[1,4]diazepino[6,7,1-*hi*]indole-7-carbaldehyde *O*-Methyl-oxime (29 and 30). A solution **3** (0.050 g, 0.234 mmol) and $MeONH_2\cdot$HCl (0.020 g, 0.242 mmol) in EtOH (5 mL) and pyridine (5 mL) was refluxed for 20 h. The reaction mixture was then evaporated to dryness. The residue was taken up in H_2O and extracted with EtOAc several times. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated. The crude was purified by flash silica gel chromatography eluting with a gradient of 0−1% MeOH in $CHCl_3$ to give 0.036 g of the (*E*) and 0.013 g of the (*Z*) isomer.

Compound 29. (*E*) isomer: mp 173−175 °C. ^{1}H NMR (DMSO-d_6): δ 3.55 (br s, 2H), 3.87 (s, 3H), 4.37 (br s, 2H), 7.27 (t, 1H, J = 7.5 Hz), 7.75 (s, 1H), 7.91 (d, 1H, J = 7.5 Hz), 8.24 (d, 1H, J = 7.5 Hz), 8.34−8.38 (m, 2H). HRMS calcd for $C_{13}H_{13}N_3O_2$ (M^+), 243.1008; found (M^+), 243.1016. Anal. ($C_{13}H_{13}N_3O_2\cdot$0.25 H_2O) C, H, N.

Compound 30. (*Z*) isomer: mp 210−212 °C. ^{1}H NMR (DMSO-d_6): δ 3.54−3.58 (m, 2H), 3.96 (s, 3H), 4.43 (br s, 2H), 7.27 (t, 1H, J = 9.0 Hz), 7.89−7.92 (m, 2H), 8.14 (d, 1H, J = 9.0 Hz), 8.21 (s, 1H), 8.35−8.39 (m, 1H). HRMS calcd for $C_{13}H_{13}N_3O_2$ (M^+), 243.1008; found (M^+), 243.1020. Anal. ($C_{13}H_{13}N_3O_2\cdot$0.1$H_2O\cdot$0.1EtOAc) C, H, N.

7-(1-Hydroxy-ethyl)-3,4-dihydro-2*H*-[1,4]diazepino[6,7,1-*hi*]indol-1-one (31). MeLi (1.5 M) (3.744 mmol, 2.5 mL) was added to a solution of **3** (1.17 mmol, 0.250 g) in 100 mL of THF at −78 °C. The reaction mixture was warmed to room temperature and stirred for 5−10 min. Upon consumption of **3** as indicated by TLC, the reaction was quenched with H_2O and then extracted with EtOAc several times. The combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated to give a yellow solid. The solid was purified by flash silica gel chromatography eluting with a gradient of 0−5% MeOH in $CHCl_3$ to give 0.222 g (69%) of a pale yellow solid; mp 295−297 °C. ^{1}H NMR (DMSO-d_6): δ 1.47 (d, 3H, J = 6.0 Hz), 3.50−3.55 (m, 2H), 4.29−4.31 (m, 2H), 4.95 (d, 1H, J = 6.0 Hz), 4.97−5.03 (m, 1H), 7.10 (t, 1H, J = 6.0 Hz), 7.25 (s, 1H), 7.81 (d, 1H, J = 6.0 Hz), 7.86 (d, 1H, J = 6.0 Hz), 8.25 (t, 1H, J = 6.0 Hz). HRMS calcd for $C_{13}H_{14}N_2O_2$ (M^+), 231.1134; found (M^+), 231.1143. Anal. ($C_{13}H_{14}N_2O_2$) C, H, N.

7-Acetyl-3,4-dihydro-2*H*-[1,4]diazepino[6,7,1-*hi*]indol-1-one (32). *o*-Iodooxybenzoic acid (2.217 mmol, 0.621 g) was added to a solution of **31** (0.739 mmol, 0.170 g) in DMSO (8 mL) at room temperature, and the mixture was stirred at for 2.5 h. The solvent was removed in vacuo, and the residue was taken up in EtOAc and washed with 5% $Na_2S_2O_3$/5% $NaHCO_3$,

H_2O, and brine. The organic layer was dried over anhydrous $MgSO_4$ and concentrated to give an orange solid. The solid was purified by flash silica gel chromatography eluting with a gradient of 0−5% MeOH in $CHCl_3$ to give 0.094 g (75%) of a pale pink solid; mp 285−287 °C. ^{1}H NMR (DMSO-d_6): δ 2.42 (s, 3H), 3.56−3.61 (m, 2H), 4.44 (br s, 2H), 7.32 (t, 1H, J = 6.0 Hz), 7.92 (d, 1H, J = 6.0 Hz), 8.40−8.44 (m, 3H). HRMS calcd for $C_{13}H_{12}N_2O_2$ (M^+), 228.0899; found (M^+), 228.0890. Anal. ($C_{13}H_{12}N_2O_2$) C, H, N.

7-(1-Hydroxyimino-ethyl)-3,4-dihydro-2*H*-[1,4]diazepino[6,7,1-*hi*]indol-1-one (33). NH_2OH·HCl (1.928 mmol, 0.134 g) was added to a solution of **32** (0.241 mmol, 0.055 g) in pyridine (6 mL) at room temperature. The reaction mixture was heated at 70−80 °C for 5 h. The solvent was removed, and ice-cold H_2O was added to the residue, whereupon a precipitate formed, which was then filtered, washed with H_2O, and dried to give 0.040 g (68%) of a pale yellow solid; mp 238−240 °C. ^{1}H NMR (DMSO-d_6): δ 2.16 (s, 3H), 3.56 (br s, 2H), 4.36 (br s, 2H), 7.19 (t, 1H, J = 6.0 Hz), 7.77 (s, 1H), 7.87 (d, 1H, J = 6.0 Hz), 8.33 (t, 1H, J = 6.0 Hz), 8.38 (d, 1H, J = 6.0 Hz), 10.67 (s, 1H). HRMS calcd for $C_{13}H_{13}N_3O_2$ (M^+), 243.1008; found (M^+), 243.0997. Anal. ($C_{13}H_{13}N_3O_2$) C, H, N.

7-(1-Hydroxy-1-phenyl-methyl)-3,4-dihydro-2*H*-[1,4]-diazepino[6,7,1-*hi*]indol-1-one (34). Using the procedure described for the preparation of **31**, **3** was exposed to phenyllithium yielding 74% of **34** as a yellow solid; mp 178−180 °C. ^{1}H NMR (DMSO-d_6): δ 3.51−3.52 (m, 2H), 4.28−4.29 (m, 2H), 5.70 (d, 1H, J = 6.0 Hz), 5.96 (d, 1H, J = 6.0 Hz), 7.05 (t, 1H, J = 6.0 Hz), 7.14 (s, 1H), 7.17−7.22 (m, 1H), 7.30 (t, 2H, J = 6.0 Hz), 7.45 (d, 2H, J = 6.0 Hz), 7.72 (d, 1H, J = 6.0 Hz), 7.79 (d, 1H, J = 6.0 Hz), 8.24 (t, 1H, J = 6.0 Hz). HRMS calcd for $C_{18}H_{16}N_2O_2$ (M^+), 292.1212; found (M^+), 292.1202. Anal. ($C_{18}H_{16}N_2O_2$·0.25 H_2O) C, H, N.

7-(1-Phenyl-methanoyl)-3,4-dihydro-2*H*-[1,4]diazepino-[6,7,1-*hi*]indol-1-one (35). Using the procedure described for the preparation of **32**, *o*-iodooxybenzoic acid and **34** were used to synthesize **35** in 80% yield as a pale yellow solid; mp 229−230 °C. ^{1}H NMR (DMSO-d_6): δ 3.58−3.61 (m, 2H), 4.47 (br s, 2H), 7.40 (t, 1H, J = 6.0 Hz), 7.52−7.65 (m, 3H), 7.79−7.82 (m, 2H), 7.98 (d, 1H, J = 6.0 Hz), 8.08 (s, 1H), 8.44 (t, 1H, J = 6.0 Hz), 8.51 (d, 1H, J = 6.0 Hz). HRMS calcd for $C_{18}H_{14}N_2O_2$ (M^+), 290.1055; found (M^+), 290.1042. Anal. ($C_{18}H_{14}N_2O_2$) C, H, N.

7-(1-Hydroxyimino-1-phenyl-methyl)-3,4-dihydro-2*H*-[1,4]diazepino[6,7,1-*hi*]indol-1-one (36). Using the procedure described for the preparation of **33**, NH_2OH·HCl and **35** were used to synthesize **36** in 76% yield as a pale yellow solid; mp 263−265 °C (mixture of syn and anti oximes). ^{1}H NMR (DMSO-d_6): δ 3.51 (br s, 2H), 3.60 (br s, 2H), 4.29 (br s, 2H), 4.45 (br s, 2H), 6.97−7.04 (m, 3H), 7.24 (t, 1H, J = 6.0 Hz), 7.34−7.46 (m, 10H), 7.82 (d, 1H, J = 6.0 Hz), 7.89−7.93 (m, 2H), 8.31−8.36 (m, 3H), 10.74 (s, 1H), 11.37 (s, 1H). HRMS calcd for $C_{18}H_{15}N_3O_2$ (M^+), 305.1164; found (M^+), 305.1177. Anal. ($C_{18}H_{15}N_3O_2$·0.1 H_2O) C, H, N.

6-(4-Chloro-phenyl)-1-oxo-1,2,3,4-tetrahydro[1,4]diazepino[6,7,1-*hi*]indole-7-carbaldehyde (37). $POCl_3$ (0.3 mL, 3.19 mmol) was slowly added to DMF (3 mL) at 0 °C. The reaction mixture was stirred for 15 min and then was treated with a solution of **15** (0.070 g, 0.236 mmol) in DMF (2 mL) and warmed to room temperature for 4 h. After all solvent was removed, the residue was taken up in H_2O and made basic (pH 12−14) using 50% aqueous NaOH whereupon solids formed. The product was filtered, washed with water several times, and dried (0.077 g); mp 278−279 °C. ^{1}H NMR (DMSO-d_6): δ 3.41−3.52 (m, 2H), 4.20−4.22 (m, 2H), 7.43 (t, 1H, J = 9.0 Hz), 7.68 (d, 2H, J = 9.0 Hz), 7.74 (d, 2H, J = 9.0 Hz), 8.00 (d, 1H, J = 6.0 Hz), 8.47 (d, 1H, J = 6.0 Hz), 8.51 (t, 1H, J = 6.0 Hz), 9.65 (s, 1H). HRMS calcd for $C_{18}H_{13}N_2O_2Cl$ (M^+), 324.0665; found (M^+), 324.0668. Anal. ($C_{18}H_{13}N_2O_2Cl$·0.25H_2O) C, H, N.

6-(4-Chloro-phenyl)-1-oxo-1,2,3,4-tetrahydro[1,4]diazepino[6,7,1-*hi*]indole-7-carbaldehyde oxime (38). NH_2OH·HCl (0.027 g, 0.385 mmol) and NaOH (0.016 g, 0.385 mmol) were added to a suspension of **37** (0.050 g, 0.154 mmol) in EtOH (5 mL) and H_2O (0.5 mL). After the reaction mixture was heated at 80−85 °C for 3 h, it was evaporated to dryness. The residue was taken up in ice-cold H_2O when a pale yellow solid formed. The solid was filtered, washed with H_2O, and then purified by flash silica gel chromatography eluting with a gradient of 0−5% MeOH in $CHCl_3$ to give 0.035 g (67%) of the oxime; mp 249−251 °C. ^{1}H NMR (DMSO-d_6): δ 3.40 (br s, 2H), 4.0−4.1 (m, 2H), 7.30 (t, 1H, J = 9.0 Hz), 7.55 (d, 2H, 9.0 Hz), 7.64 (d, 2H, J = 9.0 Hz), 7.90 (s, 1H), 7.94 (d, 1H, J = 9.0 Hz), 8.34 (d, 1H, J = 9.0 Hz), 8.41 (t, 1H, J = 6.0 Hz), 10.83 (s, 1H). HRMS calcd for $C_{18}H_{14}N_3O_2Cl$ (M^+ + H), 340.0853; found (M^+ + H), 340.0862. Anal. ($C_{18}H_{14}N_3O_2Cl$·0.75CH_2Cl_2) C, H, N.

6-(4-Fluoro-phenyl)-1-oxo-1,2,3,4-tetrahydro[1,4]diazepino[6,7,1-*hi*]indole-7-carbaldehyde (39). Using the procedure described for the preparation of **37**, **17** was transformed to **39** in 94% yield as a white solid; mp 268−270 °C. ^{1}H NMR (DMSO-d_6): δ 3.52−3.54 (m, 2H), 4.19−4.22 (m, 2H), 7.40−7.50 (m, 3H), 7.75 (d, 1H, J = 6.0 Hz), 7.78 (d, 1H, J = 6.0 Hz), 8.46 (d, 1H, J = 6.0 Hz), 8.52 (t, 1H, J = 6.0 Hz), 9.64 (s, 1H). LRMS (M^+ + H) 309. HPLC R_t = 3.522 min.

6-(4-Fluoro-phenyl)-1-oxo-1,2,3,4-tetrahydro[1,4]diazepino[6,7,1-*hi*]indole-7-carbaldehyde Oxime (40). NH_2OH·HCl (0.325 mmol, 0.100 g) was added to a solution of **39** (0.813 mmol, 0.056 g) in pyridine (10 mL) at room temperature. The reaction mixture was stirred at room temperature for 20 h. Upon completion of the reaction, the solvent was removed in vacuo. The residue was taken up in 2 N HCl and extracted with EtOAc several times. The combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated to give 0.097 g (92%) of a pale yellow solid, which was used without further purification; mp 277−279 °C. ^{1}H NMR (DMSO-d_6): δ 3.50 (br s, 2H), 4.12−4.14 (m, 2H), 7.30 (t, 1H, J = 6.0 Hz), 7.43 (t, 2H, J = 9.0 Hz), 7.57−7.62 (m, 2H), 7.89 (s, 1H), 7.94 (d, 1H, J = 9.0 Hz), 8.33 (d, 1H, J = 6.0 Hz), 8.41 (t, 1H, J = 6.0 Hz), 10.80 (s, 1H). HRMS calcd for $C_{18}H_{14}N_3O_2F$ (M^+), 323.1070; found (M^+), 323.1066. Anal. calcd for $C_{18}H_{14}N_3O_2F$·0.3H_2O: % C, 65.76; % H, 4.48; % N, 12.78. Found: % C, 66.06; % H, 4.51; % N, 12.32.

6-(4-Fluoro-phenyl)-1-oxo-1,2,3,4-tetrahydro[1,4]diazepino[6,7,1-*hi*]indole-7-carbonitrile (41). Thiocarbonyldiimidazole (2.33 mmol, 0.415 g) was added to a solution of **40** (0.932 mmol, 0.301 g) in THF (70 mL) at room temperature. The reaction mixture was stirred at room temperature for 4 h. Upon consumption of **40**, the solvent was removed in vacuo. The residue was dissolved in EtOAc and washed with 10% HCl and then with saturated $NaHCO_3$. The organic layer was dried over anhydrous $MgSO_4$ and concentrated to give a yellow oil, which was purified by flash silica gel chromatography eluting with a gradient of 0−3% MeOH in $CHCl_3$ to give 0.268 g (94%) of a pale yellow solid; mp 248−250 °C. ^{1}H NMR (DMSO-d_6): δ 3.52 (br s, 2H), 4.29−4.31 (m, 2H), 7.41−7.53 (m, 3H), 7.77 (d, 1H, J = 6.0 Hz), 7.80 (d, 1H, J = 6.0 Hz), 7.90 (d, 1H, J = 6.0 Hz), 8.01 (d, 1H, J = 6.0 Hz), 8.55 (t, 1H, J = 6.0 Hz). HRMS calcd for $C_{18}H_{12}N_3OF$ (M^+), 305.0964; found (M^+), 305.0951. Anal. ($C_{18}H_{12}N_3OF$·0.1H_2O) C, H, N.

6-(4-Fluoro-phenyl)-1-oxo-1,2,3,4-tetrahydro[1,4]diazepino[6,7,1-*hi*]indole-7-carboxylic Acid Amide (42). A suspension of **41** (0.164 mmol, 0.050 g) in 85% H_3PO_4 (7 mL) was heated at 90−100 °C for 22 h. Upon completion (as indicated by TLC), the reaction mixture was poured into cold H_2O and extracted with EtOAc several times. The combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated to give a pink oil, which was purified by flash silica gel chromatography eluting with a gradient of 0−5% MeOH in $CHCl_3$ to give 0.042 g (79%) of a pale yellow solid; mp 287−289 °C. ^{1}H NMR (DMSO-d_6): δ 3.47 (br s,2H), 3.98−4.06 (m, 2H), 6.46 (br s, 1H), 7.09 (br s, 1H), 7.28 (t, 1H, J = 6.0 Hz), 7.38 (t, 2H, J = 9.0 Hz), 7.56 (d, 1H, J = 6.0 Hz), 7.60 (d, 1H, J = 6.0 Hz), 7.90 (d, 1H, J = 6.0 Hz), 8.15 (d, 1H, J = 6.0 Hz), 8.40 (t, 1H, J = 6.0 Hz). HRMS calcd for $C_{18}H_{14}N_3O_2F$ (M^+), 323.1070; found (M^+), 323.1063. Anal. ($C_{18}H_{14}N_3O_2F$·0.5H_2O) C, H, N.

6-(4-Fluoro-phenyl)-1-oxo-1,2,3,4-tetrahydro[1,4]diazepino[6,7,1-*hi*]indole-7-carbothioic Acid Amide (43). In an opened sealed tube apparatus, H_2S gas was bubbled into a solution of **41** (0.5 mmol, 0.153 g) in Et_3N (1 mL) and pyridine (2.4 mL) at 0 °C for 1 h until saturated. The tube was then carefully sealed, allowed to warm to room temperature, and stirred at room temperature for 4 days. The tube was cooled to 0 °C and carefully vented, and the remaining H_2S was purged with argon. The dark green solution was diluted with EtOAc and washed with 2 N HCl and then with H_2O. The organic layer was dried over anhydrous $MgSO_4$ and concentrated to give a yellow solid, which was purified by flash silica gel chromatography eluting with a gradient of 0−3% MeOH in $CHCl_3$ to give 0.107 g (63%) of a yellow solid; mp 238−240 °C. ^{1}H NMR (DMSO-d_6): δ 3.47 (br s, 2H), 4.01−4.11 (m, 2H), 7.27 (t, 1H, J = 9.0 Hz), 7.37 (t, 2H, J = 9.0 Hz), 7.54−7.58 (m, 2H), 7.88 (d, 1H, J = 9.0 Hz), 8.19 (d, 1H, J = 9.0 Hz), 8.42 (t, 1H, J = 6.0 Hz), 8.63 (br s, 1H), 9.50 (br s, 1H). HRMS calcd for $C_{18}H_{14}N_3OSF$ (M^+), 339.084162; found (M^+), 339.0833. Anal. ($C_{18}H_{14}N_3OSF\cdot0.3H_2O\cdot0.3$ MeOH) C, H, N.

6-(4-Fluoro-phenyl)-1-oxo-1,2,3,4-tetrahydro[1,4]diazepino[6,7,1-*hi*]indole-7-carboximidothioic Acid Methyl Ester (44). Iodomethane (3.218 mmol, 0.2 mL) was added to a solution of the **43** (0.354 mmol, 0.120 g) in 50 mL of THF at room temperature and stirred for 18 h. The solvent was removed to give a yellow solid (0.130 g), which was used without further purification. ^{1}H NMR (DMSO-d_6): δ 2.63 (s, 3H), 3.51 (br s, 2H), 4.01−4.05 (m, 2H), 7.42−7.53 (m, 3H), 7.62 (d, 1H, J = 6.0 Hz), 7.65 (d, 1H, J = 6.0 Hz), 8.02 (d, 1H, J = 3.0 Hz), 8.05 (d, 1H, J = 3.0 Hz), 8.57 (t, 1H, J = 6.0 Hz).

6-(4-Fluoro-phenyl)-*N*-hydroxy-1-oxo-1,2,3,4-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indole-7-carboxamidine (45). $NH_2OH\cdot HCl$ (0.852 mmol, 0.059 g) was added to a solution of the **44** (0.142 mmol, 0.05 g) in 5 mL of pyridine at room temperature and the mixture was stirred for 15 min. The solvent was removed to give an oil, which was purified by flash silica gel chromatography eluting with a gradient of 0−5% MeOH in $CHCl_3$ initially, followed by 2−10% MeOH/NH_3 in $CHCl_3$ to give 0.025 g (52%) of a pale yellow solid; mp 257−259 °C. ^{1}H NMR (DMSO-d_6): δ 3.45−3.47 (m, 2H), 4.10−4.12 (m, 2H), 5.41 (br s, 2H), 7.23 (t, 1H, J = 6.0 Hz), 7.34 (t, 2H, J = 9.0 Hz), 7.57 (d, 1H, J = 6.0 Hz), 7.59 (d, 1H, J = 6.0 Hz), 7.88 (d, 1H, J = 9.0 Hz), 7.93 (d, 1H, J = 9.0 Hz), 8.39 (br s, 1H), 9.33 (br s, 1H). HRMS calcd for $C_{18}H_{15}N_4O_2F$ (M^+), 338.1179; found (M^+), 338.1182. Anal. ($C_{18}H_{15}N_4O_2F\cdot0.5$ H_2O) C, H, N.

6-(4-Fluoro-phenyl)-*N*-amino-1-oxo-1,2,3,4-tetrahydro-[1,4]diazepino[6,7,1-*hi*]indole-7-carboxamidine Hydrochloride (46). Anhydrous hydrazine (2.92 mmol, 0.092 mL) was added to a solution of the **44** (0.139 mmol, 0.049 g) in 25 mL of acetonitrile at room temperature. The reaction mixture was stirred for 48 h, and the solvent was removed to give an oil, which was purified by flash silica gel chromatography eluting with a gradient of 0−10% MeOH in $CHCl_3$ initially, followed by 2−10% MeOH/NH_3 in $CHCl_3$ yielding 0.028 g (64%) of a white crystalline solid. This solid was dissolved in MeOH saturated with HCl gas and stirred at room temperature for 30 min. Diethyl ether was added to the solution, and the solvent was then evaporated to give an orange solid (9 mg); mp 272−274 °C. ^{1}H NMR (DMSO-d_6): δ 3.58 (br s, 2H), 4.22−4.23 (m, 2H), 5.18 (br s, 2H), 7.37−7.46 (m, 3H), 7.54−7.58 (m, 2H), 7.82 (d, 1H, J = 6.0 Hz), 8.00 (d, 1H, J = 6.0 Hz), 8.55 (t, 1H, J = 6.0 Hz), 8.79 (br s, 1H), 9.08 (br s, 1H), 10.60 (br s, 1H). HRMS calcd for $C_{18}H_{16}N_5OF$ (M^+), 337.1339; found (M^+), 337.1326. Anal. ($C_{18}H_{16}N_5OF\cdot1.0H_2O\cdot4.5HCl$) C, H, N.

6-(4-Fluoro-phenyl)-7-iodo-3,4-dihydro-2*H*-[1,4]diazepino[6,7,1-*hi*]indol-1-one (47). Using the procedure described for the preparation of **26**, **17** was converted with I_2 and KOH to **47** in 78% yield as a pale yellow solid; mp 283−285 °C. ^{1}H NMR (DMSO-d_6): δ 3.48 (br s, 2H), 4.15−4.18 (m, 2H), 7.29 (t, 1H, J = 6.0 Hz), 7.41 (t, 2H, J = 9.0 Hz), 7.58−7.64 (m, 3H), 7.94 (d, 1H, J = 6.0 Hz), 8.41 (t, 1H, J = 6.0 Hz). LRMS (M^+ + H) 407.

7-Acetyl-6-(4-fluoro-phenyl)-3,4-dihydro-2*H*-[1,4]diazepino[6,7,1-*hi*]indol-1-one (48). A solution of the **47** (0.246 mmol, 0.100 g), ethoxyvinyl tributyltin (0.320 mmol, 0.11 mL), tetrakistriphenyl phosphine palladium (0.0123 mmol, 0.014 g), and ∼1.0 mg of 2,6-di-*tert*-butyl-4-methyl phenol in 1,4-dioxane (20 mL) and DMF (1 mL) was heated at 90−95 °C for 20 h. After it was cooled to ambient temperature, the solvent was evaporated to dryness and the residue was taken up in 1 N HCl and extracted with EtOAc several times. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated to give a yellow oil, which was purified by flash silica gel chromatography eluting with a gradient of 0−3% MeOH in $CHCl_3$ to yield 0.049 g (64% crude) of a yellow solid. Further purification by preparative HPLC yielded 26% of 98% pure product using gradient solvent system of:

time (min)	H_2O w/ 0.1% TFA	CH_3CN w/ 0.1% TFA
0	90	10
2	90	10
22	35	65

mp 275−276 °C. ^{1}H NMR (DMSO-d_6): δ 1.86 (s, 3H), 3.45−3.52 (m, 2H), 3.96−3.98 (m, 2H), 7.37 (t, 1H, J = 6.0 Hz), 7.45 (t, 2H, J = 9.0 Hz) 7.64 (d, 1H, J = 6.0 Hz), 7.67 (d, 1H, J = 6.0 Hz), 7.96 (d, 1H, J = 6.0 Hz), 8.42 (t, 1H, J = 6.0 Hz), 8.55 (d, 1H, J = 6.0 Hz). HRMS calcd for $C_{19}H_{15}N_2O_2F$ (M^+), 322.1117; found (M^+), 322.1131. HPLC R_t = 10.608 min.

6-(4-Fluoro-phenyl)-7-((*E*)-2-hydroxy-1-methyl-vinyl)-3,4-dihydro-2*H*-[1,4]diazepino[6,7,1-*hi*]indol-1-one (49). $NH_2OH\cdot HCl$ (0.93 mmol, 0.066 g) was added to a solution of the **48** (0.124 mmol, 0.040 g) in 4 mL of pyridine at room temperature. The reaction mixture was stirred for 24 h whereupon the reaction mixture was evaporated to dryness. The residue was taken up in 2 N HCl and extracted with EtOAc several times. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated to give a pale yellow solid, which was purified by flash silica gel chromatography eluting with a gradient of 0−3% MeOH in $CHCl_3$ to give 0.025 g (60%) of a white solid; mp 248−250 °C. ^{1}H NMR (DMSO-d_6): δ 1.70 (s, 3H), 3.49 (br s, 2H), 4.07−4.09 (m, 2H), 7.21 (t, 1H, J = 6.0 Hz), 7.37 (t, 2H, J = 9.0 Hz), 7.51 (d, 1H, J = 6.0 Hz), 7.55 (d, 1H, J = 6.0 Hz), 7.89 (d, 1H, J = 6.0 Hz), 8.09 (d, 1H, J = 6.0 Hz), 8.37 (t, 1H, J = 6.0 Hz), 10 93 (s, 1H). HRMS calcd for $C_{19}H_{16}N_3O_2F$ (M^+), 337.1226; found (M^+), 337.1230. Anal. for ($C_{19}H_{16}N_3O_2F\cdot0.1H_2O$) C, H, N.

7-((*E*)-3-Dimethylamino-acryloyl)-6-(4-fluoro-phenyl)-3,4-dihydro-2*H*-[1,4]diazepino[6,7,1-*hi*]indol-1-one (50). N,N′-Dimethylformamide dimethyl acetal (13.88 mmol, 2 mL) was added to a solution of **48** (0.217 mmol, 0.070 g) in DMF (1 mL) at room temperature. The reaction mixture was stirred at 110−120 °C for 18 h. Upon completion of the reaction as indicated by TLC, the solvent was removed in vacuo to give 0.101 g (quantitative yield) of an orange solid, which was used without further purification. ^{1}H NMR (DMSO-d_6): δ 3.30 (s, 6H), 3.50 (br s, 2H), 3.98−4.05 (m, 2H), 4.61 (d, 1H, J = 12.0 Hz), 7.26 (t, 1H, J = 6.0 Hz), 7.35−7.43 (m, 3H), 7.54−7.58 (m, 2H), 7.89 (d, 1H, J = 6.0 Hz), 8.37−8.43 (m, 2H). LC mass (M^+ + H) 378.

6-(4-Fluoro-phenyl)-7-(2*H*-pyrazol-3-yl)-3,4-dihydro-2*H*-[1,4]diazepino[6,7,1-*hi*]indol-1-one (51). Hydrazine monohydrate (5.14 mmol, 0.26 mL) was added to a solution of **50** (0.257 mmol, 0.097 g) in 10 mL of THF at room temperature. The reaction mixture was stirred at room temperature for 42 h and then evaporated to dryness. The residue was taken up in 2 N HCl and extracted with EtOAc several times. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated to give a yellow oil, which was purified by flash silica gel chromatography eluting with a gradient of 0−3% MeOH in $CHCl_3$ to give 0.020 g (23%) of a yellow solid; mp 173−175 °C. ^{1}H NMR (DMSO-d_6): δ 3.45−3.52 (m, 2H), 4.03−4.08 (m, 2H), 5.64 (br s, 1H), 7.23 (t, 1H, J = 6.0 Hz), 7.32 (t, 2H, J = 9.0 Hz), 7.38−7.55 (m, 3H), 7.88 (d, 1H, J =

6.0 Hz), 8.36−8.43 (m, 2H), 12.67(br s, 1H). HRMS calcd for $C_{20}H_{15}N_4OF$ (M^+), 346.1221; found (M^+), 346.1225. Anal. for ($C_{20}H_{15}N_4OF \cdot 1.0MeOH$) C, H, N.

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JM030513R