Pyridazinoquinolinetriones as NMDA Glycine-Site Antagonists with Oral Antinociceptive Activity in a Model of Neuropathic Pain

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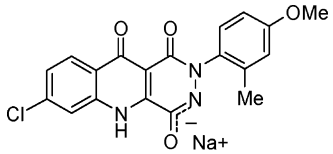
Received February 23, 2006

A series of 7-chloro-2,3-dihydro-2-[1-(pyridinyl)alkyl]-pyridazino[4,5-*b*]quinoline-1,4,10(5*H*)-triones were synthesized and found to have potent activity at the glycine site of the NMDA receptor. In some cases, these compounds possessed poor aqueous solubility that may have contributed to poor rat oral bioavailability. Subsequently, compounds have been identified with improved aqueous solubility and oral bioavailability. Several of these compounds were examined in a rat chronic constrictive injury (CCI) model of neuropathic pain and found to have potent activity when dosed orally.

Introduction

N-Methyl-D-aspartate (NMDA) receptors are ligand-gated ion channels that are activated by the excitatory amino acid L-glutamate. These receptors also require the coagonist glycine for activation of the receptor.[1] The fully functional NMDA receptor is a heteromultimeric complex composed of at least one NR1 subunit and one NR2 subunit.[2] The NR1 subunit comes from a single gene, but can exist as eight different isoforms.[3] The NR2 subunit can arise from four different genes and is divided into the subtypes NR2A, NR2B, NR2C, and NR2D.[4,5] An NR3 subunit is also known and possibly has implications in regulation during development.[6] The various sites of ligand interaction are well characterized as it pertains to receptor subtype. The glycine binding site is associated with the NR1 subunit, whereas the glutamate site is associated with the NR2 subunit.[7−9] Polyamine-site antagonists such as ifenprodil are thought to bind at the NR2B subunit.[10] A high-affinity Zn^{2+} binding site is located on the NR2A subunit and shares some similarities to the ifenprodil site found on the NR2B subunit.[11]

Painful peripheral neuropathy is the result of changes in both the peripheral and central nervous systems following nerve damage due to trauma, disease, and certain toxins.[12−14] Central sensitization, an abnormal hyperexcitable state of spinal cord dorsal horn neurons evoked by activity at glutamatergic NMDA synapses, has been implicated as one of the key central changes.[15] "Wind-up", a hyperexcitable condition in dorsal horn neurons evoked in normal animals by repetitive input from C-fiber nociceptors, is also believed to be mediated via NMDA synapses.[16] Central sensitization is also implicated in the abnormal pain syndromes that follow injury to the spinal cord.[17] Central sensitization is believed to be at least partly responsible for the hyperalgesia (supernormal pain caused by a normally painful stimulus) and allodynia (pain caused by a stimulus that would ordinarily be painless) that are seen in patients with painful peripheral neuropathies.[18]



1, ZD9379

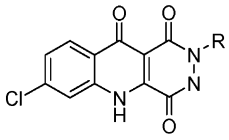


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Figure 1. The 7-chloro-2,3-dihydro-2-[1-(pyridinyl)alkyl]-pyridazino-[4,5-*b*]quinoline-1,4,10(5*H*)-trione (PQT) class of compounds.

NMDA receptors are known to play a role in central sensitization in the dorsal horn of spinal cord.[19−21] It is reported that NMDA antagonists block and reverse this phenomena.[19] The condition of "wind-up" has also been linked to NMDA receptors.[22−23] It has been reported that ketamine,[24] memantine,[25] and MK-801[25] inhibit wind-up on dorsal horn neurons. It has been established that compounds which block activation of the NMDA receptor also demonstrate activity in models of neuropathic pain.[26] However, antagonists blocking the glutamate site or the ion channel give rise to unacceptable motor side effects.[27] There is evidence that indicates that antagonists may attenuate pain in neuropathic pain models via interacting with the glycine site of the NMDA receptor.[28,29]

We had previously identified the 7-chloro-2,3-dihydro-2-[1-(pyridinyl)alkyl]-pyridazino[4,5-*b*]quinoline-1,4,10(5*H*)-triones (PQTs), such as ZD9379, **1**, as potent glycine-site antagonists targeted for the prevention of stroke when administered intravenously.[30] We sought to re-examine this class of compounds, specifically those related to substructure **2**, as possible compounds for use in the oral treatment of neuropathic pain. In doing so, part of our strategy was to optimize binding affinity and aqueous solubility, anticipating that this would result in compounds with good oral bioavailability and activity in neuropathic pain models.

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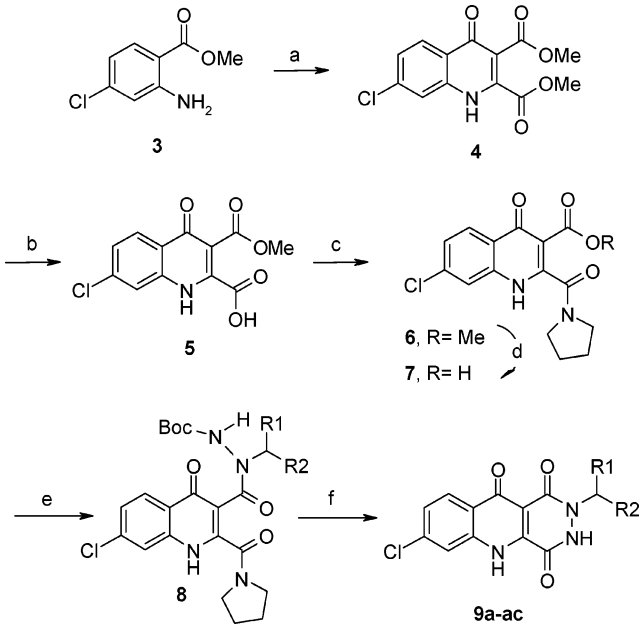
10.1021/jm060212s CCC: $37.00
Published on Web 06/02/2007

Scheme 1. General Synthesis of 7-Chloro-2,3-dihydro-2-[1-(pyridinyl)alkyl]-pyridazino[4,5-*b*]quinoline-1,4,10(5*H*)-triones[a]

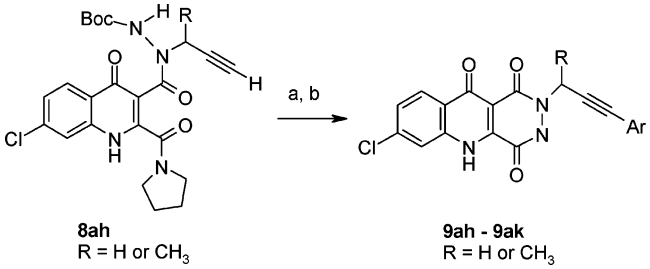


[a] Reagents and conditions: (a) KO^{t}Bu, DMAD, ^{t}BuOH, reflux; (b) NaOH, H_2O, 60 °C; (c) pyrrolidine, DCC, THF; (d) KOH, H_2O, 60 °C; (e) $R_1R_2NHNH^t$Boc, CMC or EDCI, THF or CH_2Cl_2, cat. DMAP; (f) CH_3SO_3H, THF.

Chemistry

The general synthetic route to the core pyridazinoquinolinetrione scaffold can be seen in Scheme 1. Reaction of the anthrinilate ester **3** and dimethyl acetylenedicarboxylate provided the intermediate diester **4**. Selective hydrolysis of the ester in the 2-position and subsequent amide formation afforded the pyrrolidine amide **6**. The remaining ester was then hydrolyzed to give the acid-amide intermediate **7**, which served as a useful diversification point for construction of the pyridazinoquinolinetriones. The intermediate **7** was coupled with *tert*-butyl carbamate-protected hydrazines. The intermediate **8** was then cyclized using methanesulfonic acid to give the desired PQTs **9a**−**ac**.

Scheme 3. Alternative Synthesis of Acetylenic Pyridazinoquinolinetriones[a]

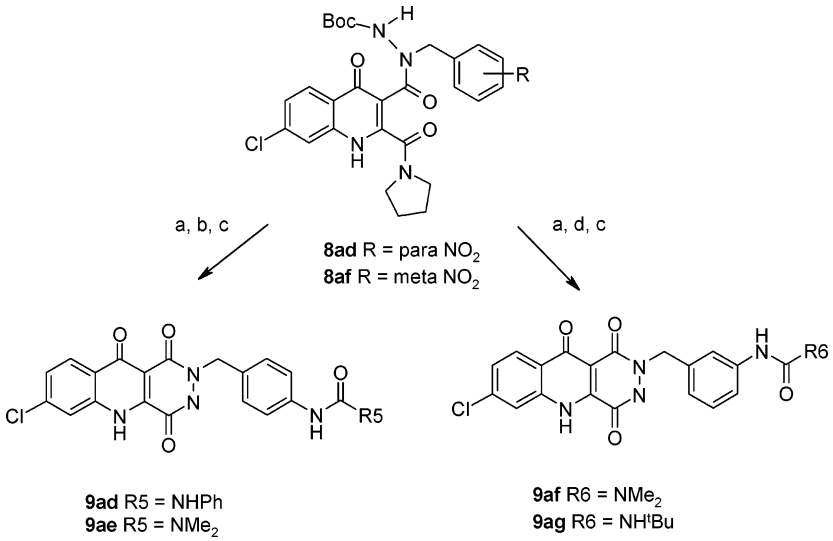


[a] Reagents and conditions: (a) Ar/HetArX, cat. $Pd(PPh_3)_2Cl_2$, cat. CuI, Et_3N, BHT, CH_2Cl_2; (b) CH_3SO_3H, THF.

While the general synthetic route of the pyridazinoquinolinetriones is outlined in Scheme 1, a few of the intermediates **8** were further diversified en route to **9**; see Schemes 2 and 3. For example, in Scheme 2, aromatic nitro groups present on intermediate **8** were reduced and the subsequent anilines converted to ureas using standard protocols. These urea products were cyclized under the standard conditions to afford the final PQT's **9ad**−**ag**. The acetylenic PQTs, Scheme 3, were accessed via palladium-catalyzed coupling of **8ah** with the appropriate aryl or heteroaryl halides under Sonogashira conditions.[31] These intermediates were then cyclized to afford the final PQTs **9ah**−**ak**. Diversification at the penultimate step was required as attempts to introduce substituents directly to the cyclized acetylenic compound **9** were hindered by the general insolubility of the final products. Thus, while the aryl or heteroaryl halides could be effectively coupled to the cyclized acetylenic PQT **9ag**, purification was not feasible.

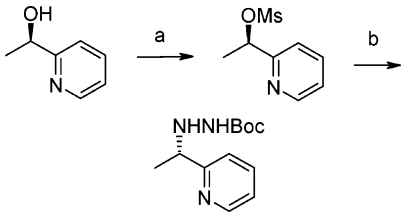
Commercially available and synthesized hydrazines were employed in the construction of intermediates **8**. Many of the hydrazines were synthesized using standard protocols, either beginning with the appropriate ketone or aldehyde and proceeding via the hydrazone intermediate, or synthesized from *tert*-butyl carbazate and the appropriate halide. The synthesis of propargyl hydrazines was performed by coupling propargyl alcohol with aryl bromides or iodides using Sonogashira conditions[31] to give the aryl propargylic alcohols. These alcohols were then converted to the corresponding halides, which were then treated with *tert*-butyl carbazate to afford the *tert*-butyl

Scheme 2. Synthesis of a Subset of Pyridazinoquinolinetriones[a]



[a] Reagents and conditions: (a) Dioctadecyl-4,4′-bipyridinium dibromide, sodium dithionate, K_2CO_3, CH_2Cl_2–H_2O; (b) phenyl isocyanate or *N*,*N*-dimethylcarbamoyl chloride, Et_3N, cat. DMAP, CH_2Cl_2; (c) $MeSO_3H$, THF; (d) dimethylcarbamoyl chloride or *tert*-butyl isocyanate, Et_3N, CH_2Cl_2.

Scheme 4. Enantioselective Synthesis of Hydrazine Intermediates[a]



[a] Reagents and conditions: (a) MsCl, Et_3N, CH_2Cl_2; (d) ^{t}BocNHNH$_2$, iPr_2NEt, DMF, 90 °C, 6 h.

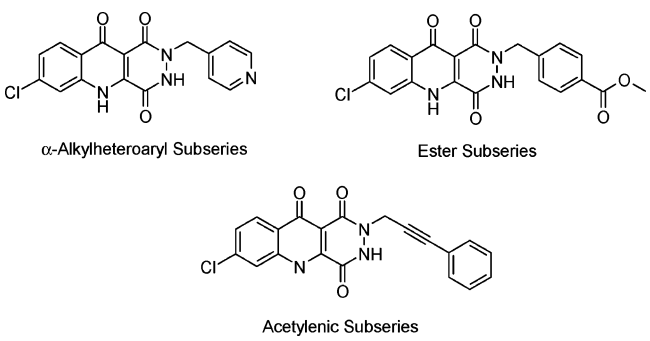


Figure 2. Three pyridazinoquinolinetrione starting points.

carbamate-protected hydrazines. Synthetic details for the synthesized hydrazines can be found in the Experimental Section.

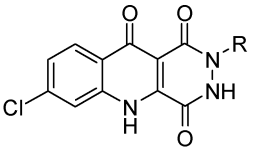
Chiral hydrazines were synthesized according to Scheme 4. Preparation of (*R*)-1-pyridin-2-yl-ethanol was performed using the procedure previously described.[32] The alcohol was converted to the secondary mesylate, and then displacement occurred with inversion of the stereocenter using the Boc-protected hydrazine. The reaction proceeded with good enantioselectivity (>95% ee), but with relatively poor yield (18%). Alternatively, the chiral hydrazines used for preparation of compounds **9d** and **9e** could be separated from the racemic hydrazine using chiral preparatory chromatography, details are given in the Experimental Section.

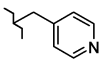
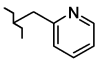
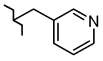
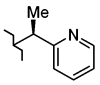
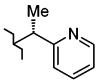
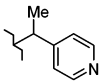
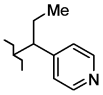
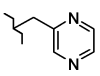
Discussion

The NMDA glycine-site antagonist project for the treatment of neuropathic pain employed a pool of ~3800 compounds previously synthesized for a glycine-site NMDA antagonist program targeting intravenous treatment of stroke.[30] Those compounds that had a reasonable binding affinity ([^{3}H]-glycine $IC_{50} \leq 1$ μM)[30] for the glycine site of the NMDA receptor were then screened in a high throughput blood level assay (HTBLA) to determine oral PK parameters.[33] Binding affinity, oral PK data, and structural diversity were considered to allow prioritization of compounds for assessment in the chronic constrictive injury (CCI) model of neuropathic pain.[34] Three chemical subseries that were chosen for further optimization are shown in Figure 2. Additional analogues of these *in vivo* active compounds were synthesized with the goal of achieving improved oral bioavailability. Here we describe our strategies for achieving good oral activity by optimizing the binding affinity and aqueous solubility within the three subseries.

α-Alkylheteroaryl Series. The lead in the α-alkyl heteroaryl subseries was the 4-pyridyl analogue **9a** (K_i = 115 nM, Table 1). The two positional isomers of this compound (**9b** and **9c**) did not show improvements in binding affinity, but did possess enhanced aqueous solubility. It was hypothesized that incorporation of alkyl substitution α to the pyridazinoquinolinetrione core might distort the planarity of these compounds, affording improved aqueous solubility. Substitution of this type at the α position, in general, led to a very slight decrease in binding affinity as evidenced by the comparison of **9a** with **9f** and **9b** with **9d**. This introduction of branching did result in improved aqueous solubility in the 4-pyridyl compounds as shown by the comparison of **9a** with **9f**. Because of the solubility method that was used, it is not possible to determine whether solubility was enhanced with α position substitution in the 2- or 3-pyridyl series, but solubility was not limiting in those series as it was in the 4-pyridyl series. Substitution of an ethyl group as in **9g** led to a sharp decrease in binding affinity (K_i = 1.9 μM), as did any groups larger than methyl.[35] The two enantiomers of the α-methyl-2-pyridyl-substituted PQT were tested, and interestingly there was a clear binding preference for the (*S*)-stereoisomer **9d** (K_i = 207 nM) over the (*R*)-stereoisomer **9e** (K_i = 8.2 μM). The pyrazine **9h** did not show improvements over the initial lead with respect to binding affinity but had improved aqueous solubility.

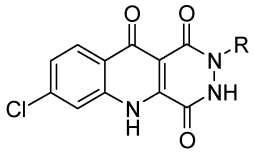
Table 1. *In Vitro* Activity of α-Pyridyl Analogues

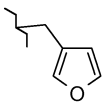
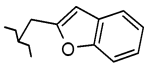
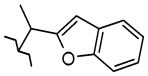
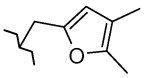
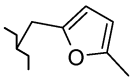
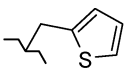
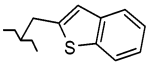
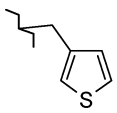
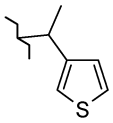
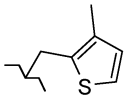
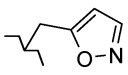
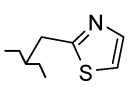


entry	R	K_i, nM[a]	aqueous solubility, mg/mL[b]	log D[c]
9a[d]		115 ± 59	0.04	<0.3
9b[d]		146 ± 34	>0.2	<0.3
9c[d]		100 ± 9	>0.14	<0.3
9d[d]		207 ± 51	>0.32	<0.5
9e[d]		8220 ± 2520	>0.32	<0.5
9f[d]		249 ± 70	>0.29	<0.3
9g[d]		1940 ± 410	>0.16	0.6
9h[d]		261 ± 130	>0.16	<0.5

[a] K_i for [^{3}H] MDL105519 binding. The average ± standard deviation of at least two experiments is reported. [b] Solubilities were measured in the presence of NaCl, see Experimental Section. [c] Recorded at pH 7.4, see Experimental Section. [d] The methanesulfonate salt was tested.

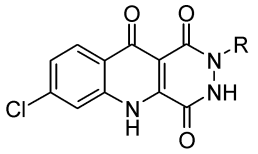
Table 2. *In Vitro* Activity of Five-membered Ring Heterocycles and Benzofused Analogues

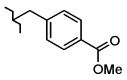
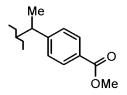
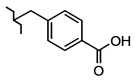
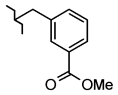
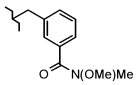
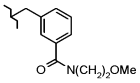
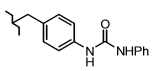
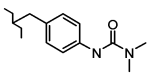
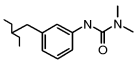
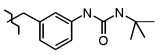


entry	R	K_i, nM[a]	aqueous solubility, mg/mL[b]	log D[c]
9i		24 ± 28	0.054	<0.5
9j		44 ± 8	0.008	2.1
9k		64 ± 3	0.001	2.0
9l		175 ± 70	0.02	1.0
9m		47 ± 10	0.14	<0.5
9n		29 ± 1	0.07	1.52
9o		65 ± 10	0.003	2.0
9p		43 ± 10	0.046	1.2
9q		135 ± 72	0.17	0.9
9r		13 ± 2	0.019	1.4
9s		39 ± 10	0.22	<0.5
9t[d]		128 ± 41	>0.16	<0.5

[a] K_i for [^{3}H] MDL105519 binding. The average ± standard deviation of at least two experiments is reported. [b] Solubilities were measured in the absence of NaCl, see Experimental Section. [c] Recorded at pH 7.4, see Experimental Section. [d] The methanesulfonate salt was tested.

Table 3. *In Vitro* Activity of Ester Subseries Analogues

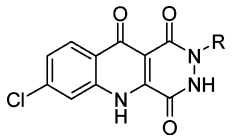


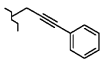
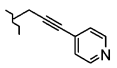
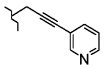
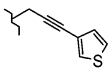
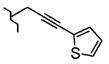
entry	R	K_i, nM[a]	aqueous solubility, mg/mL	log D[d]
9u		45 ± 40	0.0089[b]	1.17
9v		268 ± 18	0.04[c]	1.3
9w		16 ± 5	>0.2	<0.5
9x		96 ± 20	0.001[c]	1.1
9y		65 ± 4	0.54[c]	0.7
9z		126 ± 7	0.12[c]	1.2
9aa		110 ± 10	<0.012[c]	ND[f]
9ab		60 ± 1.1	0.09[c]	1.1
9ac		112 ± 41	0.1[c]	<0.5
9ad		73[e]	0.043[c]	>1.8

[a] K_i for [^{3}H] MDL105519 binding. The average ± standard deviation of at least two experiments is reported. [b] Solubilities were measured in the presence of NaCl, see Experimental Section. [c] Solubilities were measured in the absence in NaCl, see Experimental Section. [d] Recorded at pH 7.4, see Experimental Section. [e] Measured only once. [f] ND = Not determined.

In vivo data on these compounds are reported in Table 5. The initial lead **9a** was active in the CCI model of neuropathic pain at an oral dose of 3 mg/kg but was found to have a limited rat oral bioavailability of only 5%. The corresponding pyridyl isomers, **9b** and **9c**, were also tested in the CCI model. **9c** was found to be active at 15 mg/kg but **9b** was inactive when tested at 30 mg/kg. The lack of *in vivo* activity of **9b** cannot be explained by binding affinity since it is nearly equipotent with the other pyridyl isomers. Poor oral bioavailability could be the cause; however, it was not assessed (see footnote c in Table 5). Interestingly, the α-methyl analogues of **9b** (**9d** and **9e**) were both active in the CCI model, even though **9e** possessed weak binding affinity (K_i = 8.2 μM). This can be explained by the fact that they possessed oral bioavailability

Table 4. *In Vitro* Activity of Acetylenic Aromatic and Heterocyclic Analogues



entry	R	K_i, nM[a]	aqueous solubility, mg/mL	log D[d]
9ae		21 ± 7	0.0012[b]	1.78
9af		49 ± 9	0.11[c]	1.4
9ag		203 ± 35	0.54[c]	<0.5
9ah[e]		68 ± 20	0.057[c]	1.7
9ai[e]		15 ± 3	0.01[c]	2.4
9aj		6.1 ± 2	0.004[c]	1.9
9ak		8.3 ± 0.3	0.003[c]	2.4

[a] K_i for [^{3}H] MDL105519 binding. The average ± standard deviation of at least two experiments is reported. [b] Solubilities were measured in the presence of NaCl, see Experimental Section. [c] Solubilities were measured in the absence of NaCl, see Experimental Section. [d] Recorded at pH 7.4, see Experimental Section. [e] The methanesulfonate salt was tested.

of >40%, and lends support to the hypothesis that low oral bioavailability of **9b** may have led to its inactivity in the CCI model when dosed orally. Introduction of an α-methyl group led to increases in oral bioavailability as evidenced by the comparison of **9a** (5% bioavailable) with **9f** (30% bioavailable).

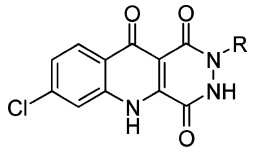
A logical extension of the work around the pyridyl lead was to prepare five-membered ring heterocycles in place of the pyridine ring. Hopefully, this would allow us to maintain and potentially improve potency. A number of five-membered ring heterocycles were prepared and tested (Table 2). In general, these compounds showed improved *in vitro* potency over the α-pyridyl series (Table 1) but with lower aqueous solubilities. Not surprisingly, the benzofused compounds **9j**, **9k**, and **9o** had higher log *D*s and were much less soluble than their monocyclic counterparts. The incorporation of an α-methyl substituent to distort planarity and potentially improve solubility was also attempted in this series. Interestingly, in the benzofuran case (**9j** versus **9k**) this did not lead to an increase in aqueous solubility and had no impact on binding affinity (**9j**, K_i = 44 nM, **9k**, K_i = 64 nM). In the 3-thiophene case (**9p** versus **9q**) introduction of the α-methyl was detrimental to the binding affinity (43 nM compared with 135 nM).

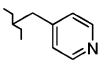
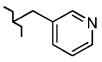
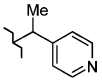
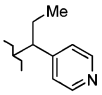
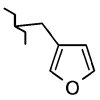
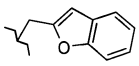
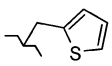
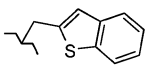
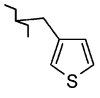
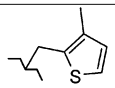
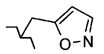
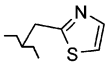
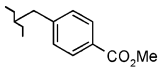
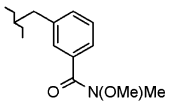
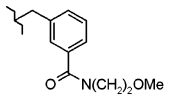
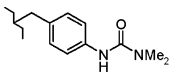
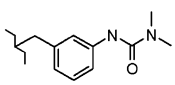
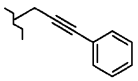
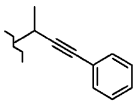
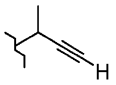
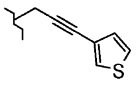
One intriguing observation in this group of compounds concerns *in vivo* activity in the CCI model, Table 5. Interestingly, all three thiophenes tested (**9n**, **9p**, and **9r**) were inactive at the doses surveyed (15 or 30 mg/kg *tid*). In contrast, two of the three furans (**9i** and **9j**) tested and the isoxazole **9s** and thiazole **9t** were active in the CCI assay when tested at 15 mg/kg *tid* (5 mg/kg for **9j**). The CCI-inactive thiophene **9r** is one of the most potent binders in this group (K_i = 13 nM), with a rat oral bioavailability of 28%, although its aqueous solubility is rather low. The less potent binder **9j** (K_i = 44 nM) has essentially the same aqueous solubility and oral bioavailability yet is active at 5 mg/kg *tid* in the CCI model. The most encouraging compound of this group, the isoxazole **9s**, possesses a K_i of 39 nM, aqueous solubility of 0.22 mg/mL, activity in the CCI model at 15 mg/kg and 40% rat oral bioavailability; this puts it on par with the best of the α-pyridyl compounds outlined in Table 1.

Ester Subseries. The methyl ester **9u** was one of the lead compounds for further optimization efforts. While it possessed fairly potent binding affinity (K_i = 45 nM, Table 3), it had very poor aqueous solubility (0.0089 mg/mL) and underwent rapid ester hydrolysis *in vivo* (data not shown). Even though the compound is active when dosed orally in the CCI model at 30 mg/kg *tid*, the rat oral biovailability is merely 7% (Table 5). This poor oral bioavailability is attributable to both the poor aqueous solubility and hydrolytic instability. The α-methyl analogue **9v** was prepared to improve solubility, as was successful in the pyridyl series. In this case, more than a 5-fold drop off in binding affinity was observed (K_i = 45 nM compared with K_i = 268 nM) with a 4-fold increase in aqueous solubility (0.0089 mg/mL compared with 0.04 mg/mL). The carboxylic acid **9w** and the tetrazole analogue (not shown) were equipotent with the parent methyl ester in the binding assay. These compounds were not tested *in vivo* because of anticipated poor brain penetration, but they provided evidence that polarity would be tolerated in the 4-position of the phenyl ring. The methyl ester at the 3-position, **9x**, was prepared for binding affinity determination to assess whether changes to the 3-position of the phenyl ring would be tolerated, as they were in the 4-position. It was found to be nearly equipotent in binding with the parent ester at the 4-position **9u**. The compounds, not surprisingly, possessed very similar physicochemical properties. This compound was not assessed *in vivo* because of the assumption that the methyl ester would be hydrolytically unstable, as it was in **9u**. A variety of analogues at the 3- and 4-positions were prepared to maintain or improve the binding affinity of this class of phenyl compounds with a corresponding improvement in physical properties, particularly aqueous solubility and hydrolytic stability. In general, the ureas and amides prepared showed a tolerance for a variety of alkyl and alkyl-ether substituents when measured in the *in vitro* binding assay, as they lost only ca. 2−5 fold in binding affinity. Carbamates (data not shown) had similar profiles. A few examples of the prepared compounds are presented in Table 3. In many cases, the solubilities are close to or above 0.1 mg/mL, a significant improvement over the methyl ester at 0.0089 mg/mL. In short, analogues of the methyl esters **9u** and **9x** were synthesized that were much more soluble than the parent ester, hydrolytically more stable, and in some cases possessed robust activity in the CCI model when tested at 15 mg/kg, such as the amide **9y** and the urea **9ab** (Table 5).

Acetylenic Subseries. In the acetylenic series, the lead phenyl-substituted compound, **9ae**, demonstrated *in vivo* activity at 30 mg/kg in the CCI model (Table 5). This initial compound possessed very good binding affinity (K_i = 21 nM, Table 4) but very poor aqueous solubility (0.0012 mg/mL). In a strategy similar to that used in the previous subseries, we attempted to improve aqueous solubility by the incorporation of an α-methyl

Table 5. *In Vivo* Data



entry	R	dose mg/kg	CCI model: % decrease hyperalgesia vs vehicle group (mean ± S.E.M.)[d]	% oral bioavailability (10 mg/kg, rat)[e]
9a		3[b]	62 ± 8	5
9b		30[a,c]	NA	ND
9c		15[a]	35 ± 11	12
9d		5[a]	46 ± 9	50
9e		30[a]	76 ± 9	48
9f		30[a]	NA	30
9g		30[a]	NA	17
9h		15[a]	39 ± 24	37
9i		15[a]	12 ± 7	ND
9j		5[a]	29 ± 9	25
9n		15[a]	NA	ND
9o		30[a]	NA	12
9p		15[a]	NA	1.2
9r		30[a]	NA	28
9s		15[a]	49 ± 15	40
9t		30[a]	26 ± 9	ND
9u		30[a]	96 ± 24	7
9y		15[a]	47 ± 18	ND
9z		15[a]	NA	ND
9ab		15[a]	80 ± 17	<1
9ac		15[a]	NA	ND
9ae		30[a]	55 ± 11	16
9af		15[a]	NA	ND
9ag		15[a]	NA	ND
9aj		15[a]	NA	ND

[a] Dosing frequency *tid*. [b] Dosing frequency *qid*. [c] Based on the HTBLA data, the AUC for **9b** was 4.3, compared to 12.1 for **9a**. Because of the poor oral exposure in this model, detailed oral bioavailabilty experiments were not done. Nonetheless, the compound was tested in the CCI model at the top dose and found to be inactive. [d] Reported data are statistically significant compared to vehicle control. Gabapentin was used every 2 months as a positive control. [e] Data shown for one experiment. NA = Not active. ND = Not determined.

group. Direct comparison of the α-methyl phenyl acetylene **9af** with **9ae** led to a solubility improvement of 2 orders of magnitude at the expense of a slight decrease in binding potency (Table 4). Surprisingly, the α-methylated **9af** was void of activity in the CCI model when tested at 15 mg/kg. The terminal acetylene compound **9ag** demonstrated that the phenyl substitu-

ent in **9ae** was important, as deletion of this phenyl moiety led to an approximately 10-fold reduction in binding affinity and a loss of oral activity. However, this modification led to an increase in aqueous solubility and reduction of lipophilicity. Acetylenic heteroaryl analogues were also prepared. Potencies and aqueous solubilities were analogous to the phenyl-substituted compounds with the 2- and 3-thiophene derivatives exhibiting single-digit nanomolar binding affinities.

Conclusion

The strategy to optimize binding potency and aqueous solubility in the pyridazinoquinolinetriones has led to NMDA glycine-site antagonists with oral activity in the CCI model of neuropathic pain. Within all subseries, compounds were found with improved aqueous solubility over the starting point without substantial loss in binding affinity. Our strategy to enhance aqueous solubility was aimed at enhancement of oral bioavailability, which would afford oral activity in the CCI model. However, metabolic stability, which would drastically affect the oral bioavailability of these compounds, was not assessed. In general, compounds with good solubility, potency and oral bioavailability proved to be active in the CCI model (e.g., **9d**, **9h**, **9s**, **9j**). However, there are some compounds that did not fit this hypothesis. For example, compound **9ab** has relatively poor oral bioavailability, but is active in the CCI model. Another example is **9e**, a compound with good oral bioavailability, but poor *in vitro* activity. Although it would be expected that this compound would not be active, it is active at the highest dose tested. A possible explanation for compounds that show these disconnects would be the generation of an active metabolite with a different potency or PK profile. For example, in the case of **9e**, racemization, even a small amount, could contribute to some CCI activity. Although interesting from a scientific perspective, we chose not to follow-up with these exceptions, but to put our efforts in profiling the best compounds that met our criteria. From the three starting points, several promising compounds were identified. Four compounds (**9d**, **9h**, **9s**, **9j**) within the α-alkylheteroaryl subseries were found to have improved oral exposures over **9a** while maintaining activity in the CCI model. Two compounds (**9y** and **9ab**) were identified from the ester subseries having CCI activity and improved aqueous solubility over the parent compound **9u**. The most efficacious compound in the ester subseries, **9ab**, was found to have poor oral bioavailability. In the acetylenic subseries, although compounds with potent binding affinities were identified, none were found to be active in the CCI model apart from the starting compound **9ae**.

Experimental Section

Chemistry. ^{1}H NMR spectra were obtained at 300 MHz using a Bruker DPX300 spectrometer and were referenced to TMS. Elemental analyses (C, H, N) were performed on an Exeter Analytical CE-440 elemental analyzer, and all compounds are within 0.4% of theory unless otherwise indicated; the data can be found in the Supporting Information. For compounds that do not have elemental analysis data, the results of HPLC-MS in two diverse chromatographic conditions can be found in the Supporting Information. Unless otherwise noted, all materials were obtained commercially and used without further purification.

Compound 7 (7-Chloro-4-oxo-2-(pyrrolidinylcarbonyl)hydroquinoline-3-carboxylic Acid). Dimethyl 7-Chloro-4-hydroxyquinoline-2,3-dicarboxylate (4). A stirred mixture of methyl 2-amino-4-chlorobenzoate (2.50 g, 13.5 mmol) and dimethyl acetylenedicarboxylate (2.05 g, 14.4 mmol) in *tert*-butanol (22 mL) was refluxed for 7 h under a N_2 atmosphere. After adding additional dimethyl acetylenedicarboxylate (1.16 g, 8.13 mmol) and refluxing another 2.5 h, the reaction mixture was allowed to cool to rt and potassium *tert*-butoxide (1.56 g, 13.9 mmol) was added in one portion. A precipitate formed and the resulting mixture was refluxed for 1.5 h. The mixture was cooled to rt and filtered to separate the solids, which were washed with *tert*-butanol and Et_2O. The solids were dissolved in water and acidified with 1 N H_2SO_4 to form a precipitate. The resulting mixture was extracted with CH_2Cl_2, and the combined extracts were washed with brine and water, dried over $MgSO_4$, filtered, and concentrated to give a green solid. Recrystallization of this material from MeOH provided **4** (1.15 g, 47%) as an off-white solid, mp 232−233 °C. Anal. ($C_{13}H_{10}ClNO_5$): C, H, N.

3-Carbomethoxy-7-chloro-4-hydroxyquinoline-2-carboxylic Acid (5). To a stirred suspension of dimethyl 7-chloro-4-hydroxyquinoline-2,3-dicarboxylate (1.0 g, 3.38 mmol) in H_2O (20 mL) was added an aqueous solution of NaOH (0.27 g, 6.75 mmol). Upon addition, the suspension dissolved. The reaction mixture was warmed to 60 °C for 1 h. After this time the reaction was cooled to rt and acidified with concentrated HCl. The product was then extracted into Et_2O and EtOAc. The organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to provide the title compound as a solid (900 mg). This material was purified by recrystallization employing an EtOAc/hexane cosolvent system to provide the title compound (571 mg, 60%) as a white solid; mp 296 °C (dec). Anal. ($C_{12}H_8NO_5Cl\cdot 0.45\ CH_3CO_2CH_2CH_3\cdot 0.10\ H_2O$): C, H, N. ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.90 (s, 3H); 7.28 (dd, J = 8.7, 1.8 Hz, 1H); 7.92 (d, J = 1.8 Hz, 1H); 8.22 (d, J = 8.7 Hz, 1H).

3-Carbomethoxy-2-pyrrolidinocarbamide-7-chloro-4-hydroxyquinoline (6). To a suspension of 3-carbomethoxy-7-chloro-4-hydroxyquinoline-2-carboxylic acid **5** (2.25 g, 8.0 mmol) in THF (20 mL) at ambient temperature under a N_2 atmosphere were added DCC (1.65 g, 8.0 mmol) and pyrrolidine (0.596 g, 8.4 mmol). The reaction was stirred at rt for 15 h after which time the byproduct urea was removed via filtration. The desired product was purified via flash column chromatography on silica gel employing 5% MeOH in $CHCl_3$ to provide the title compound (2.52 g, 94.3%) as a tan solid, mp = 215 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.80−1.96 (m, 4H); 3.27−3.33 (m, 2H); 3.40−3.49 (m, 2H); 3.69 (s, 3H); 7.47 (dd, 1H, J = 8.8, 2.0 Hz); 7.60 (d, 1H, J = 1.8 Hz); 8.12 (d, J = 8.7 Hz, 1H).

7-Chloro-4-oxo-2-(pyrrolidinylcarbonyl)hydroquinoline-3-carboxylic Acid (7). To a suspension of 3-carbomethoxy-2-pyrrolidinocarbamide-7-chloro-4-hydroxyquinoline **6** (2.52 g, 7.5 mmol) in deionized H_2O (40 mL) was added dropwise a solution (20 mL) of aqueous KOH (882 mg, 15.75 mmol). Upon complete addition, the reaction was warmed to 60 °C. After 3 h, the reaction was filtered to remove a small amount of insoluble material. The filtrate was then acidified to pH = 1 which yielded a white precipitate. The solid was isolated by vacuum filtration, washed with H_2O, and dried at 30 °C *in vacuo* for 16 h. This provided the title compound (1.5 g, 64%) as a white solid, mp 225−228 °C. ^{1}H NMR (30 MHz, DMSO-d_6): δ 1.83−1.98 (m, 4H).; 3.17−3.19 (m, 2H); 3.52−3.57 (m, 2H); 7.64 (d, 1H, J = 8.7); 7.77 (s, 1H); 8.28 (d, J = 8.8 Hz, 1H).

General Procedures. Coupling of Compound 7 to Hydrazines. Method A. To a stirred mixture of 7-chloro-4-oxo-2-(pyrrolidinylcarbonyl)hydroquinoline-3-carboxylic acid (**7**, 1 equiv) and dry THF (15 mL/mmol) under N_2 was added 1-cyclohexy1−3-(2-morpholinoethyl)carbodiimide metho-*p*-toluenesulfonate (CMC, 1.5−1.6 equiv) in portions over 10 min. After the bright yellow reaction mixture was stirred for an additional 20−60 min, a solution of the BOC-protected hydrazine (1.3 equiv) in THF (5.9 mL/mmol) was rapidly added and the mixture was stirred overnight. The reaction mixture was filtered, and the filter cake was washed with CH_2Cl_2 (or THF). The filtrate and washings were combined, washed with H_2O, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the product typically as a solid or foam. The solid was triturated with Et_2O and then filtered. The filter cake was dried at 45 °C *in vacuo* to give the desired product as a solid.

When required, the product was further purified by chromatography on silica gel using 1:1 hexanes:EtOAc or 95:5 CH_2Cl_2:MeOH as eluent.

Method B. To a stirred mixture of 7-chloro-4-oxo-2-(pyrrolidinylcarbonyl)hydroquinoline-3-carboxylic acid (**7**, 1 equiv) in THF (13 mL/mmol)) was added 1-cyclohexy1−3-(2-morpholinoethyl)-carbodiimide metho-p-toluenesulfonate (CMC, 1.2 equiv), and the reaction was stirred for 5 min. To this mixture was added dropwise a solution of the BOC-protected hydrazine (1.0−1.3 equiv) and DMAP (0.17 equiv) in THF (2.6 mL/mmol). The mixture was stirred at rt for 45 min and then refluxed for 3 to 18 h. The cooled solution was filtered, and the collected insolubles were washed with CH_2Cl_2 (2×). The combined filtrate and washes were concentrated *in vacuo* to dryness. The resultant yellow foam was subjected to chromatography on silica gel using $CHCl_3$:MeOH or CH_2Cl_2:MeOH (usually 95:5 or 90:10) as eluent to give the desired product as a solid or a foam.

Coupling of Aryl Halides to Compound 8. Method C. A solution of the appropriate aryl iodide or bromide (1.9 equiv), bis-(triphenylphosphine)palladium(II) chloride (10 mol %), copper(I) iodide (0.18−0.20 equiv), and 2,6-di-*tert*-butyl-4-methylphenol (0.20−0.25 equiv) in CH_2Cl_2 (15 mL/mmol) was treated sequentially with triethylamine (2.4 equiv) and *N*′-[7-chloro-4-oxo-2-(pyrrolidine-1-carbonyl)-1,4-dihydroquinoline-3-carbonyl]-*N*′-(1-methyl-prop-2-ynyl)-hydrazinecarboxylic acid *tert*-butyl ester (1 equiv) or *N*-[(*tert*-butoxy)carbonylamino][7-chloro-4-oxo-2-(pyrrolidinylcarbonyl)(3-hydroquinolyl)]-*N*-prop-2-ynylcarboxamide (1 equiv). The reaction was stirred at rt under N_2 overnight. The reaction mixture was concentrated to a thick brown oil and purified by flash chromotography on silica gel using a gradient of 100:0 to 90:10 CH_2Cl_2:MeOH. The desired product was generally obtained as a solid or foam.

Cyclization of Compounds 8 to Final Products 9. Method D. To a stirred mixture of compound **8** (1.0 equiv) and dry THF (20 mL/mmol) under N_2 was added methanesulfonic acid (35−40 equiv) in one portion. The mixture was stirred overnight and then filtered to separate the solids. The collected solids were successively washed with THF (2×), MeOH (2×), and Et_2O (1×). The filter cake was then suspended in MeOH and the resulting mixture sonicated for 20 min. The solids were collected by filtration and washed with MeOH (2 times) and Et_2O (1 time) and then dried at 45 °C *in vacuo* to give the desired final product **9** as a solid.

Method E. To a stirred mixture of compound **8** (1.0 equiv) and dry THF (20 mL/mmol) under N_2 was added methanesulfonic acid (35−40 equiv) in one portion. The mixture was stirred overnight, the volatiles were removed *in vacuo*, and the resultant oil was poured onto crushed ice. A fine precipitate formed which was then isolated by filtration. The material was washed with water and Et_2O, suspended in 1:1 Et_2O:MeOH, sonicated for 15 min, and then filtered. The collected solids were again suspended in 1:1 Et_2O:MeOH, sonicated for 15 min, filtered, and then washed with the same solvent system or Et_2O. The material was dried at 55 °C *in vacuo* to give the desired final product **9** as a solid.

Method F. To a stirred mixture of compound **8** (1.0 equiv) and dry THF (20 mL/mmol) under N_2 was added methanesulfonic acid (35−40 equiv) in one portion. The mixture was stirred overnight. The volatiles were removed *in vacuo*, and to the resultant oil was added Et_2O. The mixture was stirred vigorously for 10 min and then allowed to stand until two layers formed. The top layer was decanted away to leave an oil. To this oil was added water, and the mixture was stirred until a fine precipitate formed. This precipitate was filtered to give a solid. This material was washed with Et_2O, sonicated twice in 7:1 Et_2O:MeOH for 15 min, and filtered. The insoluble materials were collected, washed with the same solvent system and dried at 55 °C *in vacuo* to give the desired final product **9** as a solid.

Method G. To a stirred mixture of compound **8** (1.0 equiv) and dry THF (20 mL/mmol) under N_2 was added methanesulfonic acid (35−40 equiv) in one portion. The mixture was stirred overnight and then poured into ice−water. The resulting mixture was filtered, and the collected solids were successively rinsed with water and Et_2O or MeOH, suspended in MeOH, sonicated for 30 min, and then filtered. The collected solids were sonicated two more times and then air-dried or dried *in vacuo* at 30−45 °C to provide the desired final product **9** as a solid.

Preparation of Noncommercially Available Hydrazines. Preparation from the Corresponding Halide. Method H. To a stirred solution of *tert*-butyl carbazate (4.9−5.6 equiv) in dry DMF (1.2−1.6 mL/mmol)) under N_2 was added Et_3N (2.8−3.2 equiv) followed by the appropriate chloride or bromide (1 equiv; note: both the free bases and the hydrochloride salts were employed). The reaction mixture was stirred at rt for 1 h, heated at 75 °C for 5 h, and allowed to cool to rt. The reaction mixture was diluted with H_2O and the resulting mixture extracted with EtOAc (4×). The combined EtOAc extracts were concentrated under reduced pressure, and the residue was dissolved in Et_2O. The resulting solution was washed successively with H_2O (3×) and brine (1×). The aqueous layer was checked for product using TLC and if necessary extracted with EtOAc until it no longer contained product. The combined organic layers were washed with brine and then dried over Na_2SO_4. The Na_2SO_4 was removed by filtration, and the filtrate was concentrated under reduced pressure to give the crude BOC-protected hydrazine. This product was typically purified by flash chromatography on silica gel eluting with 1:1 hexane:EtOAc to give the desired product generally as a foam or solid. In some cases, the product was successfully purified by trituration in 1:1 hexanes:Et_2O.

Preparation of the Hydrazones from the Corresponding Aldehyde or Ketone. Method I. To a stirred solution of *tert*-butyl carbazate (1 equiv) in THF (2.4 mL/mmol) was added the appropriate aldehyde or ketone (1 equiv), followed by 3−10 drops of concentrated HCl. After 1−6 h, the reaction turned cloudy, and the solvent was removed *in vacuo*. The resultant solid was triturated with hexanes and filtered to give the hydrazone as a solid.

Preparation of the Hydrazines from the Corresponding Hydrazone. Method J. The hydrazone (1 equiv) was dissolved in MeOH (9.4 mL/mmol) and placed in a Parr shaker bottle. To this was added 10% Pd/C (100 mg/mmol) and the reaction was hydrogenated at 40 psi for 24 h. The mixture was filtered through diatomaceous earth and washed with MeOH (3×). The combined filtrate and washes were concentrated *in vacuo*. The resultant BOC-protected hydrazines were typically triturated in 90:10 hexanes:CH_2Cl_2 and isolated by filtration or were used in the subsequent reaction without further purification.

Preparation of the Hydrazines from the Hydrazinecarboxylic Acid *tert*-Butyl Ester. Method K. The required hydrazinecarboxylic acid *tert*-butyl ester (1 equiv) in MeOH (5 mL/mmol) was added $NaCNBH_3$ (5 equiv) followed by enough acetic acid to adjust to pH 3. This solution was heated to 65 °C. At 1 and 3 h, more $NaCNBH_3$ was added (ca. 180 mg/mmol each time). After a reaction time of 4 h, the reaction was then cooled to rt and diluted with H_2O, and the MeOH was removed under reduced pressure. The remaining material was diluted with EtOAc and washed with saturated aqueous $NaHCO_3$, H_2O, and brine and then dried over Na_2SO_4. The mixture was filtered and concentrated to give the title compound as an oil or a solid. When required, the material was purified by silica gel chromatography using 4:1 hexanes:EtOAc as the eluent.

Specific Examples. Compound 9a. 7-Chloro-4-hydroxy-2-(4-pyridylmethyl)-1,2,5,10-tetrahydropyridazino[4,5-*b*]quinoline-1,10-dione methanesulfonate.

(*tert*-Butoxy)-*N*-[(4-pyridylmethyl)amino]carboxamide. The title compound was prepared from *tert*-butyl carbazate (174 g, 1.36 mol) and 4-picolyl chloride hydrochloride (40.0 g, 0.243 mol) according to Method G as an off-white foam (24.46 g, 45%). ^1H NMR (300 MHz, DMSO-d_6): δ 1.36 (s, 9H); 3, 90 (d, 2H, J = 4.0 Hz); 5, 04 (d, 1H, J = 4.0 Hz); 7.34 (d, 1H, J = 4.5 Hz); 8.48 (d, 1H, J = 4.5 Hz).

***N*-[(*tert*-butoxy)carbonylamino][7-chloro-4-oxo-2-(pyrrolidinylcarbonyl)(3-hydroquinolyl)]-*N*-(4-pyridylmethyl)carboxamide**. The title compound was prepared from 7-chloro-4-oxo-2-(pyrrolidinylcarbonyl)hydroquinoline-3-carboxylic acid (**7**) (24.29 g, 75.73 mmol) and (*tert*-butoxy)-*N*-[(4-pyridylmethyl)amino]-

carboxamide (22.0 g, 98.5 mmol) according to Method A as a yellow powder (24.3 g, 61%).

7-Chloro-4-hydroxy-2-(4-pyridylmethyl)-1,2,5,10-tetrahydropyridazino[4,5-*b*]quinoline-1,10-dione Methanesulfonate 9a. The title compound was prepared from *N*-[(*tert*-butoxy)carbonylamino]-[7-chloro-4-oxo-2-(pyrrolidinylcarbonyl)(3-hydroquinolyl)]-*N*-(4-pyridylmethyl)carboxamide (24.0 g, 45.62 mmol) according to Method D. The desired product was obtained as a yellow powder (12.1 g, 59%); mp >250 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.32 (s, 3H), 5.36 (s, 2H); 7.49 (dd, 1H, J = 8.1 Hz, J = 2.1 Hz); 7.86 (d, 1H, J = 6.6 Hz); 8.06 (d, 1H, J = 2.1 Hz); 8.12 (d, 1H, J = 8.1 Hz); 8.82 (d, 1H, J = 6.6 Hz); 12.6 (br s, 1H); 12.84 (br s, 1H). Anal. ($C_{17}H_{11}ClN_4O_3 \cdot CH_3SO_3H \cdot 0.8H_2O$): C, H, N.

Compound 9b. 7-Chloro-4-hydroxy-2-(2-pyridylmethyl)-1,2,5,10-tetrahydropyridazino[4,5-*b*]quinoline-1,10-dione Methanesulfonate. (*tert*-Butoxy)-*N*-[(2-pyridylmethyl)amino]carboxamide. The title compound was prepared from *tert*-butyl carbazate (174 g, 1.53 mol) and 2-picolyl chloride hydrochloride (54.0 g, 0.33 mol) according to Method H as an off-white solid (33.4 g, 45% yield). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.38 (s, 9H); 3.96 (d, 2H, J = 4.0 Hz); 4.98 (d, 1H, J = 4.0 Hz); 7.24 (dd, 1H, J = 7.8 Hz, J = 7.8 Hz); 7.48 (d, 1H); 7.74 (dd,1H, J = 7.5 Hz, J = 7.8 Hz); 8.32 (s, br, 1H); 8.47 (d, 1H, J = 4.8 Hz).

***N*-[(*tert*-butoxy)carbonylamino][7-chloro-4-oxo-2-(pyrrolidinylcarbonyl)(3-hydroquinolyl)]-*N*-(2-pyridylmethyl)carboxamide.** The title compound was prepared from 7-chloro-4-oxo-2-(pyrrolidinylcarbonyl)hydroquinoline-3-carboxylic acid (**7**) (17.5 g, 54.7 mmol) and (*tert*-butoxy)-*N*-[(2-pyridylmethyl)amino]carboxamide (16.5 g, 73.9 mmol) according to Method A as a light tan powder (24.3 g, 61% yield).

7-Chloro-4-hydroxy-2-(2-pyridylmethyl)-1,2,5,10-tetrahydropyridazino[4,5-*b*]quinoline-1,10-dione Methanesulfonate 9b. The title compound was prepared from *N*-[(*tert*-butoxy)carbonylamino]-[7-chloro-4-oxo-2-(pyrrolidinylcarbonyl)(3-hydroquinolyl)]-*N*-(2-pyridylmethyl)carboxamide (24.0 g, 0.045 mol) according to Method D. The desired product was obtained as an orange powder (12.1 g, 59%), mp >300 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.33 (s, 3H), 5.35 (s, 2H); 7.46 (d, 1H, J = 8.7 Hz); 7.64 (d, 1H, J = 7.8 Hz); 7.68 (dd, 1H, J = 4.8 Hz, J = 6.6 Hz); 8.02 (s, 1H); 8.14 (d, 1H, J = 8.7 Hz); 8.19 (dd, 1H, J = 6.6 Hz, J = 7.8 Hz); 8.73 (d, 1H, J = 4.8 Hz); 10.06 (s, br, 1H); 12.84 (s, br, 1H). Anal. ($C_{17}H_{11}ClN_4O_3 \cdot CH_3SO_3H$): C, H; N: calcd, 12.43; found, 12.01.

Compound 9c. 7-Chloro-4-hydroxy-2-(3-pyridylmethyl)-1,2,5,-10-tetrahydropyridazino[4,5-*b*]quinoline-1,10-dione Methanesulfonate. (*tert*-Butoxy)-*N*-[3-pyridylmethyl)amino]carboxamide. The title compound was prepared from *tert*-butyl carbazate (203.6 g, 1.54 mol) and 3-picolyl chloride hydrochloride (50.0 g, 0.30 mol) according to Method H as an off-white solid (23.3 g, 34%). ^{1}H NMR (300 MHz, DMSO-d_6): d 1.36 (s, 9H); 3.88 (d, 2H, J = 4.0 Hz); 4.96 (d, 1H, J = 4.0 Hz); 7.33 (dd, 1H, J = 7.7 Hz, J = 4.8 Hz); 7.71 (d, 1H, J = 7.7 Hz); 7.44 (d, 1H, J = 4.7 Hz); 8.49 (s, 1H).

***N*-[(*tert*-butoxy)carbonylamino][7-chloro-4-oxo-2-(pyrrolidinylcarbonyl)(3-hydroquinolyl)]-*N*-(3-pyridylmethyl)carboxamide.** The title compound was prepared from 7-chloro-4-oxo-2-(pyrrolidinylcarbonyl)hydroquinoline-3-carboxylic acid (**7**) (20 g, 62.4 mmol) and (*tert*-butoxy)-*N*-[(3-pyridylmethyl)amino]carboxamide (20.9 g, 93.6 mmol) according to Method A as an off-white powder (32.8 g, 100%).

7-Chloro-4-hydroxy-2-(3-pyridylmethyl)-1,2,5,10-tetrahydropyridazino[4,5-*b*]quinoline-1,10-dione Methanesulfonate 9c. The title compound was prepared from *N*-[(*tert*-butoxy)carbonylamino]-[7-chloro-4-oxo-2-(pyrrolidinylcarbonyl)(3-hydroquinolyl)]-*N*-(3-pyridylmethyl)carboxamide (32.8 g, 62 mmol) according to Method D. The desired product was obtained as a white solid (19.4 g, 66%); mp >300 °C. ^{1}H NMR (300 MHz, DMSO-d_6): d 2.33 (s, 3H); 5.29 (s, 2H)); 7.46 (dd, 1H, J = 9.0 Hz, J = 2.1 Hz); 7.94 (dd, 1H, J = 9.0 Hz, J = 5.6 Hz); 8.04 (d, 1H, J = 1.8 Hz); 8.16 (d, 1H J = 8.7 Hz); 8.37 (d, 1H, J = 8.1 Hz); 8.82 (d, 1H J = 4.8 Hz); 8.89 (s, 1H). Anal. ($C_{17}H_{11}ClN_4O_3 \cdot CH_3SO_3H \cdot H_2O$): C, H, N.

Compound 9d. (−)-7-Chloro-4-hydroxy-2-(2-pyridylethyl)-1,2,5,10-tetrahydropyridazino[4,5-*b*]quinoline-1,10-dione Methanesulfonate. *N*-((1*Z*)-1-Aza-2-(2-pyridyl)prop-1-enyl)(*tert*-butoxy)-carboxamide. The title compound was prepared from *tert*-butyl carbazate (2.18 g, 16.5 mmol) and 2-acetylpyridine (2.00 g, 16.5 mmol) according to Method I as a white solid (3.12 g, 80%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.49 (s, 9H); 7.38 (dd, 1H, J = 4.8, 6.7 Hz); 7.94 (m, 1H); 7.99 (d, 1H, J = 7.5 Hz); 8.58 (d, 1H, J = 4.2 Hz); 10.04 (s, 1H).

(±)-(*tert*-Butoxy)-*N*-[(2-pyridylethyl)amino]carboxamide. The title compound was prepared from *N*-((1*Z*)-1-aza-2-(2-pyridyl)prop-1-enyl)(*tert*-butoxy)carboxamide (2.0 g, 8.5 mmol) according to Method J. The compound formed an oil (ca. 1.8 g) and was used in the following reaction without further purification. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.19 (d, 3H, J = 6.6 Hz); 1.33 (s, 9H); 4.11 (m, 1H); 4.79 (m, 1H); 7.22 (m, 1H); 7.49 (d, 1H, J = 7.8 Hz); 8.22 (m, 1H, J = 1.5, 2.4 Hz); 8.49 (d, 1H, J = 4.2 Hz).

(−)-(*tert*-Butoxy)-*N*-[(2-pyridylethyl)amino]carboxamide. The racemic mixture was subjected to chiral HPLC preparatory chromatography using CHIRALPAK-AD column (5 cm × 50 cm). Approximately 10 g was resolved giving 4.5 g of peak 1 (>99% ee) and 4.7 g of peak 2 (98.6% ee) using acetonitrile as solvent. Peak 1 (t_R = 5.07 min) had a (−) rotation and was identified as the title compound. The other enantiomer was obtained as peak 2 (t_R = 6.15 min) with a (+) rotation. Characterization of Peak 1: ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.19 (d, 3H, J = 6.6 Hz); 1.33 (s, 9H); 4.11 (m, 1H); 4.79 (m, 1H); 7.22 (m, 1H); 7.49 (d, 1H, J = 7.8 Hz); 8.22 (m, 1H, J = 1.5, 2.4 Hz); 8.49 (d, 1H, J = 4.2 Hz). $[\alpha]_D^{20} = -128.78$, ($c$ = 0.49).

The (*R*)-configuration was assigned to (−)-(*tert*-butoxy)-*N*-[(2-pyridylethyl)amino]carboxamide based on comparison to the chiral HPLC of a chemical synthesized sample that started from an alcohol of known configuration. The synthesis of this standard is described below and is represented in Scheme 4.

A stirred solution of (*R*)-1-pyridin-2-yl-ethanol (3.53 g, 28.7 mmol)[32] in CH_2Cl_2 was cooled to 0 °C, and to this was added methanesulfonyl chloride (3.37 mL, 4.99 g, 43.69 mmol) followed by Et_3N (6.09 mL, 4.41 g, 43.6 mmol). The reaction was stirred at 0 °C for 1.5 h and then quenched with cold $NaHCO_3$. (It should be noted that if the reaction is allowed to stir at rt for more than 2 h, displacement of the mesylate can occur from the chloride ion which results in a reduction of enantionselectivity). The organic layers were separated and washed with NaCl (sat.) and then dried over Na_2SO_4. The material was then used directly in the displacement reaction. Crude mesylate (5.78 g, 28.7 mmol) was dissolved in DMF (80 mL), and to this were added Hunigs base (7.51 mL, 5.51 g, 43.11 mmol) and *tert*-butyl carbazate (18.95 g, 143.7 mmol). The reaction was heated at 90 °C for 6 h and then poured into ethyl acetate (200 mL). The organic layers were washed with H_2O (150 mL) and NaCl (sat.). The material was concentrated and then dissolved in 1/1 ether/hexanes (30 mL). The material was then placed in a freezer overnight, and the resultant crystals were collected. The recrystallization was repeated to give pure material than matched in all respects the data for the (−) enantiomer described above as Peak 1 (1.23 g, 18%).

(−)-*N*-[(*tert*-Butoxy)carbonylamino][7-chloro-4-oxo-2-(pyrrolidinylcarbonyl)(3-hydroquinolyl]-*N*-(2-pyridylethyl)carboxamide. The title compound was prepared from 7-chloro-4-oxo-2-(pyrrolidinylcarbonyl)hydroquinoline-3-carboxylic acid (**7**) (2.82 g, 8.79 mmol) and (−)-(*tert*-butoxy)-*N*-[(2-pyridylethyl)amino]carboxamide (2.25 g, 9.49 mmol) according to Method B as a yellow foam (4.6 g, 97%). $[\alpha]_D^{20} = -30.61$, (c = 0.49, MeOH).

(−)-7-Chloro-4-hydroxy-2-(2-pyridylethyl)-1,2,5,10-tetrahydropyridazino[4,5-*b*]quinoline-1,10-dione Methanesulfonate 9d. The title compound was prepared from (−)-*N*-[(*tert*-butoxy)-carbonylamino][7-chloro-4-oxo-2-(pyrrolidinylcarbonyl)(3-hydroquinolyl]-*N*-(2-pyridylethyl)carboxamide (4.62 g, 8.55 mmol) according to Method F as an off-white powder (1.70 g, 56%); ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.77 (d, 3H, J = 6.9 Hz); 2.34 (s, 3H, CH_3SO_3H); 6.41 (q, 1H, J = 6.9 Hz); 7.44 (d, 1H, J = 8.7 Hz); 7.80 (s, 1H); 7.87 (m, 2H); 7.96 (m, 1H); 8.02 (d, 1H, J =

8.7 Hz); 8.43 (app t, 1H, $J = 7.5$ Hz); 8.86 (d, 1H, $J = 5.1$ Hz); 11.98 (s, 1H); 12.80 (s, 1H). $[\alpha]_D^{20} = -175.28$, ($c = 0.49$, MeOH). The enantiomeric excess was determined to be >95% by use of a chiral shift reagent (*N*-methylephedrine or d_{11}-(S-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol)). Anal. ($C_{18}H_{13}ClN_4O_3 \cdot CH_3SO_3H \cdot H_2O$): C, H, N.

Compound 9e. (+)-7-Chloro-4-hydroxy-2-(2-pyridylethyl)-1,2,5,10-tetrahydropyridazino[4,5-*b*]quinoline-1,10-dione Methanesulfonate. (+)-(*tert*-Butoxy)-*N*-[(2-pyridylethyl)amino]carboxamide. HPLC preparatory chromatography using CHIRALPAK-AD was described above for isolation of both the (+) and (−) enantiomers. Peak 2 was also isolated ($t_R = 6.15$ min) with a (+) rotation. Characterization of Peak 2: ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.19 (d, 3H, $J = 6.6$ Hz); 1.33 (s, 9H); 4.11 (m, 1H); 4.79 (m, 1H); 7.22 (m, 1H); 7.49 (d, 1H, $J = 7.8$ Hz); 8.22 (m, 1H, $J = 1.5$, 2.4 Hz); 8.49 (d, 1H, $J = 4.2$ Hz). $[\alpha]_D^{20} = +134.45$, ($c = 0.49$, MeOH). Similar to the (−) enantiomer, a synthetic sample was prepared from (*S*)-1-pyridin-2-yl-ethanol (3.53 g, 28.7 mmol)[32] to give a compound matching in all respects Peak 2. This was assigned the (*R*)-configuration based on the known chirality of the (*S*)-alcohol and the inversion that took place in the S_N2 displacement reaction.

(+)-*N*-[(*tert*-Butoxy)carbonylamino][7-chloro-4-oxo-2-(pyrrolidinylcarbonyl)(3-hydroquinolyl]-*N*-(2-pyridylethyl)carboxamide. The title compound was prepared from 7-chloro-4-oxo-2-(pyrrolidinylcarbonyl)hydroquinoline-3-carboxylic acid (**7**) (2.57 g, 8.03 mmol) and (+)-(*tert*-butoxy)-*N*-[(2-pyridylethyl)amino]carboxamide (2.0 g, 8.43 mmol) according to Method B as a yellow foam (4.0 g, 94%). $[\alpha]_D^{20} = +54.27$, ($c = 0.51$, MeOH).

(+)-7-Chloro-4-hydroxy-2-(2-pyridylethyl)-1,2,5,10-tetrahydropyridazino[4,5-*b*]quinoline-1,10-dione Methanesulfonate 9e. The title compound was prepared from (+)-*N*-[(*tert*-butoxy)-carbonylamino][7-chloro-4-oxo-2-(pyrrolidinylcarbonyl)(3-hydroquinolyl]-*N*-(2-pyridylethyl)carboxamide (4.0 g, 7.40 mmol) according to Method F except that 12:1 Et_2O:MeOH was used as the solvent system. The title compound was obtained as an off-white powder (1.31 g, 48%); ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.77 (d, 3H, $J = 6.9$ Hz); 2.34 (s, 3H, CH_3SO_3H); 6.41 (q, 1H, $J = 6.9$ Hz); 7.44 (d, 1H, $J = 8.7$ Hz); 7.82 (m, 2H); 7.91 (d, 1H, $J = 7.8$ Hz); 8.02 (d, 1H, $J = 8.7$ Hz); 8.39 (app t, 1H, $J = 7.5$ Hz); 8.84 (d, 1H, $J = 5.1$ Hz); 11.98 (s, 1H); 12.80 (s, 1H). $[\alpha]_D^{20} = +173.86$, ($c = 0.49$, MeOH). The enantiomeric excess was determined to be >95% by chiral shift reagent (*N*-methylephedrine or d_{11}-(S-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol)). Anal. ($C_{18}H_{13}ClN_4O_3 \cdot CH_3SO_3H \cdot 0.9H_2O$): H, N; C: calcd 47.43; found 47.84.

Compound 9f. (±)-7-Chloro-4-hydroxy-2-(4-pyridylethyl)-1,2,5,10-tetrahydropyridazino[4,5-*b*]quinoline-1,10-dione Methanesulfonate. *N*-((1*Z*)-1-aza-2-(4-pyridyl)prop-1-enyl)(*tert*-butoxy)-carboxamide. The title compound was prepared from *tert*-butyl carbazate (2.18 g, 16.5 mmol) and 4-acetylpyridine according to Method I as a white solid (3.88 g, 100%); ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.47 (s, 9H); 7.55 (dd, 2H, $J = 1.5$, 4.5 Hz); 7.97 (s, 1H); 7.99 (d, 2H, $J = 4.5$ Hz); 11.22 (s, 1H).

(±)-(*tert*-Butoxy)-*N*-[(4-pyridylethyl)amino]carboxamide. The title compound was prepared from *N*-((1*Z*)-1-aza-2-(4-pyridyl)prop-1-enyl)(*tert*-butoxy)carboxamide (2.0 g, 8.51 mmol) according to Method J as a white solid (1.34 g, 66%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.19 (d, 3H, $J = 6.6$ Hz); 1.34 (s, 9H); 4.09 (m, 1H); 4.86 (m, 1H); 7.35 (d, 2H, $J = 5.7$ Hz); 8.21 (s, 1H); 8.47 (d, 2H, $J = 5.7$ Hz).

(±)-*N*-[(*tert*-Butoxy)carbonylamino][7-chloro-4-oxo-2-(pyrrolidinylcarbonyl)(3-hydroquinolyl]-*N*-(4-pyridylethyl)carboxamide. The title compound was prepared from 7-chloro-4-oxo-2-(pyrrolidinylcarbonyl)hydroquinoline-3-carboxylic acid (**7**) (1.66 g, 5.17 mmol) and (±)-(*tert*-butoxy)-*N*-[(4-pyridylethyl)amino]carboxamide (1.3 g, 5.69 mmol) according to Method B. After stirring the reaction mixture at rt for 2 h, an additional portion of CMC (0.500 g) was added and the mixture was refluxed overnight. The solution was cooled to 50 °C, another portion of CMC was added (0.50 g), and the mixture was refluxed for 3 h. The cooled reaction mixture was filtered and material worked up and purified as usual to afford the title compound as a yellow foam (2.04 g, 73%).

(±)-7-Chloro-4-hydroxy-2-(4-pyridylethyl)-1,2,5,10-tetrahydropyridazino[4,5-*b*]quinoline-1,10-dione Methanesulfonate 9f. The title compound was prepared from (±)-*N*-[(*tert*-butoxy)-carbonylamino][7-chloro-4-oxo-2-(pyrrolidinylcarbonyl)(3-hydroquinolyl]-*N*-(4-pyridylethyl)carboxamide (2.04 g, 3.8 mmol) according to Method E as an off-white powder (0.715 g, 40%); mp 245−248 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.74 (d, 3H, $J = 6.9$ Hz); 2.31 (s, 3H, CH_3SO_3H); 6.24 (q, 1H, $J = 6.9$ Hz); 7.45 (dd, 1H, $J = 1.8$, 8.7 Hz); 7.86 (m, 2H); 8.05 (d, 1H, $J = 1.8$ Hz); 8.14 (d, 1H, $J = 8.7$ Hz); 8.82 (m, 2H); 12.03 (s, 1H); 12.71 (s, 1H). Anal. ($C_{18}H_{13}ClN_4O_3 \cdot CH_3SO_3H \cdot 0.8\ H_2O$): C, H, N.

Compound 9g. (±)-7-Chloro-4-hydroxy-2-(4-pyridylpropyl)-1,2,5,10-tetrahydropyridazino[4,5-*b*]quinoline-1,10-dione Sodium Methanesulfonate. (±)-(*tert*-Butoxy)-*N*-[(4-pyridylpropyl)-amino]carboxamide. To a stirred solution of *N*-1-aza-2-(4-pyridyl)vinyl)(*tert*-butoxy)carboxamide (2.0 g, 9.40 mmol) in THF at 0 °C was slowly added EtMgBr (18.0 mL, 18.8 mmol, 2 M solution in THF). This solution was stirred 4 h during which time it was warmed to rt. The volatiles were removed, and the reaction was carefully quenched with saturated NH_4Cl solution (30 mL). The aqueous layer was extracted with EtOAc (300 mL), and then the organic layers washed with brine. The organic layer was then dried over $MgSO_4$ and the solution concentrated *in vacuo*. The material was chromatographed (SiO_2, EtOAc as eluent) to give the title compound as a yellow oil (400 mg, 18%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.73 (t, 3H, $J = 7.5$ Hz); 1.44 (m, 2H); 3.92 (br s, 1H); 4.78 (m, 1H); 7.31 (m, 2H); 8.48 (m, 2H).

(±)-*N*-[(*tert*-Butoxy)carbonylamino][7-chloro-4-oxo-2-(pyrrolidinylcarbonyl)(3-hydroquinolyl]-*N*-(4-pyridylpropyl)carboxamide. The title compound was prepared from 7-chloro-4-oxo-2-(pyrrolidinylcarbonyl)hydroquinoline-3-carboxylic acid (**7**) (1.22 g, 3.82 mmol) and (±)-(*tert*-butoxy)-*N*-[(4-pyridylpropyl)amino]carboxamide (0.96 g, 3.82 mmol) according to Method B. An additional portion of CMC (0.300 g) was added after 1 h, and the mixture was refluxed overnight. The usual workup and purification provided the desired material as a yellow foam (1.72 g, 81%).

(±)-7-Chloro-4-hydroxy-2-(4-pyridylpropyl)-1,2,5,10-tetrahydropyridazino[4,5-*b*]quinoline-1,10-dione Sodium Methanesulfonate 9g. To a stirred solution of (±)-*N*-[(*tert*-butoxy)-carbonylamino][7-chloro-4-oxo-2-(pyrrolidinylcarbonyl)(3-hydroquinolyl]-*N*-(4-pyridylpropyl)carboxamide (1.72 g, 1.5 mmol) in THF (60 mL) was added methanesulfonic acid (9 mL), and the reaction was stirred overnight. The volatiles were removed *in vacuo*, and the resultant oil was poured onto crushed ice. To this mixture was carefully added 10 N NaOH until a solid precipitate formed. The solution was filtered to give an orange solid. This material was washed with Et_2O and then sonicated in 40 mL of 3:1 Et_2O:MeOH for 15 min. The material was washed with Et_2O to give the title compound (0.557 g, 28%) as an off-white powder; mp >265 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.88 (t, 3H, $J = 7.2$ Hz); 2.16 (m, 2H); 2.31 (s, 3H, CH_3SO_3H); 5.98 (dd, 1H, $J = 5.7$, 9.46 Hz); 7.44 (m, 3H); 8.05 (d, 1H, $J = 1.5$ Hz); 8.15 (d, 1H, $J = 8.7$ Hz); 8.58 (m, 2H); 12.04 (s, 1H); 12.69 (s, 1H). Anal. ($C_{18}H_{13}ClN_4O_3 \cdot 2CH_3SO_3Na \cdot H_2O$): C, H, N.

Compound 9h. 7-Chloro-4-hydroxy-2-(pyrazin-2-ylmethyl)-1,2,5,10-tetrahydropyridazino[4,5-*b*]quinoline-1,10-dione Methanesulfonate. 2-Chloromethylpyrazine. A solution of 2-methylpyrazine (1.0 mL, 22 mmol) in CCl_4 (80 mL) was treated with *N*-chlorosuccinimide (4.27 g, 31.5 mmol) and benzoyl peroxide (0.26 g, 1.1 mmol). The mixture was heated to reflux for 7 h and then cooled to rt. The solids were filtered through diatomaceous earth and washed with CH_2Cl_2. The filtrate was washed with aqueous sodium thiosulfate (sat., 1×), aqueous $NaHCO_3$ (sat., 1×), water (1×), and aqueous NaCl (sat., 1×). The organic layer was dried over Na_2SO_4, filtered, concentrated under reduced pressure, and used directly in the following reaction. (Contains 5−10% of the α,α-dichlorinated material). ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.88 (s, 2H), 8.65−8.68 (m, 2H); 8.85 (s, 1H).

(*tert*-Butoxy)-*N*-[(pyrazin-2-ylmethyl)amino]carboxamide. The title compound was prepared from 2-chloromethylpyrazine (1.2 g, 93 mmol) and *tert*-butyl carbazate (6.3 g, 48 mmol) according to Method E except that the extraction was carried out with Et_2O (5×) and the flash chromatography employed a 2−5% gradient of MeOH in CH_2Cl_2 as the eluent to give the title compound as a waxy brown solid (1.64 g, 79%). ^{1}H NMR (300 MHz, DMSO-d_6, TFA shake): δ 1.44 (s, 9H); 4.53 (s, 2H); 8.71−8.78 (m, 2H); 8.81 (s, 1H).

***N*-[(*tert*-Butoxy)carbonylamino][7-chloro-4-oxo-2-(pyrrolidinylcarbonyl)(3-hydroquinolyl)]-*N*-(pyrazin-2-ylmethyl)carboxamide.** The title compound was prepared from 7-chloro-4-oxo-2-(pyrrolidinylcarbonyl)hydroquinoline-3-carboxylic acid (**7**) (2.3 g, 7.2 mmol) and (*tert*-butoxy)-*N*-[(pyrazin-2-ylmethyl)amino]carboxamide (1.6 g, 7.1 mmol) according to Method B to afford the crude product as a brown foam (4.9 g) which was subjected to flash chromatography (silica gel, 2% MeOH in CH_2Cl_2) to give the pure compound (3.1 g, 82%).

7-Chloro-4-hydroxy-2-(pyrazin-2-ylmethyl)-1,2,5,10-tetrahydropyridazino[4,5-*b*]quinoline-1,10-dione Methanesulfonate 9h. The title compound was prepared from *N*-[(*tert*-butoxy)carbonylamino][7-chloro-4-oxo-2-(pyrrolidinylcarbonyl)(3-hydroquinolyl)]-*N*-(pyrazin-2-ylmethyl)carboxamide (3.1 g, 5.9 mmol) according to Method D as a white powder (2.0 g, 80%); mp 235−245 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.38 (CH_3SO_3H, s, 3H), 5.27 (s, 2H); 7.44 (dd, 1H, J = 1.8, 8.7 Hz); 8.04 (d, 1H, J = 1.8 Hz); 8.14 (d, 1H, J = 8.7 Hz); 8.58 (dd, 2H, J = 2.4, 7.5 Hz); 8.63 (s, 1 H). Anal. ($C_{16}H_{10}ClN_5O_3 \cdot CH_3SO_3H \cdot H_2O$): C, H, N.

Compound 9i. 7-Chloro-4-hydroxy-2-(furan-3-ylmethyl)-1,2,5,10-tetrahydropyridazino[4,5-*b*]quinoline-1,10-dione. *N*-1-Aza-2-(3-furyl)vinyl)(*tert*-butoxy)carboxamide. The title compound was prepared as a peach-colored solid from furan-3-carboxaldehyde (2.0 g, 21 mmol) as described in Method I (4.2 g, 97%); ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.77 (br s, 1H); 8.02 (s, 1H); 7.94 (s, 1H); 7.71 (dd, J = 1.5, 1.5 Hz, 1H); 6.77 (d, J = 1.5 Hz, 1H); 1.45 (s, 9H).

***(tert*-Butoxy)-*N*-[(3-furylmethyl)amino]carboxamide.** The title compound was prepared from *N*-1-aza-2-(3-furyl)vinyl)(*tert*-butoxy)carboxamide (2.0 g, 9.5 mmol) as a clear oil according to Method K (930 mg, 46%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.39 (s, 9H); 3.69 (s, 2H); 4.64 (br s, 1H); 6.42 (d, J = 1.2 Hz, 1H); 7.53 (s, 1H); 7.58 (dd, J = 1.5, 1.5 Hz, 1H); 8.26 (br s, 1H).

(*tert*-Butoxy)-*N*-{[7-chloro-4-oxo-2-(pyrrolidinylcarbonyl)(3-hydroquinolyl)]-*N*-3-(furylmethyl)carbonylamino}-carboxamide. The title compound was prepared from 7-chloro-4-oxo-2-(pyrrolidinylcarbonyl)hydroquinoline-3-carboxylic acid **7** (1.4 g, 4.4 mmol) and (*tert*-butoxy)-*N*-[(3-furylmethyl)amino]carboxamide (930 mg, 4.4 mmol) as described in Method B as a pale yellow solid (2.1 g, 4.1 mmol, 93%). This material was used in the subsequent reaction without further characterization.

7-Chloro-4-hydroxy-2-(furan-3-ylmethyl)-1,2,5,10-tetrahydropyridazino[4,5-*b*]quinoline-1,10-dione 9i. The title compound was prepared from (*tert*-butoxy)-*N*-{[7-chloro-4-oxo-2-(pyrrolidinylcarbonyl)(3-hydroquinolyl)]-*N*-3-(furylmethyl)carbonylamino}-carboxamide (1.4 g, 2.8 mmol) according to Method G except that the collected solid was sonicated for 15 min in 50 mL of a 10% MeOH in Et_2O solution. The resultant yellow solid was collected, rinsed with Et_2O, and dried at 30 °C and 50 mTorr for 3 h to afford the title compound as a pale yellow solid (750 mg, 75%); ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.92 (s, 2H); 6.46 (s, 1H); 7.43 (dd, J = 1.8, 8.7 Hz, 1H); 7.61 (d, J = 1.5 Hz, 1H); 7.65 (s, 1H); 8.02 (d, J = 1.5 Hz, 1H); 8.13 (d, J = 8.7 Hz, 1H); 11.91 (s, 1H); 12.63 (br s, 1H). Anal. ($C_{16}H_{10}N_3O_4Cl \cdot 0.1H_2O$): C, H, N.

Compound 9j. 7-Chloro-4-hydroxy-2-benzo[*d*]furan-2-ylmethyl-1,2,5,10-tetrahydropyridazino[4, 5-*b*]quinoline-1,10-dione. *N*-(1-aza-2-benzo[*d*]furan-2-ylvinyl)(*tert*-butoxy)carboxamide. The title compound was prepared as a white solid from benzofuran-2-carboxaldehyde (5.0 g, 34 mmol) according to Method I (9 g, 100%); ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.48 (s, 9H); 7.21 (s, 1H); 7.27 (dd, J = 7.6, 7.6 Hz, 1H); 7.37 (dd, J = 7.6, 7.6 Hz, 1H); 7.62 (d, J = 8.5 Hz, 1H); 7.67 (d, J = 7.6 Hz, 1H); 8.02 (s, 1H); 11.12 (br s, 1H).

***N*-[(Benzo[*d*]furan-2-ylmethyl)amino](*tert*-butoxy)carboxamide.** The title compound was prepared from *N*-(1-aza-2-benzo[*d*]-furan-2-ylvinyl)(*tert*-butoxy)carboxamide (4.0 g, 15 mmol) as a white solid according to Method K (3.4 g, 85%); ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.37 (s, 9H); 4.00 (s, 2H); 5.01 (br s, 1H); 6.74 (s, 1H); 7.22 (m, 2H); 7.51 (d, J = 7.7 Hz, 1H); 7.57 (d, J = 7.0 Hz, 1H); 8.36 (s, 1H).

***N*-{*N*-(Benzo[*d*]furan-2-ylmethyl)[7-chloro-4-oxo-2-(pyrrolidinylcarbonyl)(3-hydroquinolyl)]carbonylamino}(*tert*-butoxy)carboxamide.** The title compound was prepared from 7-chloro-4-oxo-2-(pyrrolidinylcarbonyl)hydroquinoline-3-carboxylic acid **7** (4.1 g, 13 mmol) and *N*-[(benzo[*d*]furan-2-ylmethyl)amino](*tert*-butoxy)-carboxamide (3.3 g, 13 mmol) as described in Method B. The desired product was obtained as a pale yellow solid and was used in the following step without characterization.

7-Chloro-4-hydroxy-2-benzo[*d*]furan-2-ylmethyl-1,2,5,10-tetrahydropyridazino[4,5-*b*]quinoline-1,10-dione 9j. The title compound was prepared from *N*-{*N*-(benzo[d]furan-2-ylmethyl)[7-chloro-4-oxo-2-(pyrrolidinyl-carbonyl)(3-hydroquinolyl)]-carbonylamino}(*tert*-butoxy)carboxamide (6.2 g, 11 mmol) according to Method G as an off-white solid (3.4 g, 78%); ^{1}H NMR (300 MHz, DMSO-d_6): δ 5.27 (s, 2H); 6.84 (s, 1H); 7.25 (m, 2H); 7.44 (dd, J = 2.0, 8.9 Hz, 1H); 7.53 (d, J = 8.1 Hz, 1H); 7.59 (d, J = 7.7 Hz, 1H); 8.04 (d, J = 1.6 Hz, 1H); 8.15 (d, J = 8.8 Hz, 1H); 11.96 (br s, 1H); 12.74 (br s, 1H). Anal. ($C_{20}H_{12}N_3O_4Cl$-0.1H_2O-0.3CH_3SO_3H): C, H, N.

Compound 9k. (±)-7-Chloro-4-hydroxy-2-(1-(benzo[*b*]furan-2-yl)ethyl)-1,2,5,10-tetrahydropyridazino[4,5-*b*]quinoline-1,10-dione. *N*′-(1-Benzofuran-2-yl-ethylidene)-hydrazinecarboxylic Acid *tert*-Butyl Ester. The title compound was prepared from benzofuran-2-yl methyl ketone (5.0 g, 31 mmol) as a white solid according to Method I (8.2 g, 30 mmol, 96%); ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.50 (s, 9H); 2.17 (s, 3H); 7.26 (m, 1H); 7.26 (s, 1H); 7.35 (dd, J = 7.2, 7.2 Hz, 1H); 7.60 (d, J = 8.1 Hz, 1H); 7.65 (d, J = 7.8 Hz, 1H); 10.03 (s, 1H).

***N*′-(1-Benzofuran-2-yl-ethyl)-hydrazinecarboxylic Acid *tert*-Butyl Ester.** The title compound was prepared from *N*′-(1-benzofuran-2-yl-ethylidene)-hydrazinecarboxylic acid *tert*-butyl ester (3.0 g, 11 mmol) as a white solid according to Method K (3.1 g, 100%). This material was used without further purification.

***N*′-(1-Benzofuran-3-yl-ethyl)-*N*′-[7-chloro-4-oxo-2-(pyrrolidine-1-carbonyl)-1,4-dihydroquinoline-3-carbonyl]-hydrazinecarboxylic Acid *tert*-Butyl Ester.** The title compound was prepared from 7-chloro-4-oxo-2-(pyrrolidinylcarbonyl)hydroquinoline-3-carboxylic acid **7** (1.77 g, 5.51 mmol) and *N*′-(1-benzofuran-2-yl-ethyl)-hydrazinecarboxylic acid *tert*-butyl ester (1.5 g, 5.51 mmol) according to Method B as a pale yellow solid. The material was used in the following reaction without further purification.

7-Chloro-4-hydroxy-2-(1-(benzo[*b*]furan-2-yl)ethyl)-1,2,5,10-tetrahydropyridazino[4,5-*b*]quinoline-1,10-dione 9k. To a 0 °C solution of *N*′-(1-benzofuran-3-yl-ethyl)-*N*′-[7-chloro-4-oxo-2-(pyrrolidine-1-carbonyl)-1,4-dihydroquinoline-3-carbonyl]-hydrazinecarboxylic acid *tert*-butyl ester (1.0 g, 1.74 mmol) in MeOH (20 mL) was added dropwise a rt solution of methanesulfonic acid (3.4 mL, 52.3 mmol) in MeOH (10 mL). This mixture was allowed to warm to rt and stirred for 24 h, at which time H_2O (ca. 100 mL) was added and the precipitate collected. This solid was sonicated (50 mL of 10% MeOH/Et_2O) for 20 min and the solid collected. This sonication step was repeated, and ultimately a tan solid was collected. This material was dried at 30 °C at 500 mTorr for 1.5 h to afford the title compound (260 mg, 36%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.71 (d, J = 6.9 Hz, 3H).; 6.41 (q, J = 7.2 Hz, 1H); 6.88 (s, 1H); 7.25 (m, 2H); 7.44 (d, J = 7.2 Hz, 1H); 7.50 (d, J = 7.5 Hz, 1H); 7.60 (dd, J = 1.5, 5.7 Hz, 1H); 8.02 (d, J = 1.8 Hz, 1H); 8.16 (d, J = 8.7 Hz, 1H); 11.93 (s, 1H); 12.56 (s, 1H). Anal. ($C_{21}H_{14}ClN_3O_4 \cdot 0.2\ H_2O$): C, H, N.

Compound 9l. 7-Chloro-2-(4,5-dimethyl-furan-2-ylmethyl)-2,3-dihydro-5*H*-pyridazino[4,5-*b*]quinoline-1,4,10-trione. The title compound was prepared as a yellow solid using 4,5-dimethyl-2-furaldehyde as the starting material and methods I, K, A, and D, except that the cyclization was performed at 0 °C. ^{1}H NMR (300

MHz, DMSO-d_6): δ 1.85 (s, 3H); 2.12 (s, 3H); 4.97 (s, 2H); 6.12 (s, 1H); 7.42 (dd, J = 8.4, 1.5 Hz, 1H); 8.02 (d, J = 1.8 Hz, 1H); 8.14 (d, J = 8.7 Hz, 1H); 11.87 (s, 1H); 12.60 (s, 1H). Anal. ($C_{18}H_{14}ClN_3O_4 \cdot 1.5\ H_2O$): C, H, N.

Compound 9m. 7-Chloro-4-hydroxy-2-[(5-methyl(furan-2-yl))methyl]-1,2,5,10-tetrahydropyridazin o[4,5-*b*]quinoline-1,10-dione. The title compound was prepared as an off-white solid via Methods I, K, B, and G using 5-methylfurfural as the starting material. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.21 (s, 3H); 5.02 (s, 2H); 6.01 (d, J = 2.1 Hz, 1H); 6.22 (d, J = 3.0 Hz, 1H); 7.43 (d, J = 8.7 Hz, 1H); 8.02 (d, J = 1.5 Hz, 1H); 8.43 (d, J = 8.7 Hz, 1H); 11.92 (s, 1H); 12.69 (br s, 1H). Anal. ($C_{17}H_{12}O_4N_3Cl \cdot 1.1\ H_2O$): C, H, N.

Compound 9n. 7-Chloro-4-hydroxy-2-(thien-2-ylmethyl)-1,2,5,10-tetrahydropyridazino[4,5-*b*]quinoline-1,10-dione. The title compound was prepared as a pale yellow solid via Methods I, K, B. and G using thiophene-2-carboxaldehyde as the starting material; this afforded 1.1 g (93%) of a solid starting from 1.0 g of **7**. ^{1}H NMR (300 MHz, DMSO-d_6): δ 5.23 (s, 2H); 6.98 (dd, J = 3.6, 5.1 Hz, 1 H); 7.10 (d, J = 3.0 Hz, 1 H); 7.42−7.45 (m, 2H); 8.02 (s, 1H); 8.14 (d, J = 8.7 Hz, 1H); 11.91 (s, 1H); 12.71 (br s, 1H).

Compound 9o. 7-Chloro-4-hydroxy-2-(benzo[*b*]thien-2-ylmethyl)-1,2,5,10-tetrahydropyridazino[4,5-*b*]quinoline-1,10-dione. Benzo[*b*]thiophene-2-carbaldehyde. To a solution of benzo[*b*]thiophene (10 g, 74.5 mmol) in dry THF (12 mL) at −78 °C was added 65 mL of 1.6 M *n*BuLi in hexanes. Ten minutes later DMF (23 mL, 298 mmol) was added. The reaction was warmed to rt and then refluxed for 3 h. The THF was evaporated, and the residue was poured into 1 N HCl and ice. The acidic solution was extracted with Et_2O (2×). The combined Et_2O extract was washed with 1 N HCl (3x), saturated $NaHCO_3$ (1×), brine (1×), and then dried over $MgSO_4$. The $MgSO_4$ was filtered off and the filtrate concentrated to an oil which was treated with $NaHSO_3$. The solid that formed was collected, treated with aqueous $NaHCO_3$, and then extracted with CH_2Cl_2. The CH_2Cl_2 solution was dried over $MgSO_4$ and evaporated to give the title compound as a yellow oil (3.2 g, 26%); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44 (dd, 1H, J = 6.9, 7.2 Hz); 7.51 (dd, 1H, J = 6.9, 8.1 Hz); 7.91 (d, 1H, J = 8.1 Hz); 7.95 (d, 1H, J = 7.8 Hz); 8.04 (s, 1H); 10.12 (s, 1H).

(*tert*-Butoxy)-*N*-(1-aza-2-benzo[*b*]thien-2-ylvinyl)carboxamide. The title compound was prepared from benzo[*b*]thiophene-2-carbaldehyde (3.2 g, 19.7 mmol) according to Method I (3.8 g, 70%); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.54 (s, 9H); 7.30−7.36 (m, 2H); 7.40 (s, 1H); 7.71−7.74 (m, 1H); 7.78−7.81 (m, 1H); 7.89 (s, 1H); 8.31 (br s,1H).

(*tert*-Butoxy)-*N*-[(benzo[*b*]thien-2-ylmethyl)amino]carboxamide. The title compound was prepared from (*tert*-butoxy)-*N*-(1-aza-2-benzo[*b*]thien-2-ylvinyl)carboxamide (1.8 g, 6.5 mmol) using Method K with the exception that *p*-toluene sulfonic acid (1.5 equiv) was used in place of acetic acid with THF as the solvent. This afforded the title compound as a white solid (1.7 g, 76%); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.44 (s, 9H); 4.68 (s, 2H); 7.36−7.45 (m, 2H); 7.45 (s, 1H); 7.78−7.86 (m, 2H).

***N*′-Benzo[*b*]thien-2-ylmethyl-*N*′-[7-chloro-4-oxo-2-(pyrrolidine-1-carbonyl)-1,4-dihydroquinoline-3-carbonyl]hydrazinecarboxylic Acid *tert*-Butyl Ester.** The title compound was prepared from 7-chloro-4-oxo-2-(pyrrolidinylcarbonyl)hydroquinoline-3-carboxylic acid **7** (1.59 g, 5.0 mmol) and (*tert*-butoxy)-*N*-[(benzo[*b*]thien-2-ylmethyl)amino]carboxamide (1.37 g, 5.0 mmol) as a yellow solid according to Method B (771 mg, 24% yield).

7-Chloro-4-hydroxy-2-(benzo[*b*]thien-2-ylmethyl)-1,2,5,10-tetrahydropyridazino[4,5-*b*]quinoline-1,10-dione 9o. The title compound was prepared from *N*′-benzo[*b*]thien-2-ylmethyl-*N*′-[7-chloro-4-oxo-2-(pyrrolidine-1-carbonyl)-1,4-dihydroquinoline-3-carbonyl]hydrazinecarboxylic acid *tert*-butyl ester (760 mg, 1.3 mmol) according to Method E except that the resulting precipitate was sonicated in MeOH and dried *in vacuo* to give the desired product as an off-white solid (470 mg, 88%); mp >300 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 5.38 (s, 2H); 7.30−7.38 (m, 2H,); 7.40 (s, 1H); 7.44 (d, 1H, J = 8.7 Hz); 7.90 (d, 1H, J = 7.2 Hz); 7.82 (d, 1H, 7.2 Hz); 8.06 (s, 1H); 8.15 (d, 1H, J = 8.7 Hz). Anal. ($C_{20}H_{12}ClN_3O_3S$): C, H, N.

Compound 9p. 7-Chloro-4-hydroxy-2-(thien-3-ylmethyl)-1,2,5,10-tetrahydropyridazino[4,5-*b*]quinoline-1,10-dione. The title compound was prepared as a pale yellow solid via Methods I, K, B, and G using thiophene-3-carboxaldehyde as the starting material (870 mg, 81%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 5.08 (s, 2 H); 7.08 (d, J = 4.5 Hz, 1 H); 7.37 (s, 1 H); 7.43 (dd, J = 1.2, 8.7, 1 H); 7.48−7.54 (m, 1 H); 8.02 (d, J = 1.5 Hz, 1 H); 8.14 (d, J = 8.7, 1 H); 11.92 (br s, 1 H); 12.64 (br s, 1 H).

Compound 9q. 7-Chloro-4-hydroxy-2-(1-(thien-3-yl)ethyl)-1,2,5,10-tetrahydropyridazino[4,5-*b*]quinoline-1,10-dione. The title compound was prepared as a pale yellow solid via Methods I, K, B, and G using 2-acetylthiophene as the starting material (224 mg, 65%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.65 (s, 3 H); 6.26 (q, J = 6.9 Hz, 1 H); 7.02 (d, J = 5.1 Hz, 1 H); 7.34 (s, 1H); 7.44 (d, J = 8.7 Hz, 1 H); 7.46−7.49 (m, 1 H); 8.02 (d, J = 1.2 Hz, 1 H); 8.15 (d, J = 8.7 Hz, 1 H); 11.90 (br s, 1 H); 12.25 (br s, 1H).

Compound 9r. 7-Chloro-4-hydroxy-2-[2-(3-methyl)thienylmethyl]-1,2,5,10-tetrahydropyridazino[4,5-*b*]quinoline-1,10-dione. (*tert*-Butoxy)-*N*-[1-aza-2-(3-methyl(2-thienyl)vinyl]carboxamide. The title compound was prepared starting with 3-methylthiophene-2-carboxaldehyde (5.03 g, 39.86 mmol) as starting material via Method I. This afforded the desired compound as an off-white powder (6.92 g, 80%); ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.45 (s, 9H); 2.24 (s, 3H); 6.91 (d, 1H, J = 5.1 Hz); 7.46 (d, 1H, J = 5.1 Hz); 8.25 (s, 1H); 10.70 (s, 1H).

(*tert*-Butoxy)-*N*-{[(3-methyl(2-thienyl))methyl]amino}-carboxamide. The title compound was prepared from (*tert*-butoxy)-*N*-[1-aza-2-(3-methyl(2-thienyl)vinyl]carboxamide (2.60 g, 10.82 mmol) via Method K with the exception that *p*-toluenesulfonic acid (1.5 equiv) was used in place of acetic acid with THF as the solvent. After purification by flash chromatography on silica gel eluting with 3:1 hexane:EtOAc, the desired compound was obtained as a colorless oil (2.44 g, 92%); ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.39 (s, 9H); 2.14 (s, 3H); 3.95 (d, 2H, J = 4.5 Hz); 4.69 (d, 1H, J = 3.9 Hz); 6.82 (d, 1H, J = 5.1 Hz); 7.29 (d, 1H, J = 5.1 Hz); 8.26 (s, 1H).

(*tert*-Butoxy)-*N*-{[7-chloro-4-hydroxy-2-(pyrrolidinylcarbonyl)-(3-quinolyl)]-*N*-[(3-methyl(2-thienyl))methyl]carbonylamino}-carboxamide. The title compound was prepared from 7-chloro-4-oxo-2-(pyrrolidinylcarbonyl)hydroquinoline-3-carboxylic acid **7** (3.56 g, 11.10 mmol) and (*tert*-butoxy)-*N*-{[(3-methyl(2-thienyl))-methyl]amino}carboxamide (2.44 g, 10.07 mmol) according to Method A except that the reaction was refluxed overnight and THF was used for the washings during filtration, and no aqueous workup was performed. The resultant yellow solid (6.72 g) was purified by flash chromatography on silica gel eluting with 95:5 CH_2Cl_2: MeOH to give the desired compound as a yellow powder (3.22 g, 59%).

7-Chloro-10-hydroxy-2-[(3-methyl(2-thienyl))methyl]-2,3-dihydropyridazino[4,5-*b*]quinoline-1,4-dione 9r. The title compound was prepared from (*tert*-butoxy)-*N*-{[7-chloro-4-hydroxy-2-(pyrrolidinylcarbonyl)(3-quinolyl)]-*N*-[(3-methyl(2-thienyl))methyl]carbonylamino}carboxamide (3.68 g, 6.77 mmol) according to Method E except that the collected solids were successively washed with water (30 mL), MeOH (20 mL), and Et_2O (150 mL) and then dried at 50 °C *in vacuo* to give the desired compound as an off-white powder (1.98 g, 78%); mp >250 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.32 (s, 3H), 5.17 (s, 2H); 6.84 (d, 1H, J = 5.1 Hz); 7.32 (d, 1H, J = 5.1 Hz); 7.43 (d, 1H, J = 8.7 Hz); 8.02 (s, 1H); 8.14 (d, 1H, J = 8.7 Hz); 11.92 (br s, 1H); 12.62 (br s, 1H). Anal. ($C_{17}H_{12}ClN_3O_3S \cdot 0.05\ CH_3SO_3H \cdot 0.05\ H_2O$): H, N; C: calcd 54.62; found, 53.96.

Compound 9s. 7-Chloro-4-hydroxy-2-(5-isoxazolino)methyl-1,2,5,10-tetrahydropyridazino[4,5-*b*]quinoline-1,10-dione. *N*′-Isoxazol-5-ylmethyl-hydrazinecarboxylic Acid *tert*-Butyl Ester. The title compound was prepared from 5-bromomethyl-isoxazole (1.62 g, 10 mmol) according to Method H except that Na_2CO_3 was used as the base, and the residual DMF and excess *tert*-butyl carbazate were removed by vacuum distillation (50 mTorr, 80 °C).

Silica gel chromatography (hexanes:EtOAc, 1:1 as eluent) afforded the desired compound as a white solid (1.01 g, 49%); ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.38 (s, 9H); 4.01 (s, 2H); 5.13 (bs, 1H); 6.38 (s, 1H); 8.38 (s, 1H); 8.48 (s, 1H).

***N′*-[7-Chloro-4-hydroxy-2-(pyrrolidine-1-carbonyl)-quinoline-3-carboxyl]-*N′*-is oxazol-5-ylmethyl-hydrazinecarboxylic Acid *tert*-Butyl Ester.** The title compound was prepared from 7-chloro-4-oxo-2-(pyrrolidinylcarbonyl)hydroquinoline-3-carboxylic acid **7** (1.51 g, 4.7 mmol) and *N′*-isoxazol-5-ylmethyl-hydrazinecarboxylic acid *tert*-butyl ester (1.0 g, 4.7 mmol) according to Method B except that the reaction mixture was heated to reflux for 1.5 h then stirred at rt for 16 h. The desired product was obtained as an off-white foam (2.09 g, 86%).

7-Chloro-4-hydroxy-2-(5-isoxazolino)methyl-1,2,5,10-tetrahydropyridazino[4,5-*b*]quinoline-1,10-dione 9s. The title compound was prepared from *N′*-[7-chloro-4-hydroxy-2-(pyrrolidine-1-carbonyl)-quinoline-3-carboxyl]-*N′*-isoxazol-5-ylmethyl-hydrazinecarboxylic acid *tert*-butyl ester (1.0 g, 1.94 mmol) according to Method E except that 9:1 Et_2O: MeOH was used for the sonication followed by filtration and washing of the solids with Et_2O. After drying *in vacuo* (500 mTorr, 30 °C) for 18 h, the desired compound was obtained as a yellow solid (0.54 g, 81%); ^{1}H NMR (300 MHz, DMSO-d_6): δ 5.27 (s, 2H); 6.44 (s, 1H); 7.45 (dd, 1H, J_o = 8.7 Hz, J_m = 1.8 Hz); 8.03 (d, 1H, J_m = 1.8 Hz); 8.15 (d, 1H, J_o = 8.7 Hz); 8.53 (s, 1H, J_m = 1.8 Hz); 11.99 (s, 1H); 12.82 (s, 1H); Anal. ($C_{15}H_9ClN_4O_4$·0.4 H_2O): C, H, N.

Compound 9t. 7-Chloro-4-hydroxy-2-(1,3-thiazo-2-ylmethyl)-1,2,5,10-tetrahydropyridazino[4,5-*b*]quinoline-1,10-dione Methanesulfonate. (*tert*-Butoxy)-*N*-[(1,3-thiazol-2-ylmethyl)amino]-carboxamide. To a stirred solution of thiazole-2-carbaldehyde (0.95 g, 8.42 mmol) and *tert*-butyl carbazate (1.17 g, 8.87 mmol) in EtOH (15 mL) was added 1.10 mL of glacial AcOH, followed by $NaCNBH_3$ (2.18 g, 34.7 mmol). The reaction mixture was heated at 50 °C and stirred for 72 h. The reaction was quenched with 2 N NaOH (30 mL), and the resulting solution was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine (40 mL) and then dried over Na_2SO_4. The Na_2SO_4 was filtered off, and the filtrate was purified bychromatography on silica gel using 1:3 EtOAc:CH_2Cl_2 as eluent to give the title compound as an off-white solid (0.62 g, 32%); ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.38 (s, 9H); 4.15 (d, 2H, J = 3.9 Hz); 5.34 (d, 1H, J = 3.9 Hz); 7.63 (d, 1H, J = 3.3 Hz); 7.70 (d, 1H, J = 3.3 Hz); 8.42 (br s, 1H).

***N*-[(*tert*-Butoxy)carbonylamino][7-chloro-4-oxo-2-(pyrrolidinylcarbonyl)(3-hydroquinolyl)]-*N*-(1,3-thiazol-2-ylmethyl)carboxamide.** The title compound was prepared from 7-chloro-4-oxo-2-(pyrrolidinylcarbonyl)hydroquinoline-3-carboxylic acid **7** (0.90 g, 2.80 mmol) and (*tert*-butoxy)-*N*-[(1,3-thiazol-2-ylmethyl)amino]-carboxamide (0.5 g, 2.20 mmol) according to Method B. The desired product was obtained as a yellow solid (0.97 g, 83%).

7-Chloro-4-hydroxy-2-(1,3-thiazo-2-ylmethyl)-1,2,5,10-tetrahydropyridazino[4, 5-*b*]quinoline-1,10-dione 9t. The title compound was prepared from *N*-[(*tert*-butoxy)carbonylamino][7-chloro-4-oxo-2-(pyrrolidinylcarbonyl)(3-hydroquinolyl)]-*N*-(1,3-thiazol-2-ylmethyl)carboxamide (760 mg, 1.3 mmol) according to Method E except that the solids were sonicated in MeOH. The desired product was obtained as an off-white solid (648 mg, 78%); mp >300 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.38 (CH_3 SO_3H, s, 3H), 5.38 (s, 2H); 7.45 (d, 1H, J = 8.7 Hz); 7.70 (d, 1H, J = 3.3); 7.76 (d, 1H, J = 3.3 Hz); 8.04 (s, 1H); 8.15 (d, 1H, 8.7 Hz). Anal. ($C_{15}H_{10}ClN_4O_3S$·H_2O·H_3CSO_3H): C, H; N: calcd 11.77; found, 11.39.

Compound 9u. Methyl 4-[(7-chloro-4-hydroxy-1,10-dioxo-2,5-dihydropyridazino[4,5-*b*]quinolin-2-yl)methyl]benzoate. Methyl 4-({[(*tert*-Butoxy)carbonylamino]amino}methyl)benzoate. The title compound was prepared from methyl 4-bromomethylbenzoate (25.0 g, 0.11 mol) and *tert*-butyl carbazate (68.65 g, 0.52 mol) according to Method H except that the extraction was carried out with CH_2Cl_2 (4 × 350 mL), and the combined organic layers were dried over $MgSO_4$. The usual purification afforded the pure compound as a clear colorless oil (26.50 g, 87% yield). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.38 (s, 9H); 3, 84 (s, 3H,); 3.92 (d, 2H, J = 4.2 Hz); 4.95 (d, 1H, J = 4.2 Hz); 7.47(d, 2H, J = 8.4 Hz); 7.90 (d, 2H, J = 8.1 Hz); 8.29 (s, 1H).

***N*-[(*tert*-Butoxy)carbonylamino][7-chloro-4-oxo-2-(pyrrolidinylcarbonyl)(3-hydroquinolyl)]-*N*-(4-carbomethoxybenzyl)carboxamide.** The title compound was prepared from 7-chloro-4-oxo-2-(pyrrolidinylcarbonyl)hydroquinoline-3-carboxylic acid (**7**) (18.38 g, 57 mmol) and methyl 4-({[(*tert*-butoxy)carbonylamino]amino}-methyl)benzoate (24.1 g, 86 mmol) according to Method A except that the crude material was preabsorbed onto silica gel using MeOH and was eluted using 5:95 MeOH:$CHCl_3$ as eluent to provide the title compound as a tan solid (33.43 g, 100%) contaminated with dicyclohexylurea. This material was used directly in the subsequent reaction.

Methyl 4-[(7-Chloro-4-hydroxy-1,10-dioxo-2,5-dihydropyridazino[4,5-*b*]quinolin-2-yl)methyl]benzoate 9u. The title compound was prepared from *N*-[(*tert*-butoxy)carbonylamino][7-chloro-4-oxo-2-(pyrrolidinylcarbonyl)(3-hydroquinolyl)]-*N*-(4-carbomethoxybenzyl)carboxamide (33.6 g, 57.3 mmol) according to Method G as a white solid (13.38 g, 40% yield); mp >290 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.83 (s, 3H), 5.18 (s, 2H); 7.43 (m, 3H,); 7.92 (d, 2H, J = 8.1 Hz); 8.02 (S, 1H); 8.14 (d, 1H, J = 8.4 Hz). Anal. ($C_{20}H_{14}ClN_3O_5$): C, H, N.

Compound 9v. 7-Chloro-4-hydroxy-2-[4-(carbomethoxy)phenyl-2-ethyl)-1,2,5,10-tetrahydropyridazino[4,5-*b*]quinoline-1,10-dione. 4-[1-(*tert*-Butoxycarbonyl-hydrazino)-ethyl]-benzoic Acid Methyl Ester. The title compound was prepared from methyl 4-acetylbenzoate (5.20 g, 29.2 mmol) and *tert*-butyl carbazate (3.85 g, 29.2 mmol) according to Method I. After drying *in vacuo* (500 mTorr, 30 °C) for 30 min, the title compound was obtained as an off-white solid (8.36 g, 98%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.49 (s, 9H); 2.22 (s, 3H); 3.34(s, 1H); 3.86 (s, 3H); 7.87 (d, 2H, J_o=8.4 Hz); 7.97 (d, 2H, J_o=8.4 Hz); 9.97 (s, 1H).

4-[1-(*tert*-Butoxycarbonyl-hydrazino)-ethyl]-benzoic Acid Methyl Ester. The title compound was prepared from 4-[1-(*tert*-butoxycarbonyl-hydrazino)-ethyl]benzoic acid methyl ester (8.35 g, 28.6 mmol) according to Method J except that the crude material was purified by flash chromatography on silica gel using a gradient of 10:90 to 20:80 EtOAc:CH_2Cl_2. The desired compound was obtained as a white solid (6.41 g, 76%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.18 (d, 3H, J = 6.6 Hz); 1.35 (s, 9H); 3.84 (s, 3H); 4.16 (m, 1H); 4.71 (m, 1H); 7.48 (d, 2H, J_o = 8.3 Hz); 7.89 (d, 2H, J_o = 8.3 Hz); 8.15 (s, 1H).

4-(1-{*N′*-*tert*-Butoxycarbonyl-*N*-[7-chloro-4-hydroxy-2-(pyrrolidine-1-carbonyl)-quinoline-3-carboxyl]-hydrazino}-ethyl)-benzoic Acid Methyl Ester. The title compound was prepared from 7-chloro-4-oxo-2-(pyrrolidinylcarbonyl)hydroquinoline-3-carboxylic acid (**4**) (2.15 g, 6.7 mmol) and 4-[1-(*tert*-butoxycarbonyl-hydrazino)-ethyl]-benzoic acid methyl ester (1.97 g, 6.7 mmol) according to Method B as an off-white solid (3.53 g, 71%).

7-Chloro-4-hydroxy-2-[4-(carbomethoxy)phenyl-2-ethyl)-1,2,5,-10-tetrahydropyridazino[4,5-*b*]quinoline-1,10-dione 9v. The title compound was prepared from 4-(1-{*N′*-*tert*-butoxycarbonyl-*N*-[7-chloro-4-hydroxy-2-(pyrrolidine-1-carbonyl)-quinoline-3-carboxyl]-hydrazino}-ethyl)-benzoic acid methyl ester (3.45 g, 5.78 mmol) in THF (50 mL) according to Method E. After drying *in vacuo* (500 mTorr, 30 °C) for 18 h, the resulting yellow solid (2.05 g, 83%) was found to be of insufficient purity by ^{1}H NMR. A portion of this material (1.73 g) was suspended in CH_3CN (10 mL) and H_2O (10 mL) to which was added 20% choline hydroxide in water dropwise until all the solids dissolved, then purified by preparative HPLC (41.4 mm × 25 cm C-18 Dynamax 60A column using a gradient 10−35% of CH_3CN in H_2O with 0.1% TFA over 50 min with a flow rate of 20 mL/min, monitoring 210 nM). Product was precipitated from the fractions containing title material by addition of 6M HCl to pH 3. The solid was collected by vacuum filtration, washed with water (2 × 50 mL) then Et_2O (2 × 50 mL), and dried *in vacuo* (500 mTorr, 30 °C) for 18 h to give the title compound as a yellow solid (1.23 g, 59%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.69 (d, 3H, J = 6.9 Hz); 3.84 (s, 3H); 6.26 (q, 1H, J = 7.2 Hz); 7.38−7.50 (m, 3H,); 7.92 (d, 2H, J_o = 8.4 Hz); 8.03 (d, 1H, J_m =

1.8 Hz); 8.15 (d, 1H, J_o = 8.7 Hz); 11.94 (s, 1H); 12.57 (s, 1H). Anal. ($C_{21}H_{16}ClN_3O_5 \cdot 0.2\ H_2O$): C, H, N.

Compound 9w. 4-[(7-Chloro-4-hydroxy-1,10-dioxo-2,5-dihydropyridazino[4,5-*b*]quinolin-2-yl)methyl]benzoic Acid. To a stirred suspension of methyl 4-[(7-chloro-4-hydroxy-1,10-dioxo-2,5-dihydropyridazino[4,5-*b*]quinolin-2-yl)methyl]benzoate (0.279 g, 0.68 mol) in H_2O (35 mL) was added NaOH (0.08 g, 2.03 mmol). The mixture was heated to 50 °C for 2 h and acidified to pH = 1, and the solid was collected by filtration. The material was dried *in vacuo* to give the title compound as a tan solid (0.133 g, 48%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 5.11 (s, 2H); 7.38−7.46 (m, 2H, J = 7.8 Hz); 7.90 (d, 2H, J = 7.8 Hz); 8.03 (s, 1H); 8.15 (d, 2H, J = 7.8 Hz. Anal. ($C_{19}H_{12}ClN_3O_5 \cdot 0.5\ H_2O$): C, H, N.

Compound 9x. Methyl 3-[(7-Chloro-4-hydroxy-1,10-dioxo-2,5-dihydropyridazino[4,5-*b*]quinolin-2-yl)methyl]benzoate. The title compound was made from methyl 3-bromomethylbenzoate as described for **9u**. After air drying, the title compound was obtained as a white solid (0.327 g, 100%); ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.84 (s, 3H); 5.17 (s, 2H); 7.44 (dd, J = 2.1, 8.7 Hz, 1H); 7.50 (t, J = 7.8 Hz, 1H); 7.62 (d, J = 7.8 Hz, 1H); 7.87 (d, J = 7.8 Hz, 1H); 7.93 (s, 1H); 8.03 (d, J = 1.8 Hz, 1H); 8.15 (d, J = 8.7 Hz, 1H); 12.62 (br s, 1H).

Compound 9y. 3-(7-Chloro-1,4,10-trioxo-3,4,5,10-tetrahydro-1*H*-pyridazino[4,5-*b*]quinolin-2-ylmethyl)-*N*-methoxy-*N*-methylbenzamide. 4-(*tert*-Butoxycarbonyl-hydrazonomethyl)-benzoic acid was prepared from 3-formylbenzoic acid largely according to Method I. This compound was coupled with *N*-methoxy-*N*-methylamine using EDCI as the coupling reagent. *N*′-[4-(Methoxy-methyl-carbamoyl)-benzylidene]-hydrazinecarboxylic acid *tert*-butyl ester was hydrogenated according to Method J to afford *N*′-[3-(methoxy-methyl-carbamoyl)-benzyl]-hydrazinecarboxylic acid *tert*-butyl ester. The coupling of 7-chloro-4-oxo-2-(pyrrolidinylcarbonyl)-hydroquinoline-3-carboxylic acid (**7**) and *N*′-[3-(methoxy-methyl-carbamoyl)-benzyl]-hydrazinecarboxylic acid *tert*-butyl ester was performed largely in accordance to Method B except that CH_2Cl_2 was used as the solvent.

The cyclization to the title compound was performed largely according to Method F to give the title compound as an off-white powder (0.08 g, 50% yield); ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.22 (s, 3H); 3.52 (s, 3H); 3.67 (m, 2H); 5.15 (s, 2H); 7.42 (m, 3H); 7.50 (m, 1H); 8.02 (s, 1H); 8.15 (d, 1H, J = 8.7 Hz); 11.94 (br s); 12.67 (br s, 1H).

Compound 9z. {**3-[(7-Chloro-4-hydroxy-1,10-dioxo-(2,5-dihydropyridazino[4,5-*b*]quinolin-2-yl))methyl]phenyl**}**-*N*-2-methoxyethyl)carboxamide.** This compound was synthesized in an analogous fashion to **9y** to afford, after cyclization, the title compound (0.120 g, 21% yield) as off-white solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.24 (s, 3H); 3.40 (m, 4H); 5.15 (s, 2H); 7.42 (m, 3H); 7.71 (d, 1H, J = 6.9 Hz); 7.78 (s, 1H); 8.02 (s, 1H); 8.15 (d, 1H, J = 8.7 Hz); 8.53 (m, 1H, J = 4.2 Hz); 11.94 (br s); 12.69 (br s, 1H).

Compound 9aa. 7-Chloro-4-hydroxy-2-(4-phenylaminocarboxamide)phenylmethyl-1,2,5,10-tetrahydropyridazino[4,5-*b*]-quinoline-1,10-dione. The title compound was prepared by the method described for **9ab** (below) from *N*-{[4-aminophenyl)methyl]-[7-chloro-4-oxo-2-(pyrrolinylcarbonyl)(3-hydroquinolyl)]amino}-(*tert*-butoxy)carboxamide and phenyl isocyanate as a yellow solid (0.55 g, 79% for the final cyclization step). ^{1}H NMR (300 MHz, DMSO-d_6): δ 5.04 (s. 2H); 6.95 (t, J = 7.2 Hz, 1H); 7.20−7.30 (m, 4H); 7.30−7.50 (m, 5H); 8.02 (s, 1H); 8.15 (d, J = 8.7 Hz, 1H); 8.65 (d, J = 12.3 Hz, 2H); 11.92 (s,1H); 12.63 (s, 1H). Anal. ($C_{25}H_{18}ClN_5O_4$): C, H, N.

Compound 9ab. 7-Chloro-4-hydroxy-2-(4-dimethylaminocarboxamide)phenylmethyl-1,2,5,10-tetrahydropyridazino[4,5-*b*]-quinoline-1,10-dione·0.15 Methanesulfonate. (*tert*-Butoxy)-*N*-{[(4-nitrophenyl)methyl]amino}carboxamide. To a solution of 4-nitrobenzyl bromide (15 g, 69 mmol) in DMF (100 mL) were added *tert*-butyl carbazate (70 g, 529 mmol) and K_2CO_3 (10 g, 75 mmol). The mixture was stirred and heated to 90 °C for 2 h under N_2. At that time, the mixture was cooled, diluted with Et_2O (400 mL), and washed with H_2O (5 × 200 mL) and brine (100 mL). The organic phase was dried over $MgSO_4$, filtered, and reduced by rotary evaporation to an oily brown solid. The residual DMF and *tert*-butyl carbazate were removed by Kugelrohr distillation at 90 °C and 50 mTorr. The residual brown solid was purified by chromatography on silica gel eluting with 10% EtOAc in CH_2Cl_2 to give the title compound as a yellow solid (15 g, 79%).

(*tert*-Butoxy)-*N*-{[7-chloro-4-oxo-2-(pyrrolidinylcarbonyl)(3-hydroquinolyl)][(4-nitrophenyl)methyl]amino}carboxamide. The title compound was prepared from 7-chloro-4-oxo-2-(pyrrolidinyl-carbonyl)hydroquinoline-3-carboxylic acid **7** (12 g, 38 mmol) and (*tert*-butoxy)-*N*-{[(4-nitrophenyl)methyl]amino}carboxamide (10 g, 38 mmol) according to Method B except that a mechanical stirrer was employed and the mixture was heated for 5 min prior to the addition of the hydrazine. The desired compound was obtained as a yellow solid (14.5 g, 68%).

***N*-{[4-Aminophenyl)methyl][7-chloro-4-oxo-2-(pyrrolinylcarbonyl)(3-hydroquinolyl)]amino}(*tert*-butoxy)carboxamide.** The (*tert*-butoxy)-*N*-{[7-chloro-4-oxo-2-(pyrrolidinylcarbonyl)(3-hydroquinolyl)][(4-nitrophenyl)methyl]amino}carboxamide (6.9 g, 12 mmol) was dissolved in CH_2Cl_2 (1 L). 1,1′-Dioctadecyl-4,4′-bipyridinium dibromide (500 mg, 600 μmol) was added, followed by H_2O (10 mL). This mixture was heated to 35 °C under N_2, at which time a solution of sodium dithionate (25.3 g, 145 mmol) and K_2CO_3 (8.4 g, 60.5 mmol) in H_2O (150 mL) was added. After 4 h, a second batch of sodium dithionate (25.4 g) and K_2CO_3 (60.5 g) in H_2O (150 mL) was added. The reaction was stirred an additional 18 h and then cooled to rt. The organic phase was separated, the aqueous was extracted with $CHCl_3$ (100 mL), and the combined organic phases were washed with brine (50 mL), dried over anhydrous $MgSO_4$, and concentrated by rotary evaporation. This material was chromatographed on silica gel with 5% MeOH in $CHCl_3$ to afford the title compound as a yellow solid (4.5 g, 69%).

(Dimethylamino)-*N*-[4-({[*tert*-butoxy)carbonylamino][7-chloro-4-oxo-2-(pyrrolidinylcarbonyl)(3-hydroquinolyl)]amino}methyl)-phenyl]carboxamide. The *N*-{[4-aminophenyl)methyl][7-chloro-4-oxo-2-(pyrrolinylcarbonyl)(3-hydroquinolyl)]amino}(*tert*-butoxy)carboxamide (1.0 g, 1.9 mmol) was dissolved in CH_2Cl_2 (50 mL), and Et_3N (350 μL, 2.5 mmol) was added, followed by DMAP (10 mg, 100 μmol) and dimethylcarbamoyl chloride (200 μL, 2 mmol). The reaction was stirred for 50 h. Four 0.2 mL portions of additional dimethylcarbamoyl chloride were added during this time. The reaction mixture was washed with H_2O and brine, dried over $MgSO_4$, and chromatographed on silica gel with 5% MeOH in CH_2Cl_2 to afford the title compound as a yellow solid (690 mg, 61%).

7-Chloro-4-hydroxy-2-(4-dimethylaminocarboxamide)phenylmethyl-1,2,5,10-tetrahydropyridazino[4,5-*b*]quinoline-1,10-dione 9ab. The title compound was prepared from (dimethylamino)-*N*-[4-({[*tert*-butoxy)carbonylamino][7-chloro-4-oxo-2-(pyrrolidinylcarbonyl)(3-hydroquinolyl)]amino}methyl)phenyl]-carboxamide (690 mg, 1.13 mmol) according to Method E except that 1:3 MeOH:Et_2O was used for the sonications. The desired compound was obtained as a yellow solid (430 mg, 86%); ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.90 (s, 6H); 5.02 (s, 2H); 7.17 (d, J = 8.4 Hz, 2H); 7.44−7.37 (m, 3H); 8.02 (s, 1H); 8.15 (d, J = 8.7 Hz, 1H); 8.27 (s, 1H); 11.91 (s, 1H); 12.61 (s, 1H). Anal. ($C_{21}H_{18}ClN_5O_4 \cdot 0.15\ H_2O \cdot 0.15\ CH_3SO_3H$): C, H, N.

Compound 9ac. 7-Chloro-4-hydroxy-2-(3-dimethylaminocarboxamide)phenylmethyl-1,2,5,10-tetrahydropyridazino[4,5-*b*]-quinoline-1,10-dione·0.35 Methanesulfonate. The title compound was prepared by the method described for **9ad** (below) from *N*-{[3-aminophenyl)methyl][7-chloro-4-oxo-2-(pyrrolinylcarbonyl)(3-hydroquinolyl)]amino}(*tert*-butoxy)carboxamide and dimethylcarbamoyl chloride to afford 0.41 g (76% for the final cyclization) of the title compound; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.89 (s, 6H); 5.05 (s, 2H); 6.87 (d, J = 7.5 Hz, 1H); 7.17 (t, J = 7.8 Hz, 1H); 7.30−7.50 (m, 3H); 8.02 (s, 1H); 8.15 (d, J = 8.7 Hz, 1H); 8.28 (s, 1H); 11.96 (s, 1H); 12.68 (s, 1H). Anal. ($C_{21}H_{18}ClN_5O_4 \cdot 0.10\ H_2O \cdot 0.35\ CH_3SO_3H$): C, H, N.

Compound 9ad. 7-Chloro-4-hydroxy-2-(4-(*tert*-butyl)aminocarboxamide)phenylmethyl-1,2,5,10-tetrahydropyridazino-[4,5-*b*]quinoline-1,10-dione. 2. *N*-[(*tert*-Butoxy)carbonylamino]-*N*-[(3-{[(*tert*-butyl)amino]carbonylamino}-phenyl)methyl][7-chloro-4-oxo-2-(pyrrolidinylcarbonyl)(3-hydroquinolyl)]-carboxamide. To a mixture of *N*-(*N*-[(3-aminophenyl)methyl][7-chloro-4-oxo-2-(pyrrolidinylcarbonyl)-(3-hydroquinolyl)]carbonylamino)(*tert*-butoxy)carboxamide (450 mg, 830 μmol) prepared in an analogous fashion to *N*-{[4-aminophenyl)methyl][7-chloro-4-oxo-2-(pyrrolinylcarbonyl)(3-hydroquinolyl)]amino}(*tert*-butoxy)-carboxamide, as prepared for **9ab** in CH_2Cl_2 (10 mL), were added *tert*-butyl isocyanate (120 μL, 1.1 mmol) and Et_3N (300 μL, 2.1 mmol). The mixture was stirred for 20 h, at which time additional *tert*-butyl isocyanate (100 μL) was added. This solution was then stirred overnight, and the reaction was diluted with EtOAc, washed with saturated aqueous NH_4Cl, water, and brine, and then dried over Na_2SO_4. This material was used in the following step without purification.

[(*tert*-Butyl)amino]-*N*-{3-[(7-chloro-4-hydroxy-1,10-dioxo-(1,2,5,10-tetrahydropyridazino[4,5-*b*]quinolin-2-yl))methyl]phenyl)carboxamide 9ad. The title compound was prepared from *N*-[(*tert*-butoxy)carbonylamino]-*N*-[(3-{[(*tert*-butyl)amino]carbonylamino}phenyl)methyl][7-chloro-4-oxo-2-(pyrrolidinylcarbonyl)(3-hydro-quinolyl)]-carboxamide (theoretically 830 μmol) according to Method G except that the solids were sonicated in 15 mL of a 10% MeOH in Et_2O solution, and the remaining solid was collected and dried at 30 °C and 50 mTorr for 3 h to afford the desired compound as a tan solid (230 mg, 490 μmol, 59% for two steps); ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.26 (s, 9H); 5.04 (s, 2H); 5.91 (s, 1H); 6.81 (d, J = 7.5 Hz, 1H); 7.15 (dd, J = 7.8, 7.8 Hz, 1H); 7.22 (s, 1H); 7.30 (d, J = 8.1 Hz, 1H); 7.44 (d, J = 8.4 Hz, 1H); 8.03 (s, 1H); 8.14 (d, J = 8.7 Hz, 1H); 8.24 (s, 1H); 11.94 (br s, 1H); 12.69 (br s, 1H).

Compound 9ae. 7-Chloro-4-hydroxy-2-(3-phenylprop-2-ynyl)-2,5-dihydropyridazino[4,5-*b*]quinoline-1,10-dione. *tert*-Butoxy-*N*-[(3-phenylprop-2-ynyl)amino]carboxamide. To a stirred solution of 3-phenylprop-2-yn-1-ol (3.52 g, 26.6 mmol), trifluroacetic anhydride (5.0 mL, 29.7 mmol), and dry CH_2Cl_2 (60 mL) at −75 °C under N_2 was added 2,6-lutidine (3.6 mL, 30.9 mmol) in small portions, maintaining the temperature between −69 °C and −75 °C. The reaction mixture was stirred at −75 °C for 5 min and then added to a stirred solution of *tert*-butyl carbazate (15.52 g, 117 mmol) in dry CH_2Cl_2 (60 mL) at −7.5 °C. The reaction mixture was stirred at −7.5 °C for 2 h and then poured into H_2O (100 mL). The resulting mixture was extracted with CH_2Cl_2 (2 × 400 mL). The combined CH_2Cl_2 extracts were successively washed with H_2O (2 × 100 mL) and brine (1 × 50 mL) and dried over $MgSO_4$. The $MgSO_4$ was filtered off, and the filtrate was concentrated *in vacuo* to afford the crude product as an oil. This crude product was purified by flash chromatography on silica gel, eluting with 1:1 hexane: Et_2O to give the title compound as a clear oil (3.5 g, 50%).

***N*-[(*tert*-Butoxy)carbonylamino][7-chloro-4-oxo-2-(pyrrolidinylcarbonyl)(3-hydroquinolinolyl)]-*N*-(3-phenylprop-2-ynyl)carboxamide.** The title compound was prepared from 7-chloro-4-oxo-2-(pyrrolidinylcarbonyl)hydroquinoline-3-carboxylic acid **7** (1.80 g, 5.61 mmol) and *tert*-butoxy-*N*-[(3-phenylprop-2-ynyl)amino]-carboxamide (1.84 g, 7.47 mmol) according to Method A (2.84 g, 92%).

7-Chloro-4-hydroxy-2-(3-phenylprop-2-ynyl)-2,5-dihydropyridazino[4,5-*b*]quinoline-1,10-dione 9ah. The title compound was prepared from *N*-[(*tert*-butoxy)carbonylamino][7-chloro-4-oxo-2-(pyrrolidinylcarbonyl)(3-hydroquinolinolyl)]-*N*-(3-phenylprop-2-ynyl)carboxamide (2.84 g, 5.17 mmol) according to Method E except that the solids were sonicated in MeOH. The collected solids were dried at 40 °C *in vacuo* to give the title compound as a yellow solid (1.55 g, 79%); mp >250 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.97 (s, 2H); 7.4 (m, 6H); 8.02 (d, 1H, J = 1.8 Hz); 8.14 (d, 1H, J = 8.67 Hz); 11.97 (s, 1H); 12.85 (s, 1H). Anal. ($C_{20}H_{12}ClN_3O_3$): C, H, N.

Compound 9af. 7-Chloro-4,10-dihydroxy-2-(1-methyl-3-phenyl-prop-2-ynyl)-2*H*-pyridazino[4,5-*b*]quinolin-1-one. The title compound was prepared as a white solid from 7-chloro-4-oxo-2-(pyrrolidinylcarbonyl)hydroquinoline-3-carboxylic acid (**7**) and *N*′-(1-methyl-3-phenyl-prop-2-ynyl)-hydrazinecarboxylic acid *tert*-butyl ester according to coupling Method A and cyclization Method D. Yields for the coupling and cyclization were 44 and 34%, respectively, mp 225−226 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.61 (d, 3H, J = 6.9 Hz); 6.17 (q, 1H, J = 6.9 Hz); 7.34−7.45 (m, 6H); 8.04 (d, 1H, J = 1.5 Hz); 8.15 (d, 1H, J = 8.7 Hz); 11.98 (s, 1H); 12.83 (s, 1H). Anal. ($C_{21}H_{14}ClN_3O_3 \cdot 0.6H_2O$): C, H, N.

Compound 9ag. 7-Chloro-4,10-dihydroxy-2-(1-methyl-prop-2-ynyl)-2*H*-pyridazino[4,5-*b*]quinolin-1-one. *N*-(1-Methyl-prop-2-ynyl)-hydrazinecarboxylic Acid *tert*-Butyl Ester. To 3-butyn-2-ol (10 mL, 127.55 mmol) in dry CH_2Cl_2 (100 mL) under N_2 was added anhydrous Et_3N (28 mL, 193.7 mmol). The stirred mixture was cooled to 0 °C. Dropwise addition of methanesulfonyl chloride (11 mL, 142.1 mmol) in CH_2Cl_2 (100 mL) resulted in formation of a white precipitate. The mixture was stirred at 0 °C for 30 min. The clear supernatant was then transferred to a solution of *tert*-butyl carbazate (60 g, 453.99 mol) in anhydrous MeOH (200 mL) via cannula at 0 °C over 15 min. The solids from the first flask were washed with CH_2Cl_2, and the solution was also transferred to the second reaction mixture. The initially clear reaction solution became yellow and was stirred at 0 °C under N_2 for 4 h. The reaction mixture was allowed to warm to rt and after 3 d was concentrated to a white solid. The solid was partitioned between saturated aqueous NaCl (250 mL) and EtOAc. The aqueous layer was extracted with EtOAc (2 × 200 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to give a white solid (14.09 g, 60%). The crude material was diluted in Et_2O/hexanes (100 mL:200 mL) and washed with H_2O (6 × 100 mL). The organic solution was dried over Na_2SO_4 and concentrated *in vacuo* to give a white solid. This was crystallized from hexanes to give the product as a white solid (12.29 g, 53%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.15 (d, 3H, J = 6.6 Hz), 1.39 (s, 9H), 3.07 (d, 1H, J = 2.1 Hz), 3.73 (d, 1H, J = 6.0 Hz), 4.58 (bs, 1H), 8.27 (bs, 1H).

***N*′-[7-Chloro-4-oxo-2-(pyrrolidine-1-carbonyl)-1,4-dihydroquinoline-3-carbonyl]-*N*′-(1-methyl-prop-2-ynyl)-hydrazinecarboxylic Acid *tert*-Butyl Ester.** The title compound was prepared from 7-chloro-4-oxo-2-(pyrrolidinylcarbonyl)hydro-quinoline-3-carboxylic acid (**7**) (5.31 g, 16.55 mmol) and *N*-(1-methyl-prop-2-ynyl)-hydrazinecarboxylic acid *tert*-butyl ester (2.76 g, 15.0 mmol) according to Method B. The crude yellow solid was chromatographed over silica gel using a gradient of 99.5:0.5 to 97.5:2.5 CH_2Cl_2:MeOH. The pure product was obtained as a pale yellow solid (7.08 g, 97%); ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.28−1.03 (m, 9H), 1.35 (d, 3H, J = 6.9 Hz), 1.87 (m, 4H), 3.47−3.31 (m, 6H), 7.51 (d, 1H, J = 7.5 Hz), 7.64 (s, 1H), 8.18 (d, 1H, J = 7.4 Hz), 9.02 (bs, 1H), 12.87 (bs, 1H).

7-Chloro-4,10-dihydroxy-2-(1-methyl-prop-2-ynyl)-2*H*-pyridazino[4,5-*b*]quinolin-1-one 9ag. The title compound was prepared from *N*′-[7-chloro-4-oxo-2-(pyrrolidine-1-carbonyl)-1,4-*d*ihydroquinoline-3-carbonyl]-*N*′-(1-methyl-prop-2-ynyl)-hydrazinecarboxylic acid *tert*-butyl ester (0.5222 g, 1.07 mmol) in THF (30 mL) according to Method G. After drying under high vacuum, the final product was obtained as an off-white solid (315.2 mg, 93%); ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.50 (d, 3H, J = 6.9 Hz), 3.31 (d, 1H, J = 2.1 Hz), 4.83 (dq, 1H, J = 6.9 Hz, J = 2.1 Hz), 7.44 (d, 1H, J = 8.4 Hz), 8.03 (s, 1H), 8.14 (d, 1H, J = 8.7 Hz), 11.97 (bs, 1 H), 12.83 (bs, 1H).

Compound 9ah. 7-Chloro-4-hydroxy-2-(3-(4-pyridyl)prop-2-ynyl)-1,2,5,10-tetrahydropyridazino[4,5-*b*]quinoline-1,10-dione·1.3 Methanesulfonate. (*tert*-Butoxy)-*N*-(prop-2-ynylamino)-carboxamide. A 5 L, three-neck flask equipped with mechanical stirrer, thermometer, and 500 mL dropping funnel with N_2 inlet was charged with powdered K_2CO_3 (124.03 g, 0.8975 mol), *tert*-butyl carbazate (355.4 g, 2.692 mol), and 2.7 L of 9:1 THF:DMF. To this stirred slurry was added a solution of propargyl bromide (100 mL, 0.898 mol, 80% in toluene), which was dissolved in 300 mL of 9:1 THF:DMF, over 1.5 h. The reaction was stirred at ambient temperature for 44 h. The mixture was then concentrated.

The residue was partitioned between 1.5 L of CH_2Cl_2 and 2 L of H_2O. The aqueous layer was extracted with CH_2Cl_2 (2 × 500 mL), and the combined organics were washed with 1000 mL water, 200 mL brine (1×), and then 400 mL water:100 mL brine several times. The organic layer was dried over Na_2SO_4 and concentrated to give a yellow oil. The crude product (365.4 g) was dissolved in 3 L of Et_2O and was treated with 1.5 L of 1 N ethereal HCl over 3 h. The thick white solids that formed were filtered and washed with Et_2O, and the filtrates were concentrated to give the desired product as a yellow oil (136.0 g). The oil was applied to a column containing 2.4 L of silica wet-packed in hexane. Elution was as follows: hexane (2 L), 90:10 hexane:Et_2O (2 L), 80:20 hexane:Et_2O (2 L), 70:30 hexane:Et_2O (6 L). The pure product was obtained as a white solid (83.6 g, 54%); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.39 (s, 9H), 3.06 (s, 1H), 3.43 (s, 2H), 4.68 (s, 1H), 8.29 (bs, 1H).

***N*-[(*tert*-Butoxycarbonylamino][7-chloro-4-oxo-2-(pyrrolidinylcarbonyl)(3-hydroquinolyl)]-*N*-prop-2-ynylcarboxamide.** To a stirred suspension of 7-chloro-4-oxo-2-(pyrrolidinylcarbonyl)-hydroquinoline-3-carboxylic acid **7** (37.86 g, 0.118 mol) in THF (600 mL) was added 1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide metho-*p*-toluenesulfonate (100.0 g, 0.236 mol). The white suspension became bright yellow immediately. To this stirred suspension was added over 30 min a solution of (*tert*-butoxy)-*N*-(prop-2-ynylamino)carboxamide (20.93 g, 0.123 mol) in THF (250 mL), and the reaction was stirred at ambient temperature for 24 h. The reaction mixture was filtered, and the collected solids were washed with THF. The filtrates and washes were combined and concentrated. The residue was partitioned between 1.5 L of CH_2Cl_2 and 1.5 L of water, and the aqueous layer was extracted once with CH_2Cl_2. The combined organic layers were washed once with brine, dried over $MgSO_4$, and concentrated. The residue was chromatographed over silica gel using the following eluents: CH_2Cl_2 (500 mL), 98:2 CH_2Cl_2/MeOH (2 L), 95:5 CH_2Cl_2/MeOH (4 L). The product was initially obtained as a foam which was then triturated with 220 mL of 1:1 hexane:Et_2O to give the title compound as a white powder (46.57 g, 83%); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.42−1.18 (m, 9H), 1.86 (m, 4H), 3.44−3.36 (m, 6H), 4.20 (s, 1H), 7.50 (d, 1H, J = 8.7 Hz), 7.64 (s, 1H), 8.18 (d, 1H, J = 8,7 Hz), 8.73 (br s, 1H), 12.90 (br s, 1H).

***N*-[(*tert*-Butoxy)carbonylamino][7-chloro-4-oxo-2-(pyrrolidinylcarbonyl)(3-hydroquinolyl)]-*N*-(3-(4-pyridyl)prop-2-ynyl)carboxamide.** The title compound was prepared from *N*-[(*tert*-butoxy)carbonylamino][7-chloro-4-oxo-2-(pyrrolidinylcarbonyl)(3-hydroquinolyl)]-*N*-prop-2-ynylcarboxamide (0.832 g, 1.76 mmol) and 4-iodopyridine (0.327 g, 1.59 mmol) according to Method C as a slightly impure oil after the initial column chromatography (0.93 g, 106%). The material was cyclized without further purification.

7-Chloro-4-hydroxy-2-(3-(4-pyridyl)prop-2-ynyl)1,2,5,10-tetrahydropyridazino[4,5-*b*]quinoline-1,10-dione·1.3 Methanesulfonate 9ah. The title compound was prepared from *N*-[(*tert*-butoxy)carbonylamino][7-chloro-4-oxo-2-(pyrrolidinylcarbonyl)(3-hydroquinolyl)]-*N*-(3-(4-pyridyl)prop-2-ynyl)carboxamide (0.87 g, 1.59 mmol) according to Method D. The final material was obtained as a light tan solid (396.2 mg, 66%), mp 238−241 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.32 (s, 4H), 5.06 (s, 2H), 7.45 (d, 1H, J = 8.4 Hz), 7.66 (d, 2H, J = 4.5 Hz), 8.04 (s, 1H), 8.15 (d, 1H, J = 8.4 Hz), 8.71 (s, 2H), 12.0 (br s, 1 H, exchangeable), 12.9 (br s, 1 H, exchangeable). Anal. ($C_{19}H_{11}ClN_4O_3$·1.3CH_3SO_3H): C, H, N.

Compound 9ai. 7-Chloro-4-hydroxy-2-(3-(3-pyridyl)prop-2-ynyl)-1,2,5,10-tetrahydropyridazino[4,5-*b*]quinoline-1,10-dione Methanesulfonate. 3-(3-Pyridyl)prop-2-yn-1-ol. To a stirred solution of 1:1 1,2-dimethoxyethane:water (250 mL), under N_2, were added K_2CO_3 (29.5 g, 213 mmol), 3-bromopyridine (10 mL, 103.8 mmol), PPh_3 (3.24 g, 12.4 mmol), copper(I) iodide (1.96 g, 10.30 mmol), and 10% Pd/C (3.22 g, 3.02 mmol Pd). The reaction mixture was stirred for 20 min at rt, and then propargyl alcohol (15 mL, 257.7 mmol) was added. The reaction mixture was heated at 80 °C for 14 h and allowed to cool to rt. The reaction mixture was filtered through diatomaceous earth, and the solids were then washed with H_2O and EtOAc. The combined filtrate and washes were acidified to pH 2−3 using a 2 N HCl solution, and the organic layer was removed *in vacuo*. The remaining aqueous phase was first extracted with toluene (3 × 50 mL), and then its pH was adjusted to 7 by addition of K_2CO_3; the neutral aqueous solution was further extracted with EtOAc (3 × 500 mL). The EtOAc extracts were washed with H_2O, dried over $MgSO_4$, and concentrated *in vacuo*. The residue gave the title compound as a yellow-brown solid (10.07 g, 73% yield); ^{1}H NMR (300 MHz, DMSO-d_6); δ 4.34 (d, 2H, J = 6 Hz); 5.44 (t, 1H, J = 6 Hz); 7.41 (dd, 1H, J = 8 Hz, J = 5 Hz); 7.86 (dt, 1H, J = 8 Hz, J = 2. Hz); 8.56 (d, 1H, J = 5. Hz), 8.63 (s, 1H).

3-(3-Bromoprop-1-ynyl)pyridine Hydrobromide. To a cold (−10 °C), stirred solution of 3-(3-pyridyl)prop-2-yn-1-ol (6.67 g, 50 mmol), in alcohol-free $CHCl_3$ (100 mL) under N_2, was added PBr_3 (3 mL, 8.55 g, 31.6 mmol). The reaction mixture was stirred at −10 °C to 0 °C for 1.5 h and allowed to warm to rt. The upper, clear yellow solution was transferred via a cannula to a new flask, and the remaining brown reaction residue was washed with additional $CHCl_3$ (50 mL) which was then combined with the first $CHCl_3$ wash. Concentration of the combined $CHCl_3$ washes gave the title compound as a pale yellow solid. On vigorous stirring of the residue in $CHCl_3$ (100 mL) which did not dissolve in the $CHCl_3$ washes, a white precipitate formed which was collected by filtration, washed with $CHCl_3$, and air-dried to provide the title compound as a pale yellow solid (total 9.90 g, 70%); ^{1}H NMR (300 MHz, DMSO-d_6); δ 4.61 (s, 2H); 7.86 (dd, 1H, J = 8 Hz, J = 5 Hz); 8.39 (dt, 1H, J = 8 Hz, J = 2 Hz); 8.83 (d, 1H, J = 5. Hz), 8.99 (s,1H).

(*tert*-Butoxy)-*N*-[(3-(3-pyridyl)prop-2-ynyl)amino]carboxamide. To a stirred mixture of *tert*-butyl carbazate (20.07 g, 151.9 mmol) and K_2CO_3 (6.25 g, 45.2 mmol) in dry DMF (50 mL) was added under N_2 a solution of 3-(3-bromoprop-1-ynyl)pyridine hydrobromide (4.50 g, 16.25 mmol) dissolved in DMF (100 mL). The reaction mixture was stirred for 5 h at rt and was filtered through diatomaceous earth to give a clear orange solution. The pad was washed with EtOAc (100 mL) and MeOH (2 × 100 mL). The organic filtrate and washes were combined, poured into water (200 mL), and extracted with Et_2O (3 × 150 mL) followed by EtOAc (2 × 200 mL). The organic extracts were combined, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give a mixture of the desired product and a large excess of remaining *tert*-butyl carbazate. This crude solid (∼43 g) was dissolved in a 1:3 Et_2O: hexanes solution (400 mL) which was washed with saturated aqueous $NaHCO_3$ solution (6 × 200 mL). The organic material was then dried over $MgSO_4$, filtered, and concentrated to give the desired pure product as a yellow oil (2.11 g, 52% yield); ^{1}H NMR (300 MHz, DMSO-d_6); δ 1.39 (s, 9H); 3.73 (d, 2H, J = 4 Hz); 4.89 (b, NH) 7.42 (dd, 1H, J = 8 Hz, J = 5 Hz); 7.84 (d, 1H, J = 8 Hz); 8.42 (b, NH); 8.55 (d, 1H, J = 3. Hz), 8.62 (d, 1H, J = 4 Hz).

(*tert*-Butoxy)-*N*-{[7-chloro-4-oxo-2-(pyrrolidinylcarbonyl)(3-hydroquinolyl)]-*N*-(3-(3-pyridyl)prop-2-ynyl)carbonylamino}-carboxamide. The title compound was prepared from 7-chloro-4-oxo-2-(pyrrolidinylcarbonyl)hydroquinoline-3-carboxylic acid **7** (4.53 g, 14.12 mmol) and (*tert*-butoxy)-*N*-[(3-(3-pyridyl)prop-2-ynyl)amino]carboxamide (3.49 g, 14.11 mmol) as described in Method B except that the reaction was not heated (complete after 14 h at rt). The desired compound was obtained as a yellow solid (1.83 g, 24%).

7-Chloro-4-hydroxy-2-(3-(3-pyridyl)prop-2-ynyl)-1,2,5,10-tetrahydropyridazino[4,5-*b*]quinoline-1,10-dione Methanesulfonate 9ai. The title compound was prepared from (*tert*-butoxy)-*N*-{[7-chloro-4-oxo-2-(pyrrolidinylcarbonyl)(3-hydroquinolyl)]-*N*-(3 -(3-pyridyl)prop-2ynyl)carbonylamino}carboxamide (1.83 g, 3.33 mmol) as described in Method G except that the solids were washed with H_2O, MeOH, and Et_2O and then air-dried. The filtrate was dried overnight at 45 °C *in vacuo* to give the title compound (0.645 g, 40%) as a yellow solid, mp 227−229 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 5.01 (s, 2H); 7.42−7.49 (m, 2H); 7.92 (d, 1H, J = 7 Hz); 8.04 (s, 1H); 8.15 (d, 1H, J = 9 Hz); 8.59 (d, 1H, J = 4

Hz); 8.67 (s, 1H); 11.94 (br s, 1H, exchangeable); 12.81 (br s, 1H, exchangeable). Anal. ($C_{19}H_{11}ClN_4O_3 \cdot 1.2\ H_2O \cdot 1.0\ CH_3SO_3H$): C, H, N.

Compound 9aj. 7-Chloro-4-hydroxy-2-(3-(3-thienyl)prop-2-ynyl)-2,5-dihydropyridazino[4,5-*b*]quinoline-1,10-dione. 3-(3-Thienyl)prop-2-yn-1-ol. To a stirred solution of 1:1 1,2-dimethoxyethane:H_2O (100 mL) were added 3-bromothiophene (4.89 g, 30 mmol), K_2CO_3 (10.3 g, 75 mmol), CuI (0.23 g, 1.2 mmol), PPh_3 (0.64 g, 2.4 mmol), and 10% Pd/C (0.630 g, 0.6 mmol Pd). The reaction mixture was stirred for 20 min at rt, and then propargyl alcohol (7.3 mL, 75 mmol) was added. The reaction mixture was heated at 80 °C for 16 h and allowed to cool to rt. The reaction mixture was filtered through diatomaceous earth, and the filtrate was extracted with EtOAc (350 mL). The EtOAc solution was washed with H_2O (250 mL) and dried over Na_2SO_4. The filtrate was filtered and concentrated *in vacuo* to give an amber oil (4.86 g). This crude product was purified by flash chromatography on silica gel, eluting with 3:2 hexane:EtOAc to give the title compound as a light amber oil (2.57 g, 62%); ^{1}H NMR (300 MHz, DMSO-d_6); δ 4.26 (d, 2H, $J = 6$ Hz); 5.32 (t, 1H, $J = 6$ Hz); 7.15 (dd, 1H, $J = 5.1$ Hz, $J = 0.9$ Hz); 7.57 (m, 1H); 7.75 (m, 1H).

3-(3-Chloroprop-1-ynyl)thiophene. To a stirred solution of 3-(3-thienyl)prop-2-yn-1-ol (2.5 g, 1.8 mmol), Et_2O (25 mL), and Et_3N (5.4 g, 54 mmol) was added thionyl chloride (6.46 g, 54 mmol) at 0 °C. The reaction mixture was allowed to warm to rt and was then heated at reflux for 1 h. The reaction mixture was cooled, and Et_2O (50 mL) was added. The resulting mixture was washed with H_2O (2 × 25 mL) and dried over Na_2SO_4. The Na_2SO_4 was filtered off, and the filtrate was concentrated under reduced pressure to give a brown oil (3.14 g). This crude product was purified by flash chromatography on silica gel, eluting with 1:1 Et_2O:hexanes to give the title compound as an amber oil (1.26 g, 47%); ^{1}H NMR (300 MHz, DMSO-d_6); δ 4.69 (s, 2H); 7.20 (dd, 1H, $J = 5.1$ Hz; $J = 1.2$ Hz); 7.64 (m, 1H); 7.88 (m, 1H).

(*tert*-Butoxy)-*N*-[(3-(3-thienyl)prop-2-ynyl)amino]carboxamide. To a stirred mixture of *tert*-butyl carbazate (10.66 g, 80 mmol), K_2CO_3 (3.3 g, 24 mmol) and dry DMF (30 mL) under N_2 was added 3-(3-chloroprop-1-ynyl)thiophene (1.26 g, 8 mmol). The reaction mixture was stirred overnight (18 h) at rt. The reaction mixture was diluted with H_2O (150 mL), and the resulting mixture extracted with Et_2O (2 × 50 mL). The combined Et_2O extracts were concentrated under reduced pressure, and the residue was dissolved in 1:1 hexanes:Et_2O (100 mL). The resulting solution was washed with H_2O (4 × 50 mL) and dried over Na_2SO_4. The Na_2SO_4 was filtered off, and the filtrate was concentrated under reduced pressure to give an amber oil (2.12 g). This crude product was purified by flash chromatography on silica gel eluting with 1:1 Et_2O:hexanes to give the title compound as an amber oil (1.57 g, 78%); ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.39 (m, 9H); 3.68 (s, 2H); 4.8 (bs, 1H); 7.12 (dd, 1H, $J = 5.1$ Hz, $J = 0.6$ Hz); 7.61 (m, 1H); 7.71 (m, 1H); 8.37 (bs, 1H).

(*tert*-Butoxy)-*N*-{[7-chloro-4-oxo-2-(pyrrolidinylcarbonyl)(3-hydroquinolyl)]-*N*-(3-(3-thienyl)prop-2-ynyl)carbonylamino}carboxamide. The title compound was prepared from 7-chloro-4-oxo-2-(pyrrolidinylcarbonyl)hydroquinoline-3-carboxylic acid **7** (2.0 g, 6.23 mmol) and (*tert*-butoxy)-*N*-[(3-(3-thienyl)prop-2-ynyl)-amino]carboxamide (1.57 g, 6.23 mmol) as described in Method B except that the reaction was stirred at rt for 0.5 h heated at 50 °C for 10 min and then allowed to cool to rt, the reaction mixture was filtered, and the filter cake was washed with THF (2 × 20 mL). After purification, the desired title compound was obtained as a yellow foam (2.26 g, 64%).

7-Chloro-4-hydroxy-2-(3-(3-thienyl)prop-2-ynyl)-2,5-dihydropyridazino[4,5-*b*]quinoline-1,10-dione 9aj. The title compound was prepared from (*tert*-butoxy)-*N*-{[7-chloro-4-oxo-2-(pyrrolidinylcarbonyl)(3-hydroquinolyl)]-*N*-(3-(3-thienyl)prop-2ynyl)-carbonylamino}carboxamide (1.26 g, 2.2 mmol) as described in Method G except that the collected solids were successively washed with H_2O (2 × 25 mL) and MeOH (2 × 25 mL) and then dried at 50 °C *in vacuo* to give title compound as a beige powder (502 mg, 59%); mp 248−250 °C; ^{1}HNMR (300 MHz, DMSO-d_6): δ 4.92 (s, 2H); 7.15 (dd, 1H, $J = 5.1$ Hz, $J = 1.2$ Hz); 7.44 (dd, 1H, $J = 8.7$ Hz, $J = 1.8$ Hz); 7.59 (m, 1H); 7.7 g (m, 1H); 8.03 (d, 1H, $J = 1.5$ Hz); 8.15 (d, 1H, $J = 1.5$ Hz); 11.98 (s, 1H); 12.85 (s, 1H). Anal. ($C_{18}H_{10}ClN_3O_3S.0.75\ H_2O$): C, H, N.

Compound 9ak. 7-Chloro-4-hydroxy-2-(3-(2-thienyl)prop-2-ynyl)-2,5-dihydropyridazino[4,5-*b*]quinoline-1,10-dione. 3-(2-Thienyl)prop-2-yn-1-ol. The title compound was prepared from 2-iodothiophene (6.30 g, 30 mmol) and propargyl alcohol (7.3 mL, 75 mmol) as described for 3-(3-thienyl)prop-2-yn-1-ol except that the diatomaceous earth was washed with DME (3 × 20 mL), and the crude residue was purified by flash chromatography on silica gel using a gradient of 75:25 to 50:50 hexanes:Et_2O as the eluent. The desired compound was obtained as a light beige oil (2.90 g, 70%); ^{1}H NMR (300 MHz, DMSO-d_6); δ 4.32 (d, 2H, $J = 6$ Hz); 5.38 (t, 1H, $J = 6$ Hz); 7.07 (m, 1H); 7.30 (d, 1H, $J = 2.7$ Hz); 7.58 (dd, 1H, $J = 5.1$ Hz; $J = 1.2$ Hz).

2-(3-Chloroprop-1-ynyl)thiophene. The title compound was prepared from 3-(2-thienyl)prop-2-yn-1-ol (2.9 g, 21 mmol) as described for 3-(3-thienyl)prop-2-yn-1-ol except that the reaction mixture was cooled and concentrated under reduced pressure to give a brown oil which was purified directly by flash chromatography on silica gel, eluting with CH_2Cl_2:MeOH (1:1) to give the title compound as an amber oil (3.2 g, 98%).

(*tert*-Butoxy)-*N*-[(3-(2-thienyl)prop-2-ynyl)amino]carboxamide. The title compound was prepared from 2-(3-chloroprop-1-ynyl)-thiophene (3.20 g, 20.4 mmol) and *tert*-butyl carbazate (27.075 g, 204.8 mmol) as described for (*tert*-butoxy)-*N*-[(3-(3-thienyl)prop-2-ynyl)amino]carboxamide except that the reaction mixture was extracted with EtOAc (2 × 100 mL) and the combined organic extracts were washed with H_2O (2 × 100 mL). After removal of the solvent *in vacuo*, the residue (3.4 g) was purified by flash chromatography on silica gel using 1:1 hexane:Et_2O as the eluent to give the desired product as a light amber oil (1.6 g, 32%).

(*tert*-Butoxy)-*N*-{[7-chloro-4-oxo-2-(pyrrolidinylcarbonyl)(3-hydroquinolyl)]-*N*-(3-(2-thienyl)prop-2-ynyl)carbonylamino}carboxamide. The title compound was prepared from 7-chloro-4-oxo-2-(pyrrolidinylcarbonyl)hydroquinoline-3-carboxylic acid **7** (2.03 g, 6.34 mmol) and (*tert*-butoxy)-*N*-[(3-(2-thienyl)prop-2-ynyl)-amino]carboxamide (1.60 g, 6.34 mmol) according to Method B except that the collected solids were washed with THF (20 mL). The desired product was obtained as a yellow foam (1.24 g, 35%).

7-Chloro-4-hydroxy-2-(3-(2-thienyl)prop-2-ynyl)-2,5-dihydropyridazino[4,5-*b*]quinoline-1,10-dione 9ak. The title compound was prepared from (*tert*-butoxy)-*N*-{[7-chloro-4-oxo-2-(pyrrolidinylcarbonyl)(3-hydroquinolyl)]-*N*-(3-(2-thienyl)prop-2ynyl)-carbonylamino}carboxamide (1.24 g, 2.20 mmol) as described in Method G except that following isolation by filtration the solids were slurried and filtered twice from CH_2Cl_2 (2 × 25 mL) and then dried overnight at 50 °C *in vacuo* to give title compound as a beige powder (0.287 g, 34% yield); mp = 235−237 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.99 (s, 2H); 7.06 (t, 1H, $J = 4.4$ Hz); 7.33 (d, 1H, $J = 3.3$ Hz); 7.44 (d, 1H, $J = 8.4$ Hz); 7.61 (d, 1H, $J = 4.8$ Hz); 8.03 (s, 1H); 8.15 (d, 1H, $J = 8.7$ Hz); 11.98 (s, 1H); 12.86 (s, 1H); Anal. ($C_{18}H_{10}ClN_3O_3S \cdot 1.0\ H_2O$): C, H, N

Biological/Physical Properties Assays. [^{3}H]-MDL105,519 Binding Assay. Fresh rat brain tissue including cortex and hippocampus was homogenized in 0.32 M sucrose and centrifuged at low speed to separate cell membrane from the rest of cell parts. The membranes were washed three times using deionized water, followed by treatment with 0.04% Triton X-100. Membranes were then washed six times in 50 mM Tris-acetate, pH 7.4, and frozen. The rat brain membranes were stored at −80 °C. The day of the experiment brain membranes were thawed and suspended in Tris-acetate buffer (50 mM Tris-acetate, pH 7.4). For competition, binding membranes (85 mg/mL) were incubated with 1.2 nM [^{3}H]-MDL105,519 (72Ci/mmol) for 30 min at rt in a total volume of 250 μL. Then, 100 μM of unlabeled MDL105,519 was used to define nonspecific binding. Compounds were dissolved as 10 or 1 mM stock solutions in water or dimethyl sulfoxide (DMSO). DMSO concentration was kept below 1%. Unbound [^{3}H]-MDL105,519 was

separated from bound by filtration on to GF/B Uniplates using Packard harvester. Filters were washed 3−5 times with ice cold binding buffer. The plates were left to dry overnight. A 35 μL amount of the microscint O was added to each well, and bound radioactivity was counted on a Packard Top Count.

Measurement of Aqueous Solubility. A known amount of test compound was incubated in 0.1 M pH 7.4 sodium phosphate buffer with or without 0.26 N NaCl for 24 h at 25 °C in a 1.5 mL centrifuge tube. After centrifugation at 12000 rpm for 30 min, the supernatant was transferred to a new vial and analyzed by HPLC-UV. A standard solution of the test compound dissolved in DMSO was used as the calibration standard for quantitation.

Measurement of log *D*. The octanol−water partition coefficient (log *D*) of test compound was determined based on the shake-flask principle using volume ratio of 10 mL 0.01 M octanol saturated sodium phosphate buffer at pH 7.4 and 100 μL of buffer saturated octanol. The aqueous buffer layer was sampled both before and after partitioning and quantified by HPLC-UV. Log *D* was calculated by the following equation log D = log(100 ([before − after]/[after])).

Bioavailability Measurements. Fed male Sprague Dawley rats were surgically prepared by inserting a cannula into the carotid artery for the purpose of taking blood samples. Following a 2-day recovery period, compounds were administered either orally or intravenously at 10 mg/kg as a solution formulation in either meglumine or hydroxypropyl-β-cyclodextrin/buffer. Blood samples were taken from the cannula over a 24 h period, and the plasma was analyzed for unchanged compound. Using polypropylene wherever possible, plasma standards and samples were diluted 1:3 with acidified (H_3PO_4) CH_3CN. Following centrifugation to remove protein, the supernatant was transferred to a clean tube and diluted 1:1 with H_2O. The samples were analyzed by reversed phase liquid chromatography with acidified (TFA or formic acid) H_2O/CH_3CN mobile phase gradient elution. Concentrations of parent compounds were quantitated using ultraviolet or mass selective (MSD) detection. The standards were fit to a calibration curve using a quadratic fit over a concentration range of 0.050 to 100 μg/mL plasma. Oral bioavailability was calculated by comparing the area under the plasma concentration curve from zero to infinity [$AUC_{(0-\infty)}$] values following oral and intravenous dosing.

Chronic Constriction Injury (CCI) Neuropathy Assay.[34] Sprague−Dawley rats (175−200 g) are anesthetized with sodium pentobarbital, and the common sciatic nerve is exposed at the level of the mid thigh by blunt dissection through the biceps femoris. A section of nerve (about 7 mm), proximal to the sciatic trifucation, is freed of tissue and ligated four times with 4-0 chromic gut suture. The suture is tied with about 1 mm spacing between ligatures. The incision is closed in layers and the animals are allowed to recover. Thermal hyperalgesia is measured using the paw-withdrawal test.[34b] Animals are habituated on an elevated glass floor. A radiant heat source is aimed at the mid-plantar hindpaw (sciatic nerve territory) through the glass floor. The latencies for the withdrawal reflex in both paws are recorded. A 20 s cutoff is used to prevent permanent injury to the skin. Injured paws with ligated nerves show shorter paw withdrawal latencies compared to the uninjured or sham operated paws. Response to test compounds is evaluated following oral administration to determine onset and duration of drug effect. Dose−response studies are conducted with multiple groups of CCI rats dosed orally with either vehicle or the test compound for 5 days. Paw withdrawal latencies are measured each day prior to the first daily dose. Data analysis is performed by multiple means comparison (Dunnett's test) and compound potencies are expressed by their minimum effective dose.

Acknowledgment. The authors thank the numerous researchers on the original NMDA glycine-site antagonist program targeted at the treatment of stroke for paving the way for this effort. We thank the following: Brian Law and George Stratton for generation of the HTBLA data; Jian Huang and Vesudha Garlapati for *in vitro* screening; JoAnne Smolka, Chris Tyler, and Sheree Logue for *in vivo* pharmacology studies; Mary Jo Bock for bioanalysis; Yun Alelyunas, James A. Osborn, and Bill George for physical property determinations; David Gurley for molecular pharmacology studies; Jim Hall for NMR assistance; Tim Blake for HPLC-MS determinations; Bill Michne for scientific discussions. We also acknowledge the efforts of the custom synthesis laboratory at AstraZeneca-Wilmington and the AstraZeneca process chemistry group at Macclesfield in the UK for providing large-scale synthetic intermediates for use in this program.

Supporting Information Available: Elemental analysis and HPLC data. This material is available free of charge via the Internet at http://pubs.acs.org.

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JM060212S