Non-Peptide RGD Surrogates Which Mimic a Gly-Asp β-Turn: Potent Antagonists of Platelet Glycoprotein IIb−IIIa

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Cyclic heptapeptide **1**, which contains an Arg-Gly-Asp sequence, has good affinity for the platelet receptor GPIIb−IIIa and was chosen for study by ^{1}H NMR techniques. The key RGD sequence of this molecule was found to reside in a conformationally defined type II′ Gly-Asp β-turn, and this information was used in the design of simple non-peptide RGD mimics. Disubstituted isoquinolones, bearing an acidic side chain at position 2 and a basic side chain at position 6, were prepared and were found to have modest affinity for GPIIb−IIIa. Systematic modification of the basic residue contained in these molecules yielded compounds with high affinity for GPIIb−IIIa.

Introduction

Activation of platelets by a variety of agonists promotes binding of the plasma−proteins fibrinogen and von Willebrand factor and leads to the formation of platelet aggregates. This aggregation phenomenon is mediated by membrane-associated glycoprotein (GP) IIb−IIIa, to which fibrinogen and other adhesive ligands bind.[1−3] While platelets play a vital role in hemostasis, uncontrolled aggregation can lead to occlusive thrombotic disorders.[4,5] Therefore, the search for agents that can modulate platelet function has been a significant area of pharmaceutical research.[6] Inhibition of platelet activation provides a means of controlling aggregation, however, due to the large number of known activating agonists, this approach has limitations. An alternative strategy would be to inhibit the final common pathway, the binding of fibrinogen to GPIIb−IIIa, thus controlling aggregation irrespective of the activator.[7,8]

The binding of fibrinogen to platelet GPIIb−IIIa is known to occur through the interaction of activated GPIIb−IIIa with at least one of two RGD (arginine-glycine-aspartic acid) tripeptide sequences located at positions 95−97 and 572−574 on the α-chain of fibrinogen.[9−12] The RGD motif has therefore become the template for development of platelet aggregation inhibitors, and extensive chemical modifications of this sequence have narrowed the functional groups required for activity to the basic group of the arginine and the acidic group of the aspartate.[13,14] Activity is not seriously affected by changing the nature of the basic residue in the arginine moiety but the configuration and length of the acidic side chain of the aspartate moiety, are critical for activity.[15] The above findings were instrumental in the discovery of modified linear peptides with enhanced activity toward GPIIb−IIIa.[16] Constraining modified RGD sequences by cyclization has also led to compounds with significantly greater affinity for GPIIb−IIIa.[17−26]

While several of these modified peptides have a clinically attractive profile for parenteral use,[6a] the metabolic liability of amide bonds may limit their use as oral drugs. Accordingly, much effort has been put into the search for non-peptide antagonists of GPIIb−IIIa. A wide variety of non-peptide antagonists of GPIIb−IIIa have been discovered using a number of methods including compound screening, modification of RGD peptides, and structure-based design.[27−43] The latter method relies on the use of structural information obtained from known biological entities (either receptor or ligand) in the design of small molecule leads. This approach may have limitations in that the experimentally determined structure may or may not represent an active conformation. Nevertheless, such data is a potentially powerful aid in the design of molecules which have the desired biological activity. Compounds identified by this approach can in turn be optimized through standard medicinal chemistry techniques. We herein describe our approach to the rational design of GPIIb−IIIa antagonists which utilized the elements of peptide structural evaluation and classic medicinal chemistry.

Structural Evaluation

As discussed, the RGD motif represents an attractive template for structure-based drug design. In an effort to understand the spatial relationship between the key pharmacophores in this sequence, a number of small peptide fragments have been examined by NMR. However, as linear peptides are quite flexible, little concrete information about the active conformation was obtained.[44] Similar results were obtained from the NMR analysis of a series of snake venom proteins (disintegrins). In these cases, the RGD motif was contained in a long flexible loop which provided little insight into mimetic design.[45,46] Recently, small, highly active RGD-containing cyclic peptides have been synthesized and studied by NMR. Significant conformational detail was obtained about the RGD triad, and this information was successfully used in the design and synthesis of active GPIIb−IIIa antagonists.[36,37,40]

We have reported the synthesis and optimization of a variety of RGD-containing cyclic peptides with high affinity toward GPIIb−IIIa.[23] Many of these molecules

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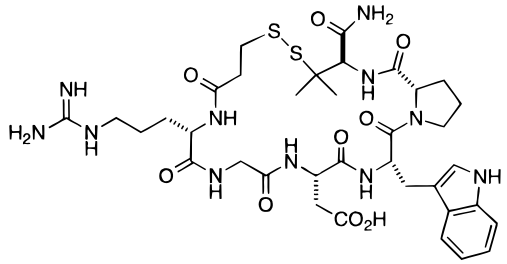


Figure 1. Structure of cyclic peptide **1**.

are heptapeptides containing a modified "RGD" sequence cyclized via an N-terminal mercaptopropionate (Mpr) and a C-terminal penicillamine (Pen). We have examined one of these peptides (**1**) using ^{1}H NMR methods with a view toward defining the conformation of the RGD region (Figure 1). The data from these experiments permitted proton assignment utilizing the classical "Wüthrich" method.[52] Spectra indicated two complete sets of resonances with a ratio of 1:2 and were attributed to the presence of *cis/trans* isomers at the Trp-Pro amide bond. Isomer assignment was based on NOE's observed across this amide bond, and integration of the Trp aromatic proton signals revealed that the *trans* form predominated. We evaluated the *trans* isomer but were aware that either isomer could represent the active species.

Using the proton assignments, distance constraints could be designated from the cross peaks in the 2D-ROESY[53] experiment, and ultimately 15 were identified for use in subsequent calculations. All ROESY cross peaks were assigned to either intraresidue or sequential NOE's, and no long-range NOE's were observed. The Trp-5 amide proton was found to be resistant to D_2O exchange, suggesting its involvement in hydrogen bonding. While the Trp amide plays an important role in the solution conformation, the identity of its hydrogen bond acceptor could not be determined directly by NMR experiments.

Given the constraints of the peptide backbone connectivity and the observed NOE measurements, the carbonyl oxygens of the Mpr, Pen, and Arg residues were potentially accessible for hydrogen bonding to the Trp amide proton. In order to ascertain the identity of the acceptor, each of these possible hydrogen-bond partners were evaluated using distance geometry calculations. When the hydrogen bond was constrained between Trp-5 and the Pen-7, the resulting structures had large violations in backbone connectivity and NOE constraints, thus precluding the Pen-7 carbonyl from being the acceptor. Calculations with the Mpr and the Arg carbonyl oxygen atoms gave structures that did not violate any of the constraints by more than 1.0 Å, indicating that both of these hydrogen bonds were reasonable. Closer examination of the data, however, revealed that conformations having a Trp-Arg hydrogen bond were better able to satisfy all of the NOE distance constraints and possessed lower overall energies than structures with a Trp-Mpr hydrogen bond. As a result, we chose to evaluate the RGD region of structures that included a Trp-Arg hydrogen bond.

The possible types of conformations for the RGD sequence and how well each satisfied the aforementioned constraints were determined next. The Trp-Arg structures, which showed β-turns at the Gly-Asp position, were classified based on the ϕ,ψ angles through

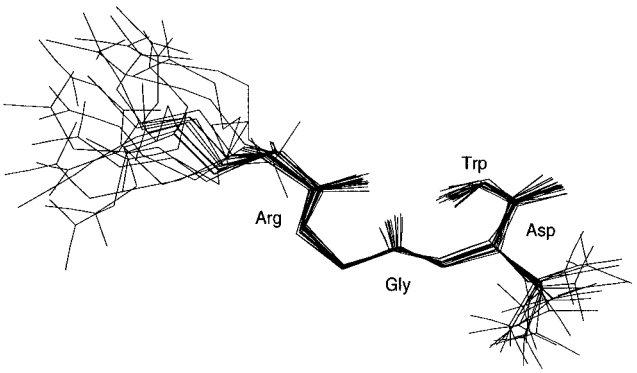


Figure 2. View of the type II′ β-turn structures resulting from a Trp-Arg hydrogen bond. Shown is the backbone of the Arg-Gly-Asp region along with the Trp amide nitrogen and proton.

the RGD triad. In all, five distinct families were identified, with examples of type I′, II, II′, III, and III′ β-turns being observed in the minimized structures of **1**; nearly half of the structures fell into the type II′ classification. To determine how well the families satisfied the experimental constraints, each was evaluated on the basis of their NOE violations. Both the type II and II′ turns consistently satisfied the entire set of constraints better than any of the other families. Thus the NOE data is most consistent with a Trp-Arg hydrogen bond and with the RGD sequence adopting a Gly-Asp type II or II′ turn. Since a majority of the calculated structures fell into the type II′ family, this structure was used as the basis for design considerations. The critical Gly-Asp segment of this structure is shown in Figure 2.

The design of the inhibitors described in this report followed directly from analysis of the structure illustrated in Figure 2. Noteworthy is the fact that the Asp and Arg side chains are flexible, but their point of attachment to the backbone and the backbone itself appear well ordered. The side chain of the aspartate and the arginine residues are roughly in the same plane and diagonally disposed across a slightly cupped Gly-Asp β-turn. Our working hypothesis for compound design was that the side chains of the aspartate and arginine residues played the dominant role in binding to GPIIb−IIIa and that other functionality found in the RGD sequence was of lesser importance. Therefore, non-peptide templates that would approximate the observed β-turn and fix these key groups close to the geometry suggested by Figure 2 were initial candidates for synthesis.

The exact nature of the β-turn surrogate was made apparent after studying a two-dimensional representation (Figure 3) of the partial structure shown in Figure 2. The turn itself contains 10 atoms and bears a resemblance to a decalin ring system substituted at the 2 and 6 positions with an acidic moiety and a basic moiety, respectively. Further analysis of this structure indicated that the basic side chain attaches to the pseudo A ring via an sp^2 center while the acidic side chain emanates from the pseudo B ring via an sp^3 center. We therefore chose to mimic this turn with a linearly fused 6,6 ring system in which the A ring was aromatic and the B ring was aliphatic. Using these considerations, we felt that an appropriately substituted 3,4-dihydro-1-oxoisoquinolone[54] would make a reasonable starting point for synthesis.

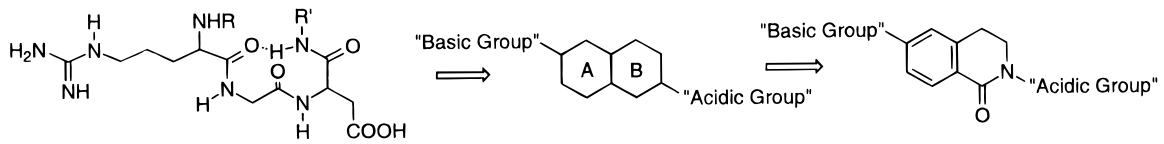
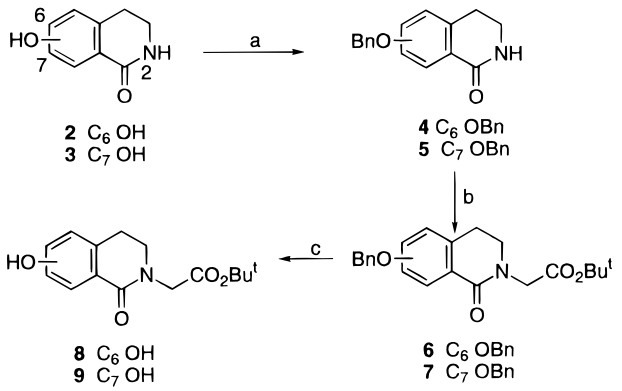


Figure 3. Two-dimensional representation of the Gly-Asp β-turn shown in Figure 2 along with idealized β-turn surrogates.

Scheme 1[a]



[a] (a) BzlBr/K_2CO_3; (b) NaH/*tert*-butyl bromoacetate; (c) H_2/PdC.

Chemistry

Isoquinolones **8** and **9** served as the foundation for all of the compounds described in this paper. Their synthesis is outlined in Scheme 1 and begins with protection of the free phenol functionality of **2** and **3**[55] with benzyl bromide which provided lactams **4** and **5**. These compounds were alkylated on nitrogen with *tert*-butyl bromoacetate to give monosubstituted derivatives **6** and **7**. The benzyl group was then removed with catalytic palladium and hydrogen to afford phenols **8** and **9**.

Compounds containing a C_6 ether-linked primary alkyl amine or guanidine were prepared as outlined in Scheme 2. In the first step, phenol **8** was allowed to react with phthalimido bromides **10a**−**f** (Table 1) in the presence of K_2CO_3 to yield derivatives **11a**−**f**. The phthalimide moiety was removed with excess aqueous hydrazine in ethanol. Treatment of the crude amine with TFA provided amino acids **12a**−**f**. The guanidine-containing compounds **14a**−**f** were obtained in a similar manner. Removal of the phthalimide with hydrazine followed by reaction of the crude amine with *N,N′*-bis-(*tert*-butoxycarbonyl)-*S*-methoxyisothiourea afforded the protected guanidines **13a**−**f**.[56] Complete deprotection was accomplished with neat TFA which provided the desired guanidino acids **14a**−**f** as their TFA salts. Both the amine- and the guanidine-containing compounds were subjected to salt exchange with HCl, as their TFA salts proved to be deliquescent. Compounds containing C_7 ether-linked alkyl guanidines were prepared from **9** in a like manner.

Incorporation of C_6 ether-linked 4-alkyl piperidines was accomplished in a similar fashion (Scheme 3). Bromides **17a**−**d** (Table 2) were allowed to react with phenol **8** in the presence of K_2CO_3 to provide adducts **18a**−**d**. These materials were subjected to TFA deprotection and salt exchange with HCl to yield piperidino acids **19a**−**d**.

Ether-linked benzamidine-substituted isoquinolones were prepared as outlined in Scheme 4. Alkylation of phenols **8** and **9** with 4-cyanobenzyl bromide in the presence of K_2CO_3 provided nitriles **20** and **21**. The two-carbon congener **26** was prepared by coupling 4-cyanophenethanol with phenol **8** using Mitsunobu [57] conditions. The nitrile moiety contained in these molecules was transformed into a BOC-protected amidine by using a series of transformations, namely (1) conversion to the thioamide with H_2S, (2) alkylation with methyl iodide, (3) reaction of the intermediate thioimidate with ammonium acetate, and (4) Boc protection of the formed amidine to provide **22, 23,** and **27**.[58] Removal of the Boc and *tert*-butyl moieties was accomplished simultaneously with neat TFA to afford the desired amidino acids **24, 25,** and **28**.

Compounds containing alkyl substitution at C_6 were prepared via triflate **29** as outlined in Scheme 5. Triflate **29** was allowed to react with (4-cyanophenyl)-acetylene[59] in the presence of palladium to provide acetylenic compound **33**.[60] The nitrile moiety in **33** was transformed into a Boc-protected benzamidine **34** using the same series of reactions previously described. Selective hydrogenation of **34** with palladium on $BaSO_4$ yielded the *cis*-olefin **36** while palladium on carbon afforded the alkane **38**. Bis deprotection of these compounds with TFA provided the desired amidino acids **35**, **37**, and **39**. Reaction of triflate **29** with 4-cyanostyrene by the method of Heck[61] afforded the *trans*-olefin **30**. Conversion of the nitrile **30** into the BOC-protected amidine **32** was uneventful, and deprotection with TFA afforded amidino acid **32**.

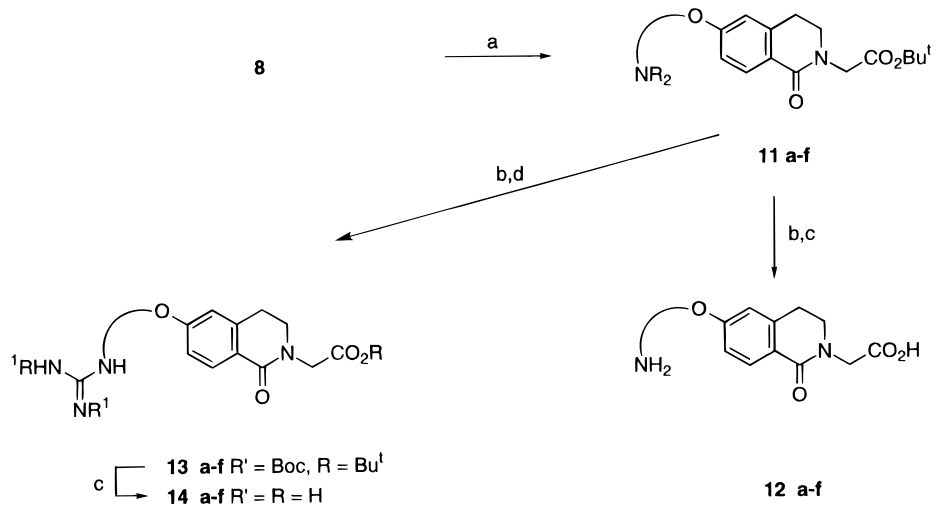
Triflate **29** also provided access to derivatives containing a C_6 acyl moiety (Scheme 6). Palladium-catalyzed carbon monoxide insertion in the presence of methanol afforded ester **40**, which could be selectively saponified with aqueous LiOH in THF to yield benzoic acid **41**. Treatment of acid **41** with oxalyl chloride and subsequent reaction with 4-aminobenzonitrile provided amide **47**. Transformation of this material into the desired amidino acid **49** was accomplished using the sequence previously described for the preparation of **24**.

An isoquinolone analog which contained C_6 nitrogen substitution was prepared from the acid **41** by Curtius rearrangement.[62] Treatment of **41** with diphenyl phosphorazidate in toluene at 85 °C smoothly effected conversion to the corresponding isocyanate which was not isolated but was reacted with benzyl alcohol to provide carbamate **42**. Catalytic hydrogenation over palladium on carbon produced aniline **43**, which was allowed to react with 4-cyanobenzoic acid in the presence of EDCI to give amide **44**. Transformation of this compound into the desired amidino acid **46** was accomplished as for previous benzamidines.

Results

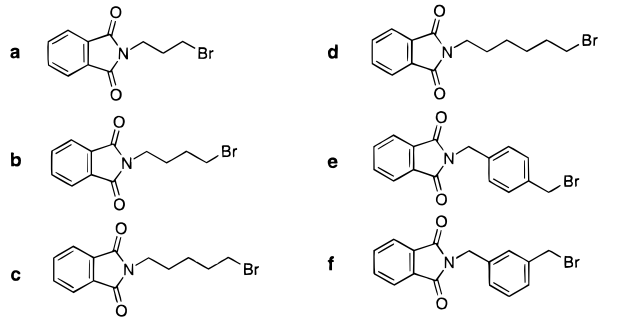
Compounds were evaluated for activity initially with an ELISA assay which employed purified human platelet GPIIb−IIIa and measured the inhibition of fibrinogen binding to immobilized GPIIb−IIIa. Compounds which displayed appropriate activity in this assay (IC_{50} < 1 μM) were further characterized in a functional assay which measured the compound's ability to inhibit the

Scheme 2[a]



[a] (a) **10a**−**f**/K_2CO_3; (b) NH_2NH_2; (c) TFA; (d) BocNHC(NBoc)SCH_3.

Table 1. Alkylating Agents **10**

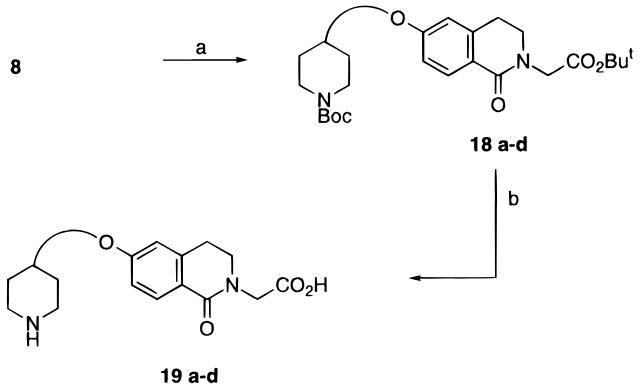


aggregation of human platelets induced by ADP (5 μM) in platelet-rich plasma (PRP). Peptide **1,** which afforded an IC_{50} of 0.035 μM in the ELISA assay and inhibited ADP induced platelet aggregation with an IC_{50} of 0.3 μM, served as a benchmark throughout this study.

The first series of compounds was designed to test the predictions afforded by the solution conformation of **1**. Four compounds were prepared (**14a**,**b**, **15**, and **16**) in which the length (four vs five atoms) and position (C_6 vs C_7) of the basic residue were varied (see Table 3). Compound **14a**, which contains a C_6-linked arginine isostere and represents an atom-for-atom mimic of the β-turn depicted in Figure 2, showed modest affinity for GPIIb−IIIa (IC_{50} = 44 μM, ELISA). The C_7 isomeric compound **15** was found to be inactive at concentrations of 100 μM in the ELISA assay. Elongation of the tether between the guanidine moiety and the backbone surrogate in each isomer by one carbon was beneficial for both series with the C_6 substitution (**14b**) maintaining better overall activity. With these simple arginine mimics, C_6 substitution afforded compounds with somewhat greater affinity for GPIIb−IIIa than those with the basic moiety attached to C_7.

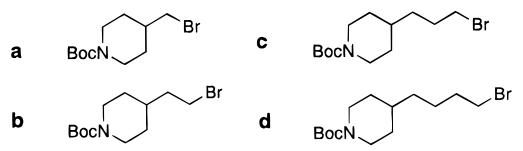
At this point, either series could have served as a lead for further optimization. The activity difference between **14b** (C_6 substitution) and **16** (C_7 substitution), while not large, did serve to focus our attention on compounds containing a C_6-linked arginine isostere. The relationship between activity and the length of the tether, as well as the nature of the basic group (Table 3), was examined next. Increasing the distance between

Scheme 3[a]



[a] (a) **17a**−**d**, K_2CO_3; (b) TFA.

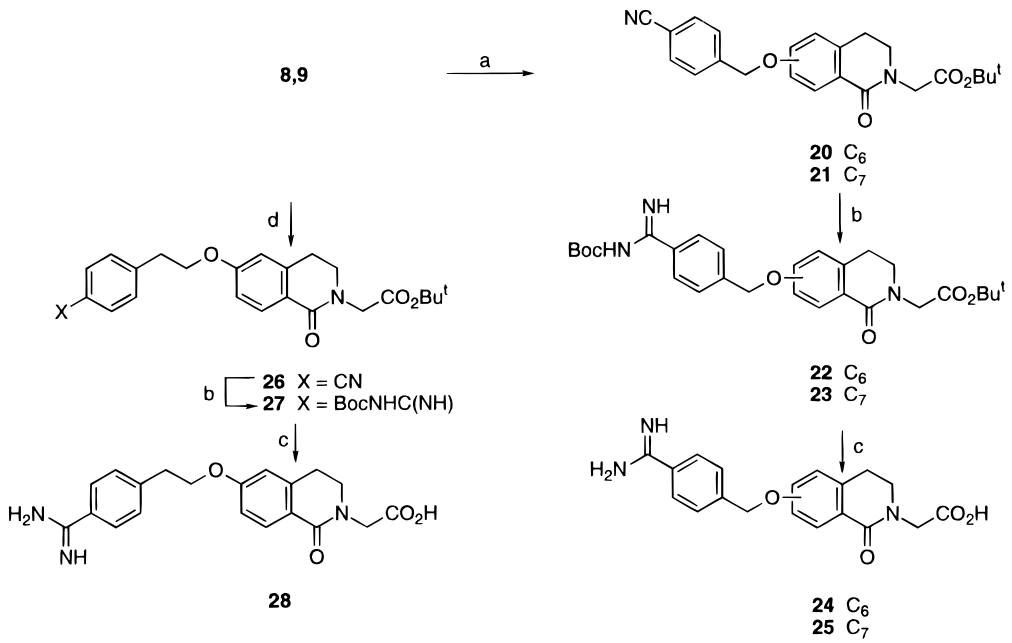
Table 2. Alkylating Agents **17**



the guanidine moiety and the isoquinolone nucleus with a chain length of four or five carbons gave modest improvements in activity (ELISA). Introduction of conformational constraint into this chain by incorporating a *para*-substituted phenyl ring (**14e**) increased activity while *meta* substitution (**14f**) decreased activity to relative to **14e**. The corresponding primary amine containing analogues **12a**−**f** followed the same trend as their guanidine-containing counterparts **14a**−**f** and afforded similar activity (Table 3). Piperidine-containing compounds displayed similar activity as evidenced by derivatives **19a**−**d** (Table 4). The cyclic secondary amine construct offers an advantage in activity (ELISA) over its amine or guanidine counterpart, and with the chain length of four carbons, modest inhibition of platelet aggregation (PRP) was observed.

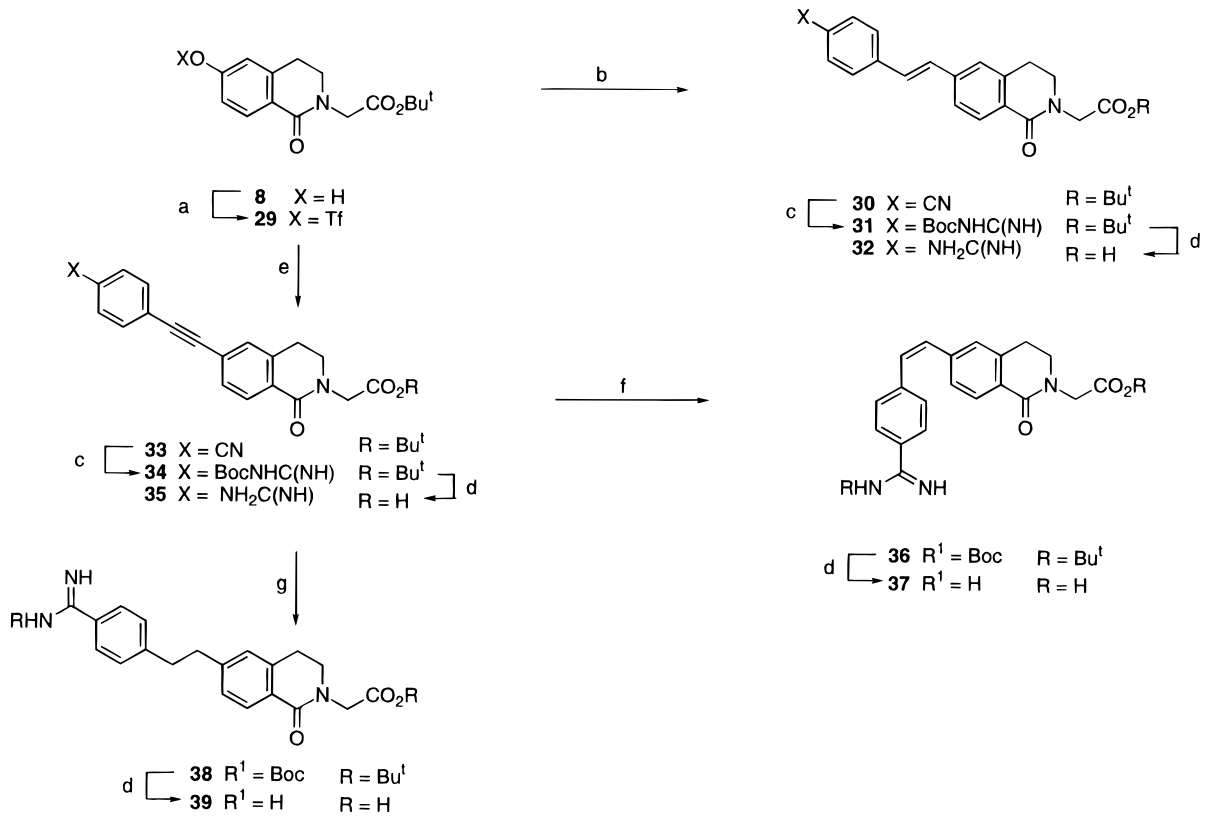
Replacing the flexible basic side chain with a benzamidine moiety afforded analog **24**, which displayed submicromolar activity (IC_{50} = 0.6 μM) in the ELISA (Table 5). Increasing the linkage by one methylene unit (**28**) resulted in a loss of activity and suggested the

Scheme 4[a]



[a] (a) α-Bromo-*p*-tolunitrile/K_2CO_3; (b) H_2S; CH_3I; NH_4OAc; Boc_2O; (c) TFA; (d) 4-cyanophenethyl alcohol, diethyl azodicarboxylate, Ph_3P.

Scheme 5[a]

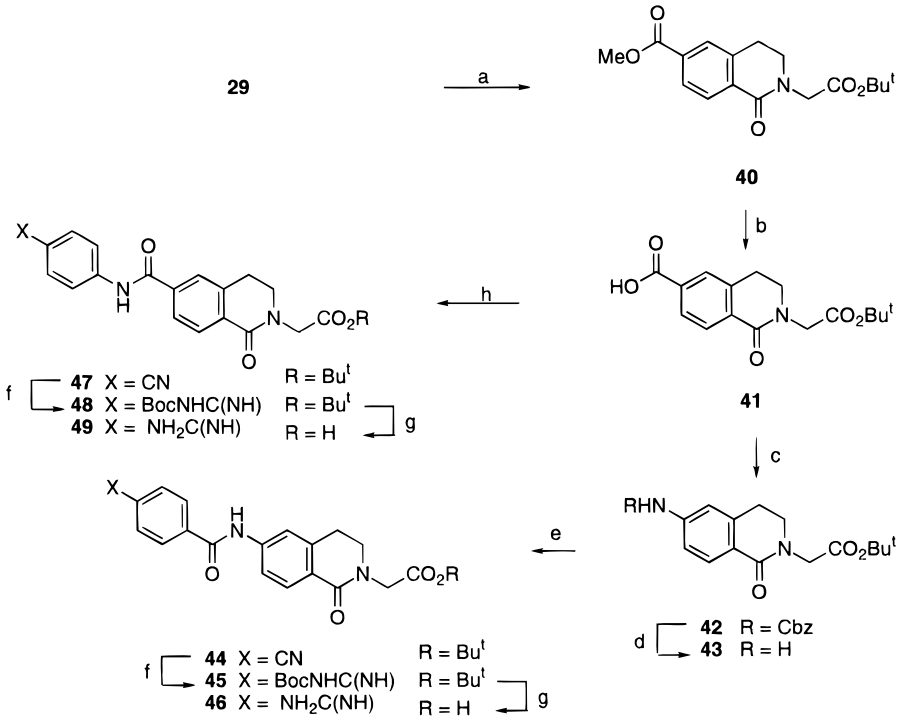


[a] (a) Tf_2O; (b) 4-cyanostyrene, $Pd(Ph_3P)_4$; (c) H_2S, MeI, NH_4OAc, Boc_2O; (d) TFA; (e) (4-cyanophenyl)acetylene, $Pd(Ph_3P)_2Cl_2$; (f) H_2, $Pd/BaSO_4$; (g) H_2, Pd/C.

single-carbon spacer was preferred. In order to verify our earlier findings regarding optimum placement of the basic side chain on the isoquinolone nucleus, the C_7-substituted isomer **25** was prepared. Activity data (ELISA) confirmed that C_7 substitution was less optimal than C_6 substitution.

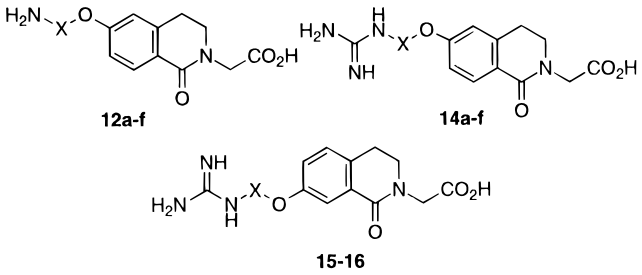
Since the benzamidine moiety afforded an increase in activity, its connectivity to the isoquinolone nucleus was next examined (Table 5). Replacement of the ether oxygen of **24** by a methylene provided compound **39**, which displayed a 5-fold activity increase in the ELISA and a 25-fold increase in the aggregation assay. Exchange of the alkyl linker for an acetylene linker gave linear construct **35**, which provided a further modest increase in activity (0.033 μM, ELISA; 0.52 μM, PRP). Partial hydrogenation of **35** provided a *cis* linkage (**37**)

Scheme 6[a]



[a] (a) CO, MeOH, $Pd(Ph_3P)_4$; (b) LiOH; (c) diphenyl phosphonazidate/BzlOH; (d) H_2, Pd/C; (e) 4-cyanobenzoic acid; (f) H_2S, MeI, NH_4OAc, Boc_2O; (g) TFA; (h) 4-aminobenzonitrile.

Table 3. Activity Data for Alkylamine- and Guanidine-Containing Isoquinolones

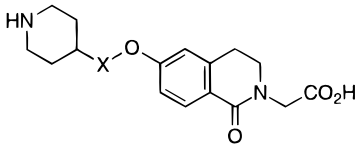


compd	X	ELISA IC_{50} (μM)[a]
12a	$(CH_2)_3$	48
12b	$(CH_2)_4$	18
12c	$(CH_2)_5$	28
12d	$(CH_2)_6$	19
12e	*p*-$CH_2(C_6H_4)CH_2$	12
12f	*m*-$CH_2(C_6H_4)CH_2$	77
14a	$(CH_2)_3$	44
14b	$(CH_2)_4$	10
14c	$(CH_2)_5$	9
14d	$(CH_2)_6$	12
14e	*p*-$CH_2(C_6H_4)CH_2$	4
14f	*m*-$CH_2(C_6H_4)CH_2$	14
15	$(CH_2)_3$	<100
16	$(CH_2)_4$	46

[a] Concentration required to reduce binding of fibrinogen to purified GPIIb−IIIa by 50%. The IC_{50} values are expressed as the average of at least two determinations. The average error for the IC_{50} determinations was ±15%.

which introduced a bend into the molecule and caused activity to decrease by 7-fold (ELISA, 0.29 μM). The isomeric *trans* compound **32**, which provided a linear relationship between the amidine and the nucleus, was roughly equipotent with **35** in the ELISA and slightly more active in the platelet aggregation assay.

Table 4. Activity Data for Alkylpiperidine-Containing Isoquinolones



compd	X	ELISA IC_{50} (μM)[a]	PRP IC_{50} (μM)[b,c]
19a	CH_2	55	nt
19b	$(CH_2)_2$	11	nt
19c	$(CH_2)_3$	6	nt
19d	$(CH_2)_4$	1.8	9.8

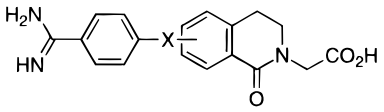
[a] As in Table 1. [b] Concentration required to reduce ADP-induced human platelet aggregation response by 50%. The IC_{50} values are expressed as the average of at least two determinations. The average error for the IC_{50} determinations was ±16%. [c] nt = not tested.

These results suggested that activity was enhanced with increased rigidity between the amidine moiety and the supporting nucleus and that a linear or *trans* array about the two linking atoms was preferred. In an effort to further probe this area of the molecule, heteroatom-based linkers that provided a *trans* geometry were examined. Toward this end, amides **46** and **49** were prepared. The amide analog derived from C_6 carboxyl substitution (**49**) was similar in potency to compound **32**, again indicating that a *trans* orientation was optimal, while the reversed amide (**46**), derived from a C_6 amine, showed a 1 order of magnitude increase in both ELISA and aggregation assays.

Discussion

Examination of the literature reveals that considerable effort has been expended in the elucidation of the topography of RGD-containing, conformationally con-

Table 5. Activity Data for Benzamidine Containing Isoquinolones



compd	basic position	X	ELISA IC_{50} (μM)[a]	PRP IC_{50} (μM)[b,c]
24	C_6	CH_2O	0.6	30
25	C_7	CH_2O	4	nt
28	C_6	$(CH_2)_2O$	6	nt
32	C_6	trans-CH=CH	0.048	0.34
35	C_6	C≡C	0.033	0.52
37	C_6	cis-CH=CH	0.29	5.7
39	C_6	CH_2CH_2	0.11	1.2
46	C_6	CONH	0.003	0.09
49	C_6	NHCO	0.076	0.56

[a] See Tables 3 and 4.

strained peptides.[47−51] A majority of these structural and computational investigations[63,64] concluded that the RGD triad is conformationally defined with the arginine and aspartate residue both held in turns separated by glycine (see Figure 4). This turn-extended-turn conformation[49] of the RGD triad fixes the position of the aspartate and the arginine side chains and imparts a cup shape to the sequence. In general, RGD-containing peptides which offer conformations other than the turn-extended-turn motif show diminished activity.[48] The apparent cup shape of the RGD sequence and the turn-extended-turn relationship have been used successfully for the design of a γ-turn mimic[37] for the aspartate region and in the design of centrally constrained RGD mimics like SB-208651[36] and G-6249[40] (see Figure 4).

Our data, derived from NMR studies of peptide **1**, are consistent with the literature in that the RGD region is conformationally defined. However, the dominant solution conformation for the RGD triad contained in this peptide is best described by a Gly-Asp β-turn and not the generally observed turn-extended-turn. Nevertheless, peptide **1** afforded good activity in the GPIIb−IIIa ELISA (0.035 μM) and aggregation assays (IC_{50} 0.3 μM). A possible explanation for this apparent contradiction is that the major conformation of **1** is not a contributor to antagonist activity and that the minor, uncharacterized conformation maintains the active turn-extended-turn topography. A comparison of the potency of isoquinolones differentially substituted at the 6 and 7 positions may provide insight about the conformation of the RGD sequence contained in peptide **1**. In general, the compounds which are substituted at the 2 and 6 positions of the isoquinolone nucleus effectively mimic the proposed Gly-Asp β-turn and display reasonable activity (Tables 3−5). In comparison, analogs with substitution at the 2 and 7 positions (**15**, **16**, and **25**), which closely mimic the turn-extended-turn motif, are in this series generally less active than their 2,6 disubstituted counterparts (**14a**,**b** and **24**). While it is not possible to define with certainty the active conformation of peptide **1**, these data suggest that a Gly-Asp β-turn may be responsible for the activity observed.

While the turn-extended-turn and Gly-Asp turn types afford different placement of the critical pharmacophores, it is apparent that either conformation is conducive to binding to GPIIb−IIIa. In an effort to rationalize this observation, it has been proposed that the receptor may have one extended or two distinct

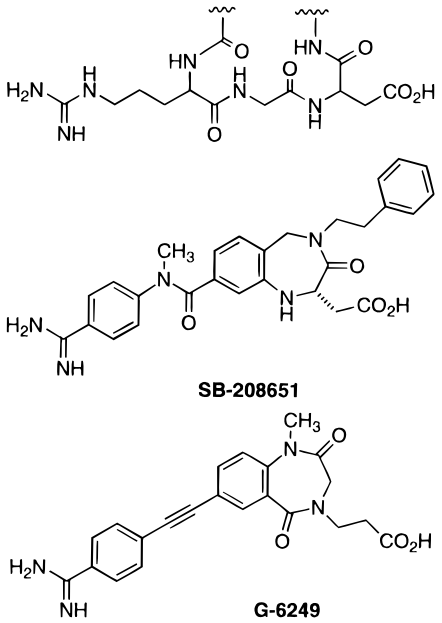


Figure 4. Shown above is a two-dimensional representation of an RGD sequence in a "turn-extended-turn" orientation and examples of active centrally constrained RGD mimics whose design followed from this conformation.

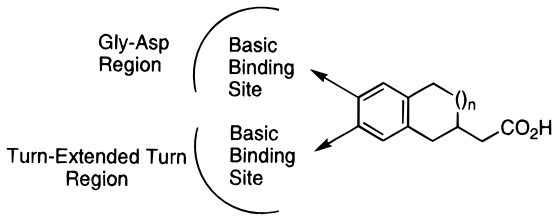


Figure 5.

cation binding sites.[65] The turn-extended-turn binding site has been suggested to be available to compounds like SB-208651 and G-6249 in which the acidic and basic moieties are angularly disposed on a central constraint (see Figure 5). It can be inferred from the literature[65,66] and the results presented in this paper that the Gly-Asp binding site accommodates compounds in which the basic and acidic residues have a linear relationship across a central constraint.[67]

One can use the above rationalization to suggest that activities from compounds like **24** and **25** result from each accessing a unique cation binding site on GPIIb−IIIa, but the data from these two compounds alone is not convincing. For either compound, the distance between the critical pharmacophores remains relatively constant. If the distance between the acidic and basic residues is in fact the key determinant for activity, it is not surprising that both compounds display activity. A more convincing argument for an extended binding site can, however, be made after comparing the activities and structures of compounds **32** and **37**. Compound **37** differs from compound **32** in that the *cis* double bond changes the overall geometry of the molecule from linear to bent and it forces the benzamidine moiety out of the plane of the central constraint. These structural changes close the distance between the acidic and basic residue by approximately 4 Å. That **37** is only 6-fold less active than **32** demonstrates that the GPIIb−IIIa receptor can accommodate a variety of ligand topographies and therefore provides additional evidence for the enlarged binding site hypothesis.[68]

Rigid molecules like **37**, **46**, **49**, and **35** offer a unique opportunity to study optimum distances and geometries for RGD mimics which occupy the Gly-Asp binding site in the GPIIb−IIIa receptor. Apparent from these structures is the fact that there is a linear relationship between the acidic and basic groups and the benzamidine moiety is coplanar with the central constraint. The distance between the terminal amine of the amidine and the carbon of the carboxylate of these four compounds is roughly 16 Å. Of interest is the fact that the central constraint chosen as a surrogate for the Gly-Asp β-turn observed for **1** is flat. Mimicking the cup shape of the RGD region and proper orientation of the Asp side chain have been thought to be important factors in the design of turn-extended-turn mimics.[40] The activity displayed by these four compounds suggest that conformational flexibility in the central constraint is of little importance for Gly-Asp β-turn mimics. Rather, this data indicates that relative position, distance, and a near coplanar relationship between the two key pharmacophores are the most important factors to consider in the design of this type of RGD mimic.

Optimization for the Gly-Asp mimic described in this paper was accomplished by adjusting the distance of the basic moiety from the central constraint, thereby fixing the critical distance between the acidic and basic moieties, and refining the nature and orientation of the basic group. Our data indicates that there is an optimum distance of roughly 15−16 Å between the carbon of the carboxylate and the terminal amine of the arginine mimic. We found that activity varies with the nature of the basic residue, with guanidine and primary amines providing modest activity in this series. Substituted piperidines have been shown to be effective arginine surrogates,[27] and we have found similar results. Consistent with other disclosures in the literature,[34,35] the benzamidine moiety provides by far the greatest increase in activity and its placement two atoms removed from the backbone mimic is optimum. Rigidification of the two-atom linkage between the benzamidine group and the central constraint provided further increases in activity with a linear or *trans* linkage providing the most benefit. Preference for a two-atom *trans* array is also seen with amide derivatives **46** and **49**. The activity of amide **49** compares favorably with that of *trans* olefin **32**, while the reversed amide **46** shows a 1 order of magnitude increase in activity. This data suggests that the amide linkage contained in derivative **46** interacts favorably, possibly through a hydrogen bond donor−acceptor relationship with complementary functionality in the receptor.

Conclusion

We have shown that the RGD sequence contained in peptide **1** likely exists in a well-defined Gly-Asp type II′ β-turn. This information was used in the design of simple 2,6-disubstituted isoquinolone analogs with modest affinity for GPIIb−IIIa. Optimization of these leads utilized standard SAR optimization techniques and resulted in the development of potent inhibitors of platelet aggregation. The activity afforded by compound **46** represents a 4 order of magnitude increase relative to the first compound in the series (**14a**) and a 3-fold increase in activity over the peptide (**1**) from which this series was modeled. Notable is the fact that this activity increase was obtained by optimization of only one of the critical pharmacophores. That significant increases in activity were made without modifying the Asp portion of the molecule suggests that additional improvements may still be achieved in this series. Efforts toward optimizing the acidic pharmacophore will be reported separately.

Experimental Section

All starting materials were commercially available or previously reported in the literature unless noted. All reactions were run in an atmosphere of dry nitrogen, and solvents and reagents were used without purification with the exception of THF which was distilled from sodium/benzophenone. Nuclear magnetic resonance spectra for characterization of synthesis products were recorded at 300 MHz on GE QE-300 and Bruker AC-300 spectrometers. Chemical shifts are reported in parts per million relative to tetramethylsilane. High-resolution mass spectra were recorded on a VG Analytical ZAB2-SE instrument, and FD mass spectra were recorded on a MAT-731 instrument. Infrared spectra were recorded on a Nicolet DX10 FT-IR spectrometer with the medium noted in the individual experiment. Melting points were recorded on a Thomas-Hoover melting point apparatus and are uncorrected. Elemental analyses were performed at Lilly Research Laboratories by the Physical Chemistry Department and are within ±0.4% of theory unless otherwise noted.

NMR Analysis and Computational Investigation of Cyclic Peptide 1. The samples for NMR were prepared by dissolving the peptide into either ^2H_2O (MSD Isotopes) or a mixture of $H_2O/^2H_2O$ (9:1) and adjusting the pH to a meter reading of 6.0, resulting in final peptide concentrations of 10−20 mM. The NMR experiments were carried out on a Varian Unity 500 MHz spectrometer. The NMR probe temperature was set to 21 °C for all the experiments.

One-dimensional spectra were recorded using 16384 complex points over a spectral width of 8000 Hz. For the spectra recorded in H_2O, continuous wave presaturation was used to suppress the solvent signal. The two-dimensional DQF-COSY,[69] TOCSY,[70,71] and ROESY[53] were recorded with spectral widths of 8000 Hz in both dimensions. The number of complex points collected in t_2 was 4096, with 512 complex FID's collected in t_1. The ROESY mixing time was 100 ms. The two-dimensional data sets were processed on a Silicon Graphics workstation using the software package Felix (Biosym Technologies, Inc.). Titration studies to determine residues that were protected from solvent exchange were carried out in a mixture of $H_2O/^2H_2O$ (9:1). The starting pH was 4.50, and the pH was decreased upon additions of 0.001 M HCl.

The initial structures were generated using the distance geometry program DGEOM (Quantum Chemistry Program Exchange). NOE constraints were classified as either strong, medium, or weak and were assigned upper limits of 2.5, 3.0, or 3.5 Å with the lower limit set to the van der Waals radii. Stereospecific assignments were not made, so NOE's to methylene protons were included as two constraints using the weakest intensity. In applying the hydrogen bond constraint, a restraint (2.2 Å) was enforced between the amide proton and the carbonyl oxygen as well as the amide nitrogen (3.3 Å) and the carbonyl oxygen. Structures having a maximum NOE violation error greater than 0.2 Å in the case of the Trp-Arg hydrogen bond and 0.5 Å for the Trp-Mpr hydrogen bond were excluded for not satisfying the NOE data.

Distance geometry structures were annealed using XPLOR (MSI) running on a Cray-2s supercomputer. The distance constraints were included in the energy function, while the electrostatic contributions were removed. Each structure was given 15 ps of high temperature (1000 K) simulated annealing, gradually cooled to 50 K, and then subjected to 500 steps of minimization. The structures were then classified based on the ϕ and ψ angles for RGD region using the clustering feature in the Quanta program (MSI). In the formation of the clusters, the lowest energy structure is taken as the nucleus of the first cluster. Any structures with an RMSD (for the torsion angles

comprising the RGD region) of no greater than 65 are grouped into a cluster. From the remaining structures, the lowest energy structure is taken as the nucleus of the second cluster, and structures with an RMSD less than 65 are grouped into the second cluster. The process is repeated until all structures are classified. An atom by atom comparison of the RMSD's was performed using the COMPAR program (QCPE).

Compound Synthesis. 7-Hydroxy-3,4-dihydro-1-oxo-2(1*H*)-isoquinoline (3). A mixture of 7-methoxyisoquinolone (2.02 g, 11.4 mmol) and CH_2Cl_2 (25 mL) was treated with BBr_3 (45.6 mL of a 1.0 M solution in CH_2Cl_2, 45.6 mmol) at −78 °C. The resulting mixture was allowed to warm to room temperature over 14 h. This solution was then cautiously quenched with MeOH (11.5 mL, 285 mmol), and the resulting solution was maintained at room temperature for 2 h. This solution was then concentrated to dryness, and the resulting solid material was recrystallized from H_2O, providing 1.8 g (95%) of **3** as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) 2.88 (t, J = 6.6 Hz, 2H), 3.47 (t, J = 6.5 Hz, 2H), 6.93 (dd, J = 2.6, 8.2 Hz, 1H), 7.13 (d, J = 8.2 Hz, 1H), 7.36 (d, J = 2.6 Hz, 1H); IR (KBr) 3324, 3157, 1658, 1608, 1591, 1329, 1256 cm^{-1}; MS (FD) *m/e* 163; mp 195−200 °C. Anal. ($C_9H_9NO_2$) C, H, N.

6-(Benzyloxy)-3,4-dihydro-1-oxo-2(1*H*)-isoquinoline (4). A mixture of phenol **2** (1.0 g, 6.13 mmol), benzyl bromide (1.15 g, 6.75 mmol), K_2CO_3 (0.93 g, 6.74 mmol), and acetone (15 mL) was maintained at reflux for 16 h. The mixture was then allowed to cool to room temperature and was diluted with EtOAc (100 mL). This mixture was washed with H_2O (2 × 25 mL), dried ($MgSO_4$), and concentrated. The crude residue was recrystallized from EtOAc/hexanes, giving 1.53 g of **4** (98%) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) 2.98 (t, J = 6.5 Hz, 2H), 3.57 (m, 2H), 5.12 (s, 2H), 5.92 (br s, 1H), 6.80 (d, J = 2.3 Hz, 1H), 6.94 (dd, J = 8.6 Hz, 1H), 7.40 (m, 5H), 8.03 (d, J = 8.6 Hz, 1H); IR (KBr) 1661, 1608, 1314, 1251, 1008 cm^{-1}; MS (FD) *m/e* 253; mp 121−124 °C. Anal. ($C_{16}H_{15}NO_2$) C, H, N.

7-(Benzyloxy)-3,4-dihydro-1-oxo-2(1*H*)-isoquinoline (5). Using the procedure described above, **5** was prepared in 75% yield, starting from **3**: ^{1}H NMR (300 MHz, $CDCl_3$) 2.93 (t, J = 6.6 Hz, 2H), 3.53 (dd, J = 2.8, 6.8 Hz, 2H), 5.11 (s, 2H), 6.18 (br s, 1H), 7.0−7.2 (m, 2H), 7.3−7.5 (m, 5H), 7.70 (d, J = 2.6 Hz, 1H); IR (KBr) 3200, 3067, 1665, 1608, 1441, 1332, 1011 cm^{-1}; MS (FD) *m/e* 253. Anal. ($C_{16}H_{15}NO_2$) C, H, N.

6-(Benzyloxy)-3,4-dihydro-1-oxo-2(1*H*)-isoquinolineacetic Acid 1,1-Dimethylethyl Ester (6). A mixture of lactam **4** (1.0 g, 3.93 mmol), NaH (0.19 g of a 60% dispersion in mineral oil, 4.72 mmol), and THF (15 mL) was maintained at reflux for 2 h and then allowed to cool to room temperature. This mixture was then treated with *tert*-butyl bromoacetate (0.84 g, 4.32 mmol), and the mixture was stirred at room temperature for 1 h. This mixture was then diluted with EtOAc (100 mL), washed with H_2O (2 × 25 mL), dried with $MgSO_4$, and concentrated. The crude residue was recrystallized from EtOAc/hexanes, giving 1.29 g (90%) of **6** as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) 1.41 (s, 9H), 3.00 (t, J = 6.5 Hz, 2H), 3.61 (t, J = 6.5 Hz, 2H), 4.22 (s, 2H), 5.09 (s, 2H), 6.74 (d, J = 2.5 Hz, 1H), 6.91 (dd, J = 2.5, 8.6 Hz, 1H), 7.36 (m, 5H), 8.02 (d, J = 8.5 Hz, 1H); IR (KBr) 1726, 1655, 1240, 780 cm^{-1}; MS (FD) *m/e* 367; mp 122−124 °C. Anal. ($C_{22}H_{25}NO_4$) C, H, N.

7-(Benzyloxy)-3,4-dihydro-1-oxo-2(1*H*)-isoquinolineacetic Acid 1,1-Dimethylethyl Ester (7). Using the procedure outlined above, intermediate **7** was obtained in 80% yield starting from **5**: ^{1}H NMR (300 MHz, $CDCl_3$) 1.52 (s, 9H), 3.03 (t, J = 6.3 Hz, 2H), 3.66 (t, J = 6.5 Hz, 2H), 4.27 (s, 2H), 5.14 (s, 2H), 7.14 (m, 2H), 7.3−7.5 (m, 5H), 7.76 (d, J = 1.9 Hz, 1H); IR (KBr) 1745, 1645, 1613, 1557, 1448, 1252, 1158 cm^{-1}; MS (FAB) *m/e* 368; mp 119−120 °C. Anal. ($C_{22}H_{25}NO_4$) C, H, N.

6-Hydroxy-3,4-dihydro-1-oxo-2(1*H*)-isoquinolineacetic Acid 1,1-Dimethylethyl Ester (8). A mixture of **6** (0.13g, 0.37 mmol), Pd/C (0.14 g, 10% on carbon), and EtOAc (5 mL) was stirred under an atmosphere of hydrogen (balloon) for 1.5 h and then filtered. The filtrate was then concentrated, providing 0.10 g (95%) of **8** as a pure white solid: ^{1}H NMR (300 MHz, $CDCl_3$) 1.43 (s, 9H), 2.97 (t, J = 6.6 Hz, 2H), 3.61 (t, J = 6.6 Hz, 2H), 4.22 (s, 2H), 6.64 (d, J = 2.3 Hz, 1H), 6.74 (dd, J = 2.3, 8.4 Hz, 1H), 7.47 (br s, 1H), 7.90 (d, J = 8.4 Hz, 1H); IR (KBr) 2984, 1739, 1609, 1231, 1154 cm^{-1}; MS (FD) *m/e* 278; mp 167−170 °C. Anal. ($C_{15}H_{19}NO_4$) C, H, N.

7-Hydroxy-3,4-dihydro-1-oxo-2(1*H*)-isoquinolineacetic Acid 1,1-Dimethylethyl Ester (9). Following the procedure outlined above, intermediate **9** was prepared in an identical manner starting from **7**: ^{1}H NMR (300 MHz, $CDCl_3$) 1.47 (s, 9H), 2.96 (t, J = 6.6 Hz, 2H), 3.62 (t, J = 6.8 Hz, 2H), 4.23 (s, 2H), 6.94 (dd, J = 2.6, 8.1 Hz, 1H), 7.06 (d, J = 8.2 Hz, 1H), 7.90 (d, J = 2.7 Hz, 1H); IR (KBr) 3345, 2980, 1734, 1646, 1606, 1493, 1152 cm^{-1}; MS (FD) *m/e* 278; mp 136−138 °C. Anal. ($C_{15}H_{19}NO_4$) C, H, N.

2-[[4-(Bromoethyl)phenyl]methyl]-1*H*-isoindole-1,3(2*H*)-dione (10e). A mixture of α,α′-dibromo-*p*-xylene (5.0 g, 18.9 mmol), potassium phthalimide (3.5 g, 18.9 mmol), and DMF (20 mL) was maintained at 100 °C for 12 h and then allowed to cool to room temperature. This mixture was diluted with EtOAc (200 mL) and washed with H_2O (50 mL × 4). The organic material was dried ($MgSO_4$) and concentrated. The crude material was purified by chromatography (silica gel 200−400 mesh, hexanes/EtOAc, 4:1), giving 1.6 g (25%) of **10e** as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) 4.46 (s, 2H), 4.85 (s, 2H), 7.36 (d, J = 8.2 Hz, 2H), 7.41 (d, J = 8.2 Hz, 2H), 7.72 (m, 2H), 7.86 (m, 2H); IR (KBr) 1767, 1718, 1433, 1391, 717 cm^{-1}; MS (FD) *m/e* 329; mp 134−136 °C. Anal. ($C_{16}H_{12}NO_2Br$) C, H, N.

2-[[3-(Bromoethyl)phenyl]methyl]-1*H*-isoindole-1,3(2*H*)-dione (10f). Using the procedure outlined above, **10f** was prepared in the same manner: ^{1}H NMR (300 MHz, $CDCl_3$) 4.45 (s, 2H), 4.83 (s, 2H), 7.30 (m, 2H), 7.37 (m, 1H), 7.45 (br s, 1H), 7.71 (m, 2H), 7.85 (m, 2H); IR (KBr) 1766, 1709, 1429, 1392, 1078 cm^{-1}; MS (FD) *m/e* 329; mp 138−140 °C. Anal. ($C_{16}H_{12}NO_2Br$) C, H, N.

General Procedure for the *O*-Alkylation of Intermediates 8 and 9. Preparation of 6-[[3-(1,3-Dihydro-1,3-dioxa-2*H*-isoindol-2-yl)propyl]oxy]-3,4-dihydro-1-oxo-2(1*H*)-isoquinolineacetic Acid 1,1-Dimethylethyl Ester (11a). A mixture of **8** (0.25 g, 0.90 mmol) and **10a** (0.28 g, 0.90 mmol) was dissolved in acetone (20 mL) and then treated with K_2CO_3. The resulting mixture was maintained at reflux for 12 h and then allowed to cool to room temperature. This mixture was diluted with EtOAc (200 mL) and then washed with H_2O (2 × 50 mL). The organic material was dried ($MgSO_4$) and concentrated. The crude residue was recrystallized from EtOAc/hexanes, which provided 0.34 g (84%) of an off-white solid: ^{1}H NMR (300 MHz, $CDCl_3$) 1.45 (s, 9H), 2.20 (m, 2H), 2.94 (t, J = 6.5 Hz, 2H), 3.58 (t, J = 6.80 Hz, 2H), 3.89 (t, J = 6.8 Hz, 2H), 4.04 (t, J = 6.0 Hz, 2H), 4.19 (s, 2H), 6.53 (d, J = 2.4 Hz, 1H), 6.65 (dd, J = 2.5, 8.7 Hz, 1H), 7.71 (m, 2H), 7.82 (m, 2H), 7.95 (d, 8.6 Hz, 1H); IR (KBr) 1768, 1738, 1705, 1654, 1278 cm^{-1}; MS (FD) *m/e* 464; mp 132−133 °C. Anal. ($C_{26}H_{28}N_2O_6$) C, H, N.

6-[[4-(1,3-Dihydro-1,3-dioxa-2*H*-isoindol-2-yl)butyl]oxy]-3,4-dihydro-1-oxo-2(1*H*)-isoquinolineacetic Acid 1,1-Dimethylethyl Ester (11b). This compound was obtained from **8** and **10b** following the general procedure: ^{1}H NMR (300 MHz, $CDCl_3$) 1.46 (s, 9H), 2.04 (m, 4H), 2.98 (t, J = 6.5 Hz, 2H), 3.60 (t, J = 6.6 Hz, 2H), 3.77 (t, J = 6.6 Hz, 2H), 4.04 (m, 2H), 4.21 (s, 2H), 6.64 (s, 1H), 6.79 (dd, J = 8.6, 2.5 Hz, 1H), 7.71 (m, 2H), 7.84 (m, 2H), 7.98 (d, J = 8.6 Hz, 1H); mp 84−86 °C. Anal. ($C_{27}H_{30}N_2O_6$) C, H, N.

6-[[5-(1,3-Dihydro-1,3-dioxa-2*H*-isoindol-2-yl)pentyl]oxy]-3,4-dihydro-1-oxo-2(1*H*)-isoquinolineacetic Acid 1,1-Dimethylethyl Ester (11c). This compound was obtained from **8** and **10c** following the general procedure: ^{1}H NMR (300 MHz, $CDCl_3$) 1.47 (s, 9H), 1.82 (m, 4H), 3.00 (t, J = 6.5 Hz, 2H), 3.61 (t, J = 6.5 Hz, 2H), 3.73 (t, J = 7.1 Hz, 2H), 3.98 (t, J = 6.4 Hz, 2H), 4.22 (s, 2H), 6.64 (s, 1H), 6.79 (d, J = 8.7 Hz, 1H), 7.72 (m, 2H), 7.85 (m, 2H), 7.99 (d, J = 8.6 Hz, 1H); IR (KBr) 1736, 1702, 1663, 1277, 1158 cm^{-1}; MS (FD) *m/e* 478; mp 92−94 °C. Anal. ($C_{28}H_{32}N_2O_6$) C, H, N.

6-[[6-(1,3-Dihydro-1,3-dioxa-2*H*-isoindol-2-yl)hexyl]oxy]-3,4-dihydro-1-oxo-2(1*H*)-isoquinolineacetic Acid 1,1-Dimethylethyl Ester (11d). This compound was obtained from **8** and **10d** following the general procedure: ^{1}H NMR (300

MHz, $CDCl_3$) 1.43 (m, 13H), 1.70 (m, 4H), 2.95 (t, J = 6.4 Hz, 2H), 3.57 (t, J = 6.5 Hz, 2H), 3.65 (t, J = 7.2 Hz, 2H), 3.93 (t, J = 6.3 Hz, 2H), 4.18 (s, 2H), 6.60 (s, 1H), 6.75 (d, J = 8.6 Hz, 1H), 7.67 (m, 2H), 7.78 (m, 2H), 7.95 (d, J = 8.2 Hz, 1H); IR ($CHCl_3$) 2943, 1772, 1737, 1712, 1606, 1155 cm^{-1}; MS (FD) *m/e* 506. Anal. ($C_{29}H_{34}N_2O_6$) C, H, N.

6-[[4-[(1,3-Dihydro-1,3-dioxa-2*H*-isoindol-2-yl)methyl]-phenyl]methoxy]-3,4-dihydro-1-oxo-2(1*H*)-isoquinolineacetic Acid 1,1-Dimethylethyl Ester (11e). This compound was obtained from **8** and **10e** following the general procedure: ^1H NMR (300 MHz, $CDCl_3$) 1.46 (s, 9H), 2.98 (t, J = 6.4 Hz, 2H), 3.59 (t, J = 6.5 Hz, 2H), 4.20 (s, 2H), 4.85 (s, 3H), 5.05 (s, 2H), 6.71 (s, 1H), 6.90 (d, J = 8.6 Hz, 1H), 7.36 (d, J = 8.1 Hz, 2H), 7.46 (d, J = 8.2 Hz, 2H), 7.70 (m, 2H), 7.84 (m, 2H), 8.01 (d, J = 8.7 Hz, 1H); IR (KBr) 1766, 1739, 1709, 1650, 1481 cm^{-1}; MS (FD) *m/e* 526; mp 170−172 °C. Anal. ($C_{31}H_{30}N_2O_6$) C, H, N.

6-[[3-[(1,3-Dihydro-1,3-dioxa-2*H*-isoindol-2-yl)methyl]-phenyl]methoxy]-3,4-dihydro-1-oxo-2(1*H*)-isoquinolineacetic Acid 1,1-Dimethylethyl Ester (11f). This compound was obtained from **8** and **10f** following the general procedure: ^1H NMR (300 MHz, $CDCl_3$) 1.46 (s, 9H), 2.95 (t, J = 6.4 Hz, 2H), 3.60 (t, J = 6.5 Hz, 2H), 4.21 (s, 2H), 4.86 (s, 2H), 5.05 (s, 2H), 6.71 (s, 1H), 6.85 (dd, J = 2.7, 8.6 Hz, 1H), 7.20−7.60 (m, 4H), 7.70 (m, 2H), 7.80 (m, 2H), 7.97 (d, J = 8.6 Hz, 1H); IR (KBr) 1771, 1740, 1714, 1651, 1605, 1393, 1153 cm^{-1}; MS (FD) *m/e* 527; mp 58−63 °C. Anal. ($C_{31}H_{30}N_2O_6$) C, H, N.

General Procedure for the Preparation of Compounds 12a−f. 6-[(3-Aminopropyl)oxy]-3,4-dihydro-1-oxo-2(1*H*)-isoquinolineacetic Acid Monohydrochloride (12a). A solution of **11a** (0.34 g, 0.70 mmol) in EtOH (2.5 mL) was treated with aqueous hydrazine (0.35 mL of an 85% solution, 7.0 mmol) and then maintained at 65 °C for 1 h. This mixture was then concentrated to dryness, and the crude residue was partitioned between EtOAc (50 mL) and saturated aqueous $NaHCO_3$ (25 mL). The layers were separated, and the organic material was washed with H_2O (25 mL), dried ($MgSO_4$), and concentrated. The crude residue was then taken up in anhydrous TFA and allowed to stand at room temperature for 1 h. This solution was then concentrated, the crude residue was dissolved in 1 N aqueous HCl, and this solution was extracted with Et_2O. The remaining aqueous material was lyophilized, providing **12a** as a white, hygroscopic solid: ^1H NMR (300 MHz, CD_3OD) 2.14 (m, 2H), 3.02 (t, J = 6.4 Hz, 2H), 3.11 (t, J = 7.1 Hz, 2H), 3.65 (t, J = 6.6 Hz, 2H), 4.16 (t, J = 5.8 Hz, 2H), 4.27 (s, 2H), 6.83 (s, 1H), 6.88 (d, J = 8.4 Hz, 1H), 7.85 (d, J = 8.6 Hz, 1H). IR (KBr) 2882, 1628, 1600, 1488, 1200, 1029 cm^{-1}; MS (FAB) *m/e* 279; mp 205−206 °C dec. Anal. ($C_{14}H_{19}N_2O_4 \cdot 1H_2O$) C, H, N.

6-[(4-Aminobutyl)oxy]-3,4-dihydro-1-oxo-2(1*H*)-isoquinolineacetic Acid Monohydrochloride (12b). Following the general procedure, **12b** was prepared starting from **11b**: ^1H NMR (300 MHz, CD_3OD) 1.87 (m, 4H), 3.01 (m, 4H), 3.66 (t, J = 6.6 Hz, 2H), 4.09 (m, 2H), 4.28 (s, 2H), 6.81 (d, J = 2.1 Hz, 1H), 6.87 (dd, J = 8.6, 2.3 Hz, 1H), 7.85 (d, J = 8.7 Hz, 1H); IR (KBr) 2936, 1723, 1633, 1485, 1021 cm^{-1}; MS (FD) *m/e* 294. Anal. ($C_{15}H_{21}N_2O_4Cl \cdot 0.25H_2O$) C, H, N.

6-[(5-Aminopentyl)oxy]-3,4-dihydro-1-oxo-2(1*H*)-isoquinolineacetic Acid Monohydrochloride (12c). Following the general procedure, **12c** was prepared starting from **11c**: ^1H NMR (300 MHz, $CDCl_3$) 1.60 (m, 2H), 1.75 (m, 2H), 1.85 (m, 2H), 2.93 (t, J = 6.9 Hz, 2H), 3.00 (t, J = 6.51 Hz, 2H), 3.62 (t, J = 6.7 Hz, 2H), 4.05 (t, J = 6.0 Hz, 2H), 4.27 (s, 2H), 6.78 (s, 1H), 6.84 (d, J = 8.3 Hz, 1H), 7.82 (d, J = 8.4 Hz, 1H); IR (KBr) 2944, 1718, 1636, 1606, 1482, 1182 cm^{-1}; MS (FAB) *m/e* 307; mp 180−185 °C dec. Anal. ($C_{16}H_{23}N_2O_4Cl$) C, H, N.

6-[(6-Aminohexyl)oxy]-3,4-dihydro-1-oxo-2(1*H*)-isoquinolineacetic Acid Monohydrochloride (12d). Following the general procedure, **12d** was prepared starting from **11d**: ^1H NMR (300 MHz, CD_3OD) 1.46 (m, 4H), 1.65 (m, 2H), 1.81 (m, 2H), 2.92 (t, J = 7.6 Hz, 2H), 3.02 (t, J = 6.6 Hz, 2H), 3.66 (t, J = 6.8 Hz, 2H), 4.05 (t, J = 6.3 Hz, 2H), 4.28 (s, 2H), 6.79 (d, J = 2.3 Hz, 1H), 6.85 (dd, J = 2.3, 8.7 Hz, 1H), 7.86 (d, J = 8.6 Hz, 1H); IR (KBr) 2943, 1713, 1650, 1611, 1482, 1277 cm^{-1}; MS (FAB) *m/e* 356.8. Anal. ($C_{17}H_{25}N_2O_4Cl$) C, H, N.

6-[[4-(Aminomethyl)phenyl]methoxy]-3,4-dihydro-1-oxo-2(1*H*)-isoquinolineacetic Acid 1,1-Dimethylethyl Ester (12e). Following the general procedure, **12e** was prepared starting from **11e**: ^1H NMR (300 MHz, $CDCl_3$) 3.00 (t, J = 6.6 Hz, 2H), 3.62 (t, J = 6.8 Hz, 2H), 4.08 (s, 2H), 4.27 (s, 2H), 5.18 (s, 2H), 6.87 (d, J = 1.9 Hz, 1H), 6.91 (dd, J = 1.9, 8.7 Hz, 1H), 7.49 (dd, J = 8.1, 19.2 Hz, 4H), 7.81 (d, J = 8.6 Hz, 1H); IR (KBr) 2932, 1724, 1625, 1604, 1483, 1185 cm^{-1}; MS (FAB) *m/e* 341. Anal. ($C_{19}H_{21}N_2O_4Cl \cdot 0.4H_2O$) C, H, N.

6-[[3-(Aminomethyl)phenyl]methoxy]-3,4-dihydro-1-oxo-2(1*H*)-isoquinolineacetic Acid 1,1-Dimethylethyl Ester (12f). Following the general procedure, **12f** was prepared starting from **11f**: ^1H NMR (300 MHz, $CDCl_3$) 3.03 (t, J = 6.6 Hz, 2H), 3.67 (t, J = 6.5 Hz, 2H), 4.14 (s, 2H), 4.29 (s, 2H), 5.20 (s, 2H), 6.90 (d, J = 2.3 Hz, 1H), 6.97 (dd, J = 2.3, 8.6 Hz, 1H), 7.45 (m, 4H), 7.85 (d, J = 8.4 Hz, 1H); IR (KBr) 2905, 1732, 1632, 1601, 1481, 1277 cm^{-1}; MS (FAB) *m/e* 341. Anal. ($C_{19}H_{21}N_2O_4Cl \cdot 0.85H_2O$) C, H, N.

General Procedure for the Preparation of Compounds 13. 6-[[3-[[*N*,*N*′-Bis[(1,1-dimethylethoxy)carbonyl]-aminoiminomethyl]amino]propyl]oxy]-3,4-dihydro-1-oxo-2(1*H*)-isoquinolineacetic Acid 1,1-Dimethylethyl Ester (13a). A solution of **11a** (0.34 g, 0.70 mmol) and EtOH (15 mL) was treated with aqueous hydrazine (0.35 mL of an 85% solution in H_2O, 7 mmol) and maintained at 65 °C for 1 h. The mixture was then concentrated to dryness. The crude material was suspended in EtOAc (100 mL), and this mixture was washed with saturated $NaHCO_3$ (4 × 20 mL). The organic material was then dried ($MgSO_4$) and concentrated. The crude material thus prepared was dissolved in CH_2Cl_2 (2 mL) and then treated with *N*,*N*′-bis(*tert*-butoxycarbonyl)-*S*-methoxyisothiourea (0.24 g, 0.84 mmol). The resulting solution was stirred at room temperature for 4 days. The solution was then concentrated to dryness, and the resulting material was purified by chromatography (silica gel 200−400 mesh, hexanes/EtOAc, 3:1), providing 0.28 g (53%) of **13a** as a clear oil: ^1H NMR (300 MHz, $CDCl_3$) 1.46 (s, 9H), 1.50 (s, 9H), 2.05 (m, 2H), 2.98 (t, J = 6.5 Hz, 2H), 3.62 (m, 4H), 4.09 (t, J = 5.7 Hz, 2H), 4.21 (s, 2H), 6.78 (d, J = 2.2 Hz, 1H), 6.85 (dd, J = 2.3, 8.2 Hz, 1H), 7.98 (d, J = 8.2 Hz, 1H), 8.71 (m, 1H); IR (KBr) 2980, 1725, 1640, 1611, 1325, 1130 cm^{-1}; MS (FAB) *m/e* 577. Anal. ($C_{29}H_{44}N_4O_8$) C, H, N.

6-[[3-[[*N*,*N*′-Bis[(1,1-dimethylethoxy)carbonyl]-aminoiminomethyl]amino]butyl]oxy]-3,4-dihydro-1-oxo-2(1*H*)-isoquinolineacetic Acid 1,1-Dimethylethyl Ester (13b). Following the procedure employed for the preparation of **13a**, **13b** was prepared in a like manner: ^1H NMR (300 MHz, $CDCl_3$) 1.46 (s, 9H), 1.48 (s, 9H), 1.49 (s, 9H), 1.90 (m, 4H), 2.99 (t, J = 6.5 Hz, 2H), 3.50 (m, 2H), 3.60 (t, J = 3.6 Hz, 2H), 4.01 (t, J = 5.1 Hz, 2H), 4.21 (s, 2H), 6.64 (d, J = 2.1 Hz, 1H), 6.80 (dd, J = 2.2, 8.2 Hz, 1H), 7.98 (d, J = 8.3 Hz, 1H), 8.38 (m, 1H); IR (KBr) 2984, 1735, 1723, 1640, 1609, 1155 cm^{-1}; MS (FAB) *m/e* 591. Anal. ($C_{30}H_{46}N_4O_8$) C, H, N.

6-[[5-[[*N*,*N*′-Bis[[(1,1-dimethylethoxy)carbonyl]-aminoiminomethyl]amino]pentyl]oxy]-3,4-dihydro-1-oxo-2(1*H*)-isoquinolineacetic Acid 1,1-Dimethylethyl Ester (13c). Following the general procedure employed for the preparation of **13a**, **13c** was prepared in a like manner: ^1H NMR (300 MHz, $CDCl_3$) 1.44 (s, 9H), 1.47 (s, 9H), 1.48 (s, 9H), 1.60 (m, 4H), 1.81 (m, 2H), 2.98 (t, J = 6.4 Hz, 2H), 3.44 (m, 2H), 3.59 (t, J = 6.6 Hz, 2H), 3.97 (t, J = 6.3 Hz, 2H), 4.19 (s, 2H), 6.63 (s, 1H), 6.79 (dd, J = 1.9, 8.6 Hz, 1H), 7.98 (d, 8.6 Hz, 1H), 8.32 (s, 1H); IR ($CHCl_3$) 2984, 1722, 1640, 1609, 1369, 1155 cm^{-1}; MS (FAB) *m/e* 605. Anal. ($C_{31}H_{48}N_4O_8 \cdot 1.75H_2O$): C, H, N.

6-[[3-[[*N*,*N*′-Bis[(1,1-dimethylethoxy)carbonyl]-aminoiminomethyl]amino]hexyl]oxy]-3,4-dihydro-1-oxo-2(1*H*)-isoquinolineacetic Acid 1,1-Dimethylethyl Ester (13d). Following the procedure employed for the preparation of **13a**, **13d** was prepared in a like manner: ^1H NMR (300 MHz, $CDCl_3$) 1.44 (s, 9H), 1.46 (s, 9H), 1.48 (s, 9H), 1.4−1.6 (m, 4H), 1.80 (m, 2H), 2.98 (t, J = 6.4 Hz, 2H), 3.40 (dd, J = 6.7, 12.3 Hz, 2H), 3.59 (t, J = 6.4 Hz, 2H), 3.96 (t, J = 6.4 Hz,

2H), 4.19 (s, 2H), 6.63 (s, 1H), 6.80 (dd, J = 1.5, 8.4 Hz, 1H), 7.97 (d, J = 8.2 Hz, 1H), 8.29 (m, 1H); IR (KBr) 2979, 2936, 1741, 1721, 1639, 1611, 1368 cm^{-1}; MS (FAB) *m/e* 619. Anal. ($C_{32}H_{50}N_4O_8$) C, H, N.

6-[[4-[[[*N*,*N*′-Bis[(1,1-dimethylethoxy)carbonyl]-aminoiminomethyl]amino]methyl]phenyl]methoxy]-3,4-dihydro-1-oxo-2(1*H*)-isoquinolineacetic Acid 1,1-Dimethylethyl Ester (13e). Following the general procedure employed for the preparation of **13a**, **13e** was prepared in a like manner: ^{1}H NMR (300 MHz, $CDCl_3$) 1.41 (s, 9H), 1.42 (s, 9H), 1.43 (s, 9H), 3.01 (t, J = 6.6 Hz, 2H), 3.62 (t, J = 6.7 Hz, 2H), 4.23 (s, 2H), 4.64 (d, J = 5.1 Hz, 2H), 5.09 (s, 2H), 6.75 (d, J = 2.2 Hz, 1H), 6.90 (dd, J = 2.2, 8.2 Hz, 1H), 7.35 (d, J = 8.2 Hz, 2H), 7.41 (d, J = 8.2 Hz, 2H), 8.05 (d, J = 8.3 Hz, 1H), 8.60 (m, 1H); IR (KBr) 3061, 3020, 1732, 1622, 1606, 1575, 1484 cm^{-1}; MS (FAB) *m/e* 639. Anal. ($C_{34}H_{46}N_4O_8$) C, H, N.

6-[[3-[[[*N*,*N*′-Bis[(1,1-dimethylethoxy)carbonyl]-aminoiminomethyl]amino]methyl]phenyl]methoxy]-3,4-dihydro-1-oxo-2(1*H*)-isoquinolineacetic Acid 1,1-Dimethylethyl Ester (13f). Following the general procedure employed for the preparation of **13a**, **13f** was prepared in a like manner: ^{1}H NMR (300 MHz, $CDCl_3$) 1.47, (s, 9H), 1.48 (s, 9H), 1.51 (s, 9H), 3.01 (t, J = 6.6 Hz, 2H), 3.63 (t, J = 6.4 Hz, 2H), 4.22 (s, 2H), 6.13 (d, J = 4.8 Hz, 2H), 5.08 (s, 2H), 6.74 (d, J = 2.5 Hz, 1H), 6.90 (dd, J = 2.5, 8.6 Hz, 1H), 7.2−7.4 (m, 4H), 8.01 (d, J = 8.6 Hz, 1H), 8.65 (br s, 1H); IR (KBr) 2960, 1710, 1699, 1640, 1620, 1160 cm^{-1}; MS (FD) *m/e* 369; mp 65−71 °C. Anal. ($C_{34}H_{46}N_4O_8$) C, H, N.

General Procedure for the Preparation of Analogs 14−16. 6-[[3-[(Aminoiminomethyl)amino]propyl]oxy]-3,4-dihydro-1-oxo-2(1*H*)-isoquinolineacetic Acid Monohydrochloride (14a). A mixture of **13a** (0.21 g, 0.36 mmol) and anhydrous TFA (10 mL) was maintained at room temperature for 1 h and then concentrated to dryness. The resulting solid was dissolved in H_2O (20 mL), and the solution was washed with Et_2O (2 × 10 mL). The aqueous material was then treated with aqueous HCl (7.3 mL of a 1 N solution, 7.3 mmol), and the resulting solution was lyophilized, providing 0.096 g (95%) of **14a** as a hygroscopic white solid: ^{1}H NMR (300 MHz, CD_3OD) 2.05 (m, 2H), 2.99 (t, J = 6.3 Hz, 2H), 3.40 (m, 2H), 3.63 (t, J = 6.5 Hz, 2H), 4.11 (t, J = 6.0 Hz, 2H), 4.27 (s, 2H), 6.82 (s, 1H), 6.88 (d, J = 8.2 Hz, 1H), 7.40 (br s, 1H), 7.84 (d, J = 8.4 Hz, 1H); IR (KBr) 3446, 3329, 3171, 1713, 1663, 1555, 1286 cm^{-1}; MS (FAB) *m/e* 321; mp 218−220 °C dec. Anal. ($C_{15}H_{21}N_4O_4Cl$) C, H, N.

6-[[4-[(Aminoiminomethyl)amino]butyl]oxy]-3,4-dihydro-1-oxo-2(1*H*)-isoquinolineacetic Acid Monohydrochloride (14b). Following the general procedure employed for the preparation of **14a**, **14b** was prepared in a like manner: ^{1}H NMR (300 MHz, CD_3OD) 1.95 (m, 4H), 2.95 (t, J = 6.6 Hz, 2H), 3.22 (t, J = 6.6 Hz, 2H), 3.59 (t, J = 6.5 Hz, 2H), 4.21 (s, 2H), 6.73 (d, J = 2.3 Hz, 1H), 6.81 (dd, J = 2.4, 8.4 Hz, 1H), 7.78 (d, J = 8.4 Hz, 1H); IR (KBr) 3344, 3170, 2935, 1739, 1667, 1630, 1608 cm^{-1}; MS (FAB) *m/e* 335; mp 175−179 °C. Anal. ($C_{16}H_{23}N_4O_4Cl$) C, H, N.

6-[[5-[(Aminoiminomethyl)amino]pentyl]oxy]-3,4-dihydro-1-oxo-2(1*H*)-isoquinolineacetic Acid Monohydrochloride (14c). Following the general procedure employed for the preparation of **14a**, **14d** was prepared in a like manner: ^{1}H NMR (300 MHz, CD_3OD) 1.60 (m, 4H), 1.83 (m, 2H), 3.00 (t, J = 6.5 Hz, 2H), 3.17 (t, J = 5.7 Hz, 2H), 3.65 (t, J = 6.6 Hz, 2H), 4.05 (t, J = 6.1 Hz, 2H), 4.26 (s, 2H), 6.78 (s, 1H), 6.84 (d, J = 8.4 Hz, 1H), 7.36 (m, 1H), 7.83 (d, J = 8.6 Hz, 1H); IR (KBr) 3331, 3204, 2942, 1715, 1679, 1646, 1597 cm^{-1}; MS (FD) *m/e* 349; mp 115−118 °C. Anal. ($C_{17}H_{25}N_4O_4Cl$) C, H, N.

6-[[4-[(Aminoiminomethyl)amino]hexyl]oxy]-3,4-dihydro-1-oxo-2(1*H*)-isoquinolineacetic Acid Monohydrochloride (14d). Following the general procedure employed for the preparation of **14a**, **14d** was prepared in a like manner: ^{1}H NMR (300 MHz, CD_3OD) 1.46−1.62 (m, 6H), 1.81 (m, 2H), 3.02 (t, J = 6.5 Hz, 2H), 3.20 (m, 2H), 3.66 (t, J = 6.5 Hz, 2H), 4.04 (t, J = 6.2 Hz, 2H), 4.28 (s, 2H), 6.80 (d, J = 2.0 Hz, 1H), 6.87 (dd, J = 2.2, 8.6 Hz, 1H), 7.30 (m, 1H), 7.85 (d, J = 8.5 Hz, 1H); IR (KBr) 3447, 3346, 1736, 1669, 1608 cm^{-1}; MS (FAB) *m/e* 363; mp 146−150 °C. Anal. ($C_{18}H_{27}N_4O_4Cl\cdot 0.25H_2O$) C, H, N.

6-[[4-[[(Aminoiminomethyl)amino]methyl]phenyl]-methoxy]-3,4-dihydro-1-oxo-2(1*H*)-isoquinolineacetic Acid Monohydrochloride (14e). Following the general procedure employed for the preparation of **14a**, **14e** was prepared in a like manner: ^{1}H NMR (300 MHz, CD_3OD) 3.00 (t, J = 6.6 Hz, 2H), 3.64 (t, J = 6.5 Hz, 2H), 4.26 (s, 2H), 4.39 (s, 2H), 5.14 (s, 2H), 6.89 (d, J = 2.4 Hz, 1H), 6.93 (dd, J = 2.4, 8.6 Hz, 1H), 7.35 (d, J = 8.2 Hz, 2H), 7.45 (d, J = 8.2 Hz, 2H), 7.81 (d, J = 8.6 Hz, 1H); IR (KBr) 3358, 3176, 1739, 1650, 1608, 1480, 1179 cm^{-1}; MS (FAB) *m/e* 383. Anal. ($C_{20}H_{23}N_4O_4Cl\cdot 1H_2O$) C, H, N.

6-[[3-[[(Aminoiminomethyl)amino]methyl]phenyl]-methoxy]-3,4-dihydro-1-oxo-2(1*H*)-isoquinolineacetic Acid Monohydrochloride (14f). Following the general procedure employed for the preparation of **14a**, **14f** was prepared in a like manner: ^{1}H NMR (300 MHz, CD_3OD) 3.02 (t, J = 6.6 Hz, 2H), 3.66 (t, J = 6.4 Hz, 2H), 4.28 (s, 2H), 4.42 (s, 2H), 5.17 (s, 2H), 6.88 (d, J = 2.4 Hz, 1H), 6.95 (dd, J = 2.4, 8.6 Hz, 1H), 7.29 (m, 1H), 7.40 (m, 3H), 7.84 (d, J = 8.6 Hz, 1H); IR (KBr) 3349, 3177, 1725, 1632, 1604, 1482, 1184 cm^{-1}; MS (FAB) *m/e* 383; mp 105−110 °C. Anal. ($C_{20}H_{23}N_4O_4Cl\cdot 0.6H_2O$) C, H, N.

7-[[3-(1,3-Dihydro-1,3-dioxa-2*H*-isoindol-2-yl)propyl]-oxy]-3,4-dihydro-1-oxo-2(1*H*)-isoquinolineacetic Acid 1,1-Dimethylethyl Ester. Following the general procedure employed for the preparation of **11a**, the title compound was prepared in a like manner: ^{1}H NMR (300 MHz, $CDCl_3$) 1.44 (s, 9H), 2.18 (m, 2H), 2.93 (t, J = 6.5 Hz, 2H), 3.57 (t, J = 6.5 Hz, 2H), 3.88 (t, J = 6.8 Hz, 2H), 4.05 (t, J = 5.9 Hz, 2H), 4.19 (s, 2H), 6.85 (dd, J = 2.6, 8.5 Hz, 1H), 7.03 (d, J = 8.3 Hz, 1H), 7.49 (d, J = 2.5 Hz, 1H), 7.69 (m, 2H), 7.82 (m, 2H); IR ($CHCl_3$) 3019, 1738, 1713, 1653, 1395, 1153 cm^{-1}; MS (FD) *m/e* 465. Anal. ($C_{26}H_{28}N_2O_6$) C, H, N.

7-[[4-(1,3-Dihydro-1,3-dioxa-2*H*-isoindol-2-yl)butyl]oxy]-3,4-dihydro-1-oxo-2(1*H*)-isoquinolineacetic Acid 1,1-Dimethylethyl Ester. Following the general procedure employed for the preparation of **11a**, the title compound was prepared in a like manner: ^{1}H NMR (300 MHz, $CDCl_3$) 1.41 (s, 9H), 1.80 (m, 4H), 2.89 (t, J = 6.49 Hz, 2H), 3.54 (t, J = 6.5 Hz, 2H), 3.69 (t, J = 6.7 Hz, 2H), 3.97 (t, J = 5.63 Hz, 2H), 6.87 (dd, J = 2.6, 8.2 Hz, 1H), 6.98 (d, J = 8.3 Hz, 1H), 7.49 (d, J = 2.5 Hz, 1H), 7.62 (m, 2H), 7.81 (m, 2H); IR ($CHCl_3$) 1772, 1713, 1650, 1398 cm^{-1}; MS (FD) *m/e* 478. Anal. ($C_{27}H_{30}N_2O_6\cdot 0.7H_2O$) C, H, N.

7-[[3-[[*N*,*N*′-Bis[(1,1-dimethylethoxy)carbonyl]-aminoiminomethyl]amino]propyl]oxy]-3,4-dihydro-1-oxo-2(1*H*)-isoquinolineacetic Acid 1,1-Dimethylethyl Ester. Following the general procedure employed for the preparation of **13a**, the title compound was prepared in a like manner: ^{1}H NMR (300 MHz, $CDCl_3$) 1.49 (s, 9H), 1.52 (s, 18H), 2.08 (m, 2H), 2.99 (t, J = 6.6 Hz, 2H), 3.65 (m, 4H), 4.17 (t, J = 6.3 Hz, 2H), 4.27 (s, 2H), 7.10 (m, 2H), 7.60 (m, 1H), 8.67 (m, 1H); IR (KBr) 2977, 1741, 1726, 1639, 1480, 1368 cm^{-1}; MS (FAB) *m/e* 577. Anal. ($C_{29}H_{44}N_4O_8$) C, H, N.

7-[[3-[[*N*,*N*′-Bis[(1,1-dimethylethoxy)carbonyl]-aminoiminomethyl]amino]butyl]oxy]-3,4-dihydro-1-oxo-2(1*H*)-isoquinolineacetic Acid 1,1-Dimethylethyl Ester. Following the general procedure employed for the preparation of **13a**, the title compound was prepared in a like manner: ^{1}H NMR (300 MHz, $CDCl_3$) 1.44 (s, 9H), 1.46 (s, 9H), 1.47 (s, 9H), 1.80 (m, 4H), 2.94 (t, J = 6.42 Hz, 2H), 3.42 (m, 2H), 3.57 (t, J = 6.5 Hz, 2H), 3.99 (t, J = 5.9 Hz, 2H), 4.19 (s, 2H), 6.92 (dd, J = 2.4, 8.6 Hz, 1H), 7.06 (d, J = 8.5 Hz, 1H), 7.54 (d, J = 2.2 Hz, 1H); IR ($CHCl_3$) 2981, 1723, 1639, 1610, 1580, 1369 cm^{-1}; MS (FD) *m/e* 591. Anal. ($C_{30}H_{46}N_4O_8\cdot 0.4H_2O$) C, H, N.

7-[[3-[(Aminoiminomethyl)amino]propyl]oxy]-3,4-dihydro-1-oxo-2(1*H*)-isoquinolineacetic Acid Monohydrochloride (15). Following the general procedure employed for the preparation of **14a**, **15** was prepared in a like manner: ^{1}H NMR (300 MHz, CD_3OD) 1.95 (m, 2H), 2.87 (t, J = 6.6 Hz, 2H), 3.29 (t, J = 6.8 Hz, 2H), 3.55 (t, J = 6.8 Hz, 2H), 3.98 (t, J = 5.9 Hz, 2H), 4.20 (s, 2H), 6.96 (dd, J = 2.7, 8.4 Hz, 1H), 7.10 (d, J = 8.35 Hz, 1H), 7.36 (d, J = 2.7 Hz, 1H); IR (film) 3329, 3162, 1734, 1653, 1605, 1053 cm^{-1}; MS (FAB) *m/e* 321. Anal. ($C_{15}H_{21}N_4O_4Cl\cdot 1.5H_2O$) C, H, N.

7-[[4-[(Aminoiminomethyl)amino]butyloxy]-3,4-dihydro-1-oxo-2(1*H*)-isoquinolineacetic Acid Monohydrochloride (16). Following the general procedure employed for the preparation of **14a**, **16** was prepared in a like manner: ^{1}H NMR (300 MHz, CD_3OD) 1.91 (m, 4H) 2.95 (t, J = 6.5 Hz, 2H), 3.24 (m, 2H), 3.63 (t, J = 6.7 Hz, 2H), 4.03 (t, J = 5.9 Hz, 2H), 4.29 (s, 2H), 7.01 (dd, J = 2.5, 8.4 Hz, 1H), 7.19 (d, J = 8.5 Hz, 1H), 7.40 (m, 1H), 7.44 (d, J = 2.5 Hz, 1H); IR (KBr) 3392, 1722, 1646, 1604, 1451 cm^{-1}; MS (FAB) *m/e* 335. Anal. ($C_{16}H_{23}N_4O_4Cl$) C, H, N.

General Procedure for the Preparation of Intermediates 18a−d. Preparation of 6-[[[*N*-[(Dimethylethoxy)carbonyl]piperidin-4-yl]methyl]oxy]-3,4-dihydro-1-oxo-2(1*H*)-isoquinolineacetic Acid (18d). A mixture of **9** (0.21 g, 0.74 mmol), bromide **17d** (0.26 g, 0.80 mmol), K_2CO_3 (0.11 g, 0.80 mmol), and acetone (10 mL) was treated with a catalytic amount of Bu_4NI and maintained at reflux for 16 h. This mixture was then diluted with EtOAc (100 mL) and washed with H_2O (2 × 25 mL). The organic material was then dried ($MgSO_4$) and concentrated. The crude residue was purified by chromatography (silica gel, 240−400 mesh, hexanes/EtOAc, 1:1), providing 0.30 g (78%) of the title compound as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) 1.15 (m, 2H), 1.25 (m, 2H), 1.43 (s, 9H), 1.45 (s, 9H), 1.46 (m, 3H), 1.60 (m, 2H), 1.75 (m, 2H), 2.62 (m, 2H), 2.95 (t, J = 6.5 Hz, 2H), 3.59 (t, J = 6.4 Hz, 2H), 3.95 (t, J = 6.4 Hz, 2H), 4.10 (m, 2H), 4.19 (s, 2H), 6.62 (d, J = 2.4 Hz, 1H), 6.79 (dd, J = 2.2, 8.6 Hz, 1H), 8.01 (d, J = 8.6 Hz, 1H); IR (KBr) 2930, 1746, 1679, 1649, 1603, 1154 cm^{-1}; MS (FAB) *m/e* 517; mp 94−95 °C. Anal. ($C_{29}H_{44}N_2O_6\cdot 0.5H_2O$) C, H, N.

6-[[[*N*-[(Dimethylethoxy)carbonyl]piperidin-4-yl]methyl]oxy]-3,4-dihydro-1-oxo-2(1*H*)-isoquinolineacetic Acid (18a). Compound **18a** was prepared following the general procedure outlined for **18d**: ^{1}H NMR (300 MHz, $CDCl_3$) 1.15 (m, 2H), 1.48 (s, 18H), 1.85 (m, 2H), 2.0 (m, 1H), 2.75 (m, 2H), 3.03 (t, J = 6.5 Hz, 2H), 3.62 (t, J = 6.4 Hz, 2H), 3.85 (d, J = 6.3 Hz, 2H), 4.08 (m, 2H), 4.23 (s, 2H), 6.66 (d, J = 2 Hz, 1H), 6.80 (dd, J = 2.5, 8.7 Hz, 1H), 8.00 (d, J = 8.6 Hz, 1H); IR (KBr) 1739, 1707, 1638, 1609, 1417, 1278 cm^{-1}; MS (FD) *m/e* 474; mp 157−160 °C. Anal. ($C_{26}H_{38}N_2O_6$) C, H, N.

6-[[[*N*-[(Dimethylethoxy)carbonyl]piperidin-4-yl]ethyl]oxy]-3,4-dihydro-1-oxo-2(1*H*)-isoquinolineacetic Acid (18b). Compound **18b** was prepared following the general procedure outlined for **18d**: ^{1}H NMR (300 MHz, $CDCl_3$) 1.20 (m, 2H), 1.44 (s, 9H), 1.46 (s, 9H), 1.75 (m, 5H), 2.73 (m, 2H), 2.99 (t, J = 6.6 Hz, 2H), 3.60 (t, J = 6.4 Hz, 2H), 4.03 (t, J = 6.1 Hz, 2H), 4.09 (m, 2H), 4.21 (s, 2H), 6.63 (d, J = 2.4 Hz, 1H), 6.79 (dd, J = 2.5, 8.6 Hz, 1H), 8.00 (d, J = 8.7 Hz, 1H); IR (KBr) 2943, 1737, 1709, 1641, 1609, 1280 cm^{-1}; MS (FD) *m/e* 488. Anal. ($C_{27}H_{40}N_2O_6$) C, H, N.

6-[[[*N*-[(Dimethylethoxy)carbonyl]piperidin-4-yl]propyl]oxy]-3,4-dihydro-1-oxo-2(1*H*)-isoquinolineacetic Acid (18c). Compound **18c** was prepared following the general procedure outlined for **18d**: ^{1}H NMR (300 MHz, $CDCl_3$) 1.0−1.2 (m, 2H), 1.45 (s, 9H), 1.46 (s, 9H), 1.30−1.50 (m, 3H), 1.60-1.85 (m, 4H), 2.71 (m, 4H), 3.00 (t, J = 6.5 Hz, 2H), 3.60 (t, J = 6.45 Hz, 2H), 3.91 (t, H = 6.4 Hz, 2H), 4.07 (m, 2H), 4.21 (s, 2H), 6.64 (d, J = 1.4 Hz, 1H), 6.79 (dd, J = 2.1, 8.7 Hz, 1H), 7.99 (d, J = 8.6 Hz, 1H); IR (KBr) 2975, 1750, 1732, 1685, 1647, 1259 cm^{-1}; MS (FD) *m/e* 502; mp 113−115 °C. Anal. ($C_{28}H_{42}N_2O_6$) C, H, N.

General Procedure for the Preparation of Compounds 19. 6-[[4-(Piperidin-4-yl)butyl]oxy]-3,4-dihydro-1-oxo-2(1*H*)-isoquinolineacetic Acid Trifluoroacetate (19d). A solution of **18d** (0.30 g, 0.58 mmol) and anhydrous TFA was allowed to stand at room temperature and then concentrated. The crude residue was taken up in H_2O (20 mL) and extracted with Et_2O (2 × 10 mL). The aqueous material was then lyophilized, providing 0.24 g (90%) of **19d** as a hygroscopic solid: ^{1}H NMR (300 MHz, DMSO) 1.14 (m, 4H), 1.45 (m, 3H), 1.81 (m, 4H), 2.80 (m, 2H), 2.94 (t, J = 6.6 Hz, 2H), 3.25 (m, 2H), 3.58 (t, J = 6.7 Hz, 2H), 4.02 (t, J = 6.4 Hz, 2H), 4.16 (s, 2H), 6.83 (s, 1H), 6.86 (dd, J = 2.2, 8.6 Hz, 1H), 7.78 (d, J = 8.6 Hz, 1H); IR (KBr) 2944, 1736, 1699, 1647, 1610, 1278 cm^{-1}; MS (FAB) *m/e* 361. Anal. ($C_{22}H_{29}N_2O_6F_3\cdot 0.5H_2O$) C, H, N.

6-[(Piperidin-4-ylmethyl)oxy]-3,4-dihydro-1-oxo-2(1*H*)-isoquinolineacetic Acid Monohydrochloride (19a). Following the general procedure outlined for the preparation of **19d**, **18a** was deprotected with TFA in a similar fashion. The crude TFA salt was then dissolved in H_2O, treated with aqueous HCl, and lyophilized, providing **19a** as a hygroscopic solid: ^{1}H NMR (300 MHz, CD_3OD) 1.59 (m, 2H), 2.05 (m, 3H), 3.0 (m, 4H), 3.2 (m, 2H), 3.68 (t, J = 6.5 Hz, 2H), 3.98 (d, J = 5.9 Hz, 2H), 4.28 (s, 2H), 6.81 (d, J = 2.3 Hz, 1H), 6.89 (dd, J = 2.5, 8.6 Hz, 1H), 7.85 (d, J = 8.7 Hz, 1H); IR (KBr) 2941, 2821, 1706, 1645, 1609, 1436, 1031 cm^{-1}; MS (FAB) *m/e* 319. Anal. ($C_{17}H_{23}N_2O_4Cl\cdot 0.5H_2O$) C, H, N.

6-[(Piperidin-4-ylethyl)oxy]-3,4-dihydro-1-oxo-2(1*H*)-isoquinolineacetic Acid Hydrochloride (19b). Following the general procedure outlined for the preparation of **19d**, **18b** was deprotected with TFA in a similar fashion. The crude TFA salt was then dissolved in H_2O, treated with aqueous HCl, and lyophilized, providing **19b** as a hygroscopic solid: ^{1}H NMR (300 MHz, CD_3OD) 1.48 (m, 2H), 1.81 (m, 2H), 1.95 (m, 1H), 2.04 (m, 2H), 3.00 (m, 4H), 3.40 (m, 2H), 3.66 (t, J = 6.9 Hz, 2H), 4.12 (t, J = 6.1 Hz, 2H), 4.28 (s, 2H), 6.83 (d, J = 2.5 Hz, 1H), 6.89 (dd, J = 2.5, 8.5 Hz, 1H), 7.85 (d, J = 8.6 Hz, 1H); IR (KBr) 2941, 1698, 1646, 1609, 1277, 1009 cm^{-1}; MS (FAB) *m/e* 333. Anal. ($C_{18}H_{25}N_2O_4Cl$) C, H, N.

6-[(Piperidin-4-ylpropyl)oxy]-3,4-dihydro-1-oxo-2(1*H*)-isoquinolineacetic Acid Hydrochloride (19c). Following the general procedure outlined for the preparation of **19d**, **18c** was deprotected with TFA in a similar fashion. The crude TFA salt was then dissolved in H_2O, treated with aqueous HCl, and lyophilized, providing **19c** as a hygroscopic solid: ^{1}H NMR (300 MHz, CD_3OD) 1.20−1.45 (m, 4H), 1.65 (m, 1H), 1.80 (m, 2H), 1.98 (br d, J = 14.5 Hz, 2H), 2.80−3.05 (m, 4H), 3.36 (br d, J = 12.7 Hz, 2H), 3.65 (t, J = 6.6 Hz, 2H), 4.03 (t, J = 6.0 Hz, 2H), 4.27 (s, 2H), 6.78 (s, 1H), 6.84 (d, J = 8.5 Hz, 1H), 7.83 (d, J = 8.6 Hz, 1H); IR (KBr) 2951, 1781, 1745, 1652, 1602, 1190 cm^{-1}; MS (FAB) *m/e* 347.1956 (347.1971 calcd for $C_{19}H_{27}N_2O_4$).

6-[(4-Cyanophenyl)methoxy]-3,4-dihydro-1-oxo-2(1*H*)-isoquinolineacetic Acid 1,1-Dimethylethyl Ester (20). A mixture of **8** (1.0 g, 3.60 mmol), α-bromo-*p*-tolunitrile (0.71 g, 3.60 mmol), K_2CO_3 (0.5 g, 3.60 mmol), and acetone (35 mL) was maintained at reflux for 4 h and then allowed to cool to room temperature. This mixture was filtered, and the filtrate was concentrated to dryness. The crude isolate was purified by chromatography (silica gel, 200−400 mesh, 1:1 hexanes/EtOAc), which provided 1.38 g of **20** as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) 1.51 (s, 9H), 3.05 (t, J = 6.5 Hz, 2H), 3.66 (t, J = 6.5 Hz, 2H), 4.26 (s 2H), 5.20 (s, 2H), 6.77 (d, J = 1.7 Hz, 1H), 6.91 (dd, J = 2.2, 8.7 Hz, 1H), 7.55 (d, J = 8.1 Hz, 2H), 7.73 (d, J = 8.0 Hz, 2H), 8.05 (d, J = 8.6 Hz, 1H); IR (KBr) 2110, 1737, 1651, 1604, 1153 cm^{-1}; MS (FD) *m/e* 392. Anal. ($C_{23}H_{30}N_2O_4$) C, H, N.

General Procedure for Conversion of Aryl Nitriles to BOC-Protected Amidines. 6-[[4-[[[(1,1-dimethylethoxy)carbonyl]amino]iminomethyl]phenyl]methoxy]-3,4-dihydro-1-oxo-2(1*H*)-isoquinolineacetic Acid 1,1-Dimethylethyl Ester (22). A mixture of **20** (0.38 g, 0.98 mmol), pyridine (5.5 mL), and Et_3N (0.55 mL) was saturated with H_2S(g) and allowed to stand at room temperature for 2 days. This solution was then diluted with H_2O, the resulting mixture was extracted with EtOAc, and the extracts were concentrated. The crude isolate was taken up in a mixture of acetone (5 mL) and CH_3I (2.5 mL) and maintained at reflux for 1 h. This mixture was allowed to cool to room temperature and then concentrated. The crude material was dissolved in MeOH (5 mL) and treated with NH_4OAc (0.23 g, 2.9 mmol) This mixture was maintained at 60 °C for 2 h and then concentrated. The material thus isolated was suspended in THF/H_2O (1:1, 6 mL) and treated with K_2CO_3 (0.179 g, 1.30 mmol) and di-*tert*-butyl dicarbonate (0.202 g, 0.95 mmol), and the resulting mixture was stirred at room temperature for 2 h. The reaction mixture was then diluted with EtOAc and washed with H_2O. The organic material was then concentrated to dryness, and the crude residue was purified by chromatography (silica gel, 30:1 $CHCl_3$/MeOH), giving 0.31 g (62%) of **22** as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) 1.46 (s, 9H), 1.54 (s, 9H), 2.98 (t, J =

6.5 Hz, 2H), 3.60 (t, J = 6.6 Hz, 2H), 4.20 (s, 2H), 5.12 (s, 2H), 6.70 (d, J = 2.3 Hz, 1H), 6.84 (dd, J = 2.4, 8.6 Hz, 1H), 7.43 (d, J = 8.1 Hz, 2H), 7.86 (d, J = 8.2 Hz, 2H), 7.91 (d, J = 8.6 Hz, 1H); IR ($CHCl_3$) 1738, 1648, 1611, 1479, 1276, 1156 cm^{-1}; MS (FAB) *m/e* 510. Anal. ($C_{28}H_{35}N_3O_6$) C, H, N.

General Procedure for the Preparation of Amidine−Acid Derivatives. Preparation of 6-[[4-(Aminoiminomethyl)phenyl]methoxy]-3,4-dihydro-1-oxo-2(1*H*)-isoquinolineacetic Acid Mono(trifluoroacetate) (24.) A mixture of **22** (0.31 g, 0.62 mmol) and anhydrous TFA (5 mL) was maintained at room temperature for 1 h and then concentrated. The residue was triturated with Et_2O, and the formed solid was collected by filtration, providing 0.31 g of **22** as a white solid: ^{1}H NMR (300 MHz, CD_3OD) 3.03 (t, J = 6.1 Hz, 2H), 3.66 (t, J = 6.4 Hz, 2H), 4.29 (s, 2H), 5.30 (s, 2H), 6.91 (d, J = 2.4 Hz, 1H), 6.98 (dd, J = 2.6, 8.7 Hz, 1H), 7.70 (d, J = 8.3 Hz, 2H), 7.81 (d, J = 8.2 Hz, 2H), 7.86 (d, J = 8.7 Hz, 1H); IR (KBr) 3333, 1696, 1669, 1605, 1458, 1118 cm^{-1}; MS (FAB) *m/e* 354. Anal. ($C_{21}H_{20}N_3O_6F_3$) C, H, N.

7-[(4-Cyanophenyl)methoxy]-3,4-dihydro-1-oxo-2(1*H*)-isoquinolineacetic Acid 1,1-Dimethylethyl Ester (21). Following the procedure employed for the preparation of **20**, **21** was prepared starting from **9** and α-bromo-*p*-tolunitrile: ^{1}H NMR (300 MHz, $CDCl_3$) 1.46 (s, 9H), 2.97 (t, J = 6.5 Hz, 2H), 3.60 (t, J = 6.6 Hz, 2H), 4.20 (s, 2H), 5.14 (s, 2H), 7.02 (dd, J = 2.7, 8.3 Hz, 1H), 7.10 (d, J = 8.3 Hz, 1H), 7.52 (d, J = 8.2 Hz, 2H), 7.64 (m, 3H); IR (KBr) 3019, 1738, 1650, 1607, 1484, 1153 cm^{-1}; MS (FD) *m/e* 392; mp 108−110 °C. Anal. ($C_{23}H_{30}N_2O_4$) C, H, N.

7-[[4-[[[(1,1-Dimethylethoxy)carbonyl]amino]-iminomethyl]phenyl]methoxy]-3,4-dihydro-1-oxo-2(1*H*)-isoquinolineacetic Acid 1,1-Dimethylethyl Ester (23). Following the general procedure employed for the preparation of **22**, **23** was formed in a like manner starting from **21**: ^{1}H NMR (300 MHz, $CDCl_3$) 1.47 (s, 9H), 1.55 (s, 9H), 2.97 (t, J = 6.5 Hz, 2H), 3.61 (t, J = 6.5 Hz, 2H), 4.22 (s, 2H), 5.13 (s, 2H), 7.06 (m, 2H), 7.47 (d, J = 8.0 Hz, 2H), 7.65 (d, J = 1.4 Hz, 1H), 7.85 (d, J = 8.0 Hz, 2H); IR (KBr) 3369, 2977, 1741, 1656, 1621, 1498, 1151 cm^{-1}; MS (FAB) *m/e* 510; mp 178−180 °C. Anal. ($C_{28}H_{35}N_3O_6$) C, H, N.

7-[[4-(Aminoiminomethyl)phenyl]methoxy]-3,4-dihydro-1-oxo-2(1*H*)-isoquinolineacetic Acid Mono(trifluoroacetate) (25). Following the procedure employed for the deprotection of **24**, **25** was prepared in a like manner: ^{1}H NMR (300 MHz, CD_3OD) 2.97 (t, J = 6.5 Hz, 2H), 3.65 (t, J = 6.5 Hz, 2H), 4.29 (s, 2H), 5.25 (s, 2H), 7.13 (m, 2H), 7.51 (d, J = 2.0 Hz, 1H), 7.68 (d, J = 8.2 Hz, 2H), 7.79 (d, J = 8.2 Hz, 2H); IR (KBr) 3334, 3109, 1670, 1606, 1494, 1134 cm^{-1}; MS (FAB) *m/e* 354; mp 216−218 °C dec. Anal. ($C_{21}H_{20}N_3O_6F_3$) C, H, N.

6-[(4-Cyanophenyl)ethoxy]-3,4-dihydro-1-oxo-2(1*H*)-isoquinolineacetic Acid 1,1-Dimethylethyl Ester (26). A solution of phenol **8** (0.20 g, 0.72 mmol), 2-(4-cyanophenyl)-ethanol (0.16 g, 0.72 mmol), triphenylphosphine (0.21 g, 0.79 mmol), and THF (10 mL) was treated with diethyl azodicarboxylate (0.14 g, 0.79 mmol) and then maintained at room temperature for 2 h. This solution was then diluted with EtOAc (100 mL) and washed with H_2O (2 × 25 mL) and concentrated. The residue was passed through a plug of silica (hexanes/EtOAc, 3:2), and the residue which was obtained after concentration was recrystallized from EtOAc/hexanes. This purification sequence provided 0.2 g (68%) of **26** as an off-white solid: ^{1}H NMR (300 MHz, $CDCl_3$) 1.42 (s, 9H), 2.94 (t, J = 6.5 Hz, 2H), 3.10 (t, J = 6.4 Hz, 2H), 3.56 (t, J = 6.6 Hz, 2H), 4.17 (m, 4H), 6.59 (d, J = 1.7 Hz, 1H), 6.74 (dd, J = 8.6, 2.1 Hz, 1H), 7.26 (s, 1H), 7.35 (d, J = 8.1 Hz, 2H), 7.54 (d, J = 8.3 Hz, 2H) 7.95 (d, J = 8.3 Hz, 1H); IR (KBr) 2220, 1736, 1724, 1654, 1613, 1236, 1152 cm^{-1}; MS (FD) *m/e* 406; mp 103−106 °C. Anal. ($C_{24}H_{26}N_2O_4$) C, H, N.

6-[[4-[[[(1,1-Dimethylethoxy)carbonyl]amino]-iminomethyl]phenyl]ethoxy]-3,4-dihydro-1-oxo-2(1*H*)-isoquinolineacetic Acid 1,1-Dimethylethyl Ester (27). Following the general sequence employed for the preparation of **22**, **27** was prepared starting from **26**: ^{1}H NMR (300 MHz, $CDCl_3$) 1.46 (s, 9H), 1.54 (s, 9H), 2.98 (t, J = 6.5 Hz, 2H), 3.13 (t, J = 6.69 Hz, 2H), 3.59 (t, J = 6.5 Hz, 2H), 4.20 (m, 4H), 6.62 (d, J = 2.3 Hz, 1H), 6.79 (d, J = 8.7 Hz, 1H), 7.26 (s, 1H), 7.34 (d, J = 8.2 Hz, 2H), 7.80 (d, J = 8.2 Hz, 2H), 7.99 (d, J = 8.7 Hz, 1H); IR (KBr) 1737, 1650, 1620, 1604, 1278 cm^{-1}; MS (FAB) *m/e* 523; mp 146−149 °C. Anal. ($C_{29}H_{37}N_3O_6$) C, H, N.

6-[[4-(Aminoiminomethyl)phenyl]ethoxy]-3,4-dihydro-1-oxo-2(1*H*)-isoquinolineacetic Acid Monohydrochloride (28). Following the general reaction outlined for the preparation of **24**, **27** was deprotected with TFA, providing **28**: ^{1}H NMR (300 MHz, CD_3OD) 3.00 (t, J = 6.7 Hz, 2H), 3.21 (t, J = 6.1 Hz, 2H), 3.65 (t, J = 6.6 Hz, 2H), 4.28 (s, 2H), 4.33 (t, J = 6.2 Hz, 2H), 6.78 (d, J = 2.2 Hz, 1H), 6.83 (dd, J = 2.5, 8.7 Hz, 1H), 7.57 (d, J = 8.4 Hz, 2H), 7.74 (d, J = 8.3 Hz, 2H), 7.82 (d, J = 8.6 Hz, 1H); IR (KBr) 3354, 3075, 1697, 1628, 1601, 1485, 1280, 1249, 1187 cm^{-1}; MS (FAB) *m/e* 368; mp 76−78 °C dec. Anal. ($C_{20}H_{22}N_3O_4Cl\cdot 2H_2O$) C, H, N.

3,4-Dihydro-1-oxo-6-[[(trifluoromethyl)sulfonyl]oxy]-2(1*H*)-isoquinolineacetic Acid 1,1-Dimethylethyl Ester (29). To a solution of **8** (9.5 g, 34.2 mmol) and freshly distilled pyridine (250 mL) was added trifluoromethanesulfonic anhydride (5.8 mL, 34.2 mmol) at 0 °C. The resulting solution was allowed to warm to room temperature and then quenched by the addition of H_2O (125 mL). The mixture was extracted with EtOAc and the extract dried ($MgSO_4$) and concentrated. The crude material was purified by chromatography (silica gel, 4:1 hexanes/EtOAc) to give 11.54 g (82%) of **29** as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) 3.12 (t, J = 6.5 Hz, 2H), 3.69 (t, J = 6.5 Hz, 2H), 4.24 (s, 2H), 7.14 (d, J = 2.2 Hz, 1H), 7.23 (dd, J = 2.3, 8.7 Hz, 1H), 8.20 (d, J = 8.7 Hz, 1H); IR ($CHCl_3$) 1660, 1425, 1250, 1153, 1141 cm^{-1}; MS (FD) *m/e* 409; mp 80−82 °C. Anal. ($C_{16}F_3H_{18}NO_6S$) C, H, N.

6-[(4-Cyanophenyl)-(*E*)-ethenyl]-3,4-dihydro-1-oxo-2(1*H*)-isoquinolineacetic Acid 1,1-Dimethylethyl Ester (30). A mixture of **29** (1.0 g, 2.44 mmol), 4-cyanostyrene (0.47 g, 3.66 mmol), palladium(II) acetate (0.55 g, 0.24 mmol), tri-*o*-tolylphosphine (0.149 g, 0.49 mmol), K_2CO_3 (1.69 g, 12.2 mmol), tetrabutylammonium iodide (0.90 g, 2.44 mmol), and anhydrous DMF (10 mL) was maintained at 120 °C for 1.5 h. The reaction mixture was then allowed to cool to room temperature where it was diluted with EtOAc (150 mL) and washed with H_2O. The organic material was concentrated, and the crude isolate was purified by chromatography (silica gel, 3:2 hexanes/EtOAc), providing 0.51 g (53%) of **30**: ^{1}H NMR (300 MHz, $CDCl_3$) 1.48 (s, 9H), 3.08 (t, J = 6.55 Hz, 2H), 3.66 (t, J = 6.5 Hz, 2H), 4.25 (s, 2H), 7.17 (dd, J = 16.21, 18.64 Hz, 2H), 7.33 (s, 1H), 7.49 (d, J = 8.1 Hz, 1H), 7.62 (dd, J = 8.4, 18.7 Hz, 4H), 8.09 (d, J = 8.3 Hz, 1H); IR ($CHCl_3$) 2227, 1738, 1648, 1153 cm^{-1}; MS (FD) *m/e* 388. Anal. ($C_{24}H_{24}N_2O_3$) C, H, N.

6-[[4-[[[(1,1-Dimethylethoxy)carbonyl]amino]-iminomethyl]phenyl]-(*E*)-ethenyl]-3,4-dihydro-1-oxo-2(1*H*)-isoquinolineacetic Acid 1,1-Dimethylethyl Ester (31). Following the procedure outlined for the synthesis of **22**, **31** was prepared in 30% yield, starting from 0.99 g of **30**: ^{1}H NMR (300 MHz, $CDCl_3$) 1.48 (s, 9H), 1.56 (s, 9H), 3.07 (t, J = 6.5 Hz, 2H), 3.65 (t, J = 6.4 Hz, 2H), 4.24 (s, 2H), 7.17 (s, 2H), 7.32 (s, 1H), 7.46 (d, J = 8.2 Hz, 1H), 7.56 (d, J = 8.5 Hz, 2H), 7.86 (d, J = 8.4 Hz, 2H), 8.05 (d, J = 8.0 Hz, 1H); IR (KBr) 3391, 1744, 1642, 1653, 1608, 1283 cm^{-1}; MS (FAB) *m/e* 506. Anal. ($C_{29}H_{30}N_3O_5$) C, H, N.

6-[[4-(Aminoiminomethyl)phenyl]-(*E*)-ethenyl]-3,4-dihydro-1-oxo-2(1*H*)-isoquinolineacetic Acid Mono(trifluoroacetate) (32). Following the procedure outlined for the preparation of **24**, **32** was prepared in 68% yield, starting from 0.14 g of **31**: ^{1}H NMR (300 MHz, CD_3OD) 3.10 (t, J = 6.6 Hz, 2H), 3.70 (t, J = 6.6 Hz, 2H), 4.32 (s, 2H), 7.41 (s, 2H), 7.53 (s, 1H), 7.59 (d, J = 8.2 Hz, 1H), 7.81 (s, 4H), 7.93 (d, J = 8.1 Hz, 1H); IR (KBr) 3337, 3120, 1672, 1608, 1483, 1188 cm^{-1}; MS (FD) *m/e* 349. Anal. ($C_{22}H_{20}N_3O_5F_3\cdot 0.2H_2O$) C, H, N.

6-[(4-Cyanophenyl)ethynyl]-3,4-dihydro-1-oxo-2(1*H*)-isoquinolineacetic Acid 1,1-Dimethylethyl Ester (33). A mixture of **29** (0.33 g, 0.79 mmol), (4-cyanophenyl)acetylene (0.14 g, 1.11 mmol), bis(triphenylphosphine)palladium(II) chloride (0.014 g, 0.02 mmol), anhydrous DMF (2.0 mL), and freshly distilled Et_3N (0.5 mL) was stirred at 90 °C for 1 h. At this time, H_2O (25 mL) was added and the mixture was extracted with EtOAc (2 × 75 mL). The extracts were dried over $MgSO_4$ and concentrated. The crude material was

purified by chromatography (silica gel, 5:2 hexanes/EtOAc) to give 0.17 g (57%) of **33** as an orange solid: ^{1}H NMR (300 MHz, $CDCl_3$) 1.47 (s, 9H), 3.06 (t, J = 6.5 Hz, 2H), 3.65 (t, J = 6.8 Hz, 2H), 4.24 (s, 2H), 7.37 (br s, 1H), 7.50 (d, J = 8.2 Hz, 1H), 7.60 (dd, J = 8.5 Hz, 4H), 8.05 (d, J = 8.0 Hz, 1H); IR (KBr) 2227, 1738, 1649, 1154, 832 cm^{-1}; MS (FD) *m/e* 386; mp 195−197 °C. Anal. ($C_{24}H_{22}N_2O_3$) C, H, N.

6-[[4-[[[(1,1-Dimethylethoxy)carbonyl]amino]-iminomethyl]phenyl]ethynyl]-3,4-dihydro-1-oxo-2(1*H*)-isoquinolineacetic Acid 1,1-Dimethylethyl Ester (34). Following the general reaction sequence employed for the synthesis of **22**, **34** was prepared starting from **33**: ^{1}H NMR (300 MHz, $CDCl_3$) 1.47 (s, 9H), 1.55 (s, 9H), 3.04 (t, J = 6.5 Hz, 2H), 3.63 (t, J = 6.4 Hz, 2H), 4.23 (s, 2H), 7.35 (br s, 1H), 7.47 (d, J = 8.0 Hz, 1H), 7.53 (d, J = 8.3 Hz, 2H), 7.84 (d, J = 8.3 Hz, 2H), 8.01 (d, J = 8.0 Hz, 1H); IR (KBr) 3400, 2990, 1640, 1620, 1150 cm^{-1}; MS (FD) *m/e* 504. Anal. Calcd for $C_{29}H_{33}N_3O_5$: C, 69.17; H, 6.61; N, 8.34. Found: C, 69.36; H, 6.71; N, 8.20.

6-[[4-(Aminoiminomethy)phenyl]ethynyl]-3,4-dihydro-1-oxo-2(1*H*)-isoquinolineacetic Acid Mono(trifluoroacetate) (35). Using the general procedure employed for the deprotection of **22**, **34** was treated with TFA, which provided **35**: ^{1}H NMR (300 MHz, CD_3OD) 3.09 (t, J = 6.71 Hz, 2H), 3.71 (t, J = 6.6 Hz, 2H), 4.86 (s, 2H), 7.50 (s, 1H), 7.54 (d, J = 8.1 Hz, 1H), 7.81 (dd, J = 8.6, 18.0 Hz, 4H), 7.96 (d, J = 8.0 Hz, 1H); IR (KBr) 1709, 1640, 1609, 1126, 732 cm^{-1}; MS (FAB) *m/e* 348; mp 300 °C dec. Anal. ($C_{22}H_{18}N_3O_5F_3 \cdot 1.5H_2O$) C, H, N.

6-[[4-[[[(1,1-Dimethylethoxy)carbonyl]amino]-iminomethyl]phenyl]-(*Z*)-ethenyl]-3,4-dihydro-1-oxo-2(1*H*)-isoquinolineacetic Acid 1,1-Dimethylethyl Ester (36). A mixture of **34** (0.070 g, 0.18 mmol), Pd/$BaSO_4$ (10%, 0.03 g), EtOAc (10 mL), and pyridine (2mL) was maintained under an atmosphere of hydrogen (balloon) for 3 h and then filtered and concentrated. The crude isolate was purified by chromatography (silica gel, 1:1 hexanes/EtOAc) to give 0.051 g (72%) of **36** as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) 1.47 (s, 9H), 1.54 (s, 9H), 2.92 (t, J = 6.65 Hz, 2H), 3.60 (t, J = 6.5 Hz, 2H), 4.22 (s, 2H), 6.66 (s, 2H), 7.01 (s, 1H), 7.15 (d, J = 8.0 Hz, 1H), 7.27 (d, J = 9.0 Hz, 2H), 7.71 (d, J = 8.3 Hz, 2H), 7.92 (d, J = 8.0 Hz, 1H); IR ($CHCl_3$) 1738, 1649, 1609, 1286, 1157 cm^{-1}; MS (FAB) *m/e* 506; mp 92−96 °C. Anal. ($C_{29}H_{30}N_3O_5$) C, H, N.

6-[[4-(Aminoiminomethyl)phenyl]-(*Z*)-ethenyl]-3,4-dihydro-1-oxo-2(1*H*)-isoquinolineacetic Acid Mono(trifluoroacetate) (37). Following the procedure employed for the synthesis of **24**, **37** was prepared in 72% yield starting from 0.051 g of **36**: ^{1}H NMR (300 MHz, CD_3OD) 2.97 (t, J = 6.7 Hz, 2H), 3.67 (t, J = 6.53 Hz, 2H), 4.87 (s, 2H), 6.82 (dd, J = 12, 19 Hz, 2H), 7.14 (m, 2H), 7.43 (d, J = 8.4 Hz, 2H), 7.66 (d, J = 8.5 Hz, 2H), 7.75 (d, J = 7.9 Hz, 1H); IR (KBr) 3101, 1761, 1666, 1606, 1428, 1183 cm^{-1}; MS (FD) *m/e* 350; mp 208−210 °C. Anal. ($C_{22}H_{20}N_3O_5F_3$) C, H, N.

6-[2-[4-[[[(1,1-Dimethylethyl)carbonyl]amino]iminomethyl]phenyl]ethyl]-3,4-dihydro-1-oxo-2(1*H*)-isoquinolineacetic Acid 1,1-Dimethylethyl Ester (38). A mixture of **34** (0.10 g, 0.26 mmol), Pd/C (10% on carbon, 0.1 g), and EtOAc (10 mL) was maintained under an atmosphere of hydrogen (balloon) for 2 h and then filtered and concentrated. The crude isolate was purified by recrystallization from EtOAc/hexanes, which provided 0.095 g (95%) of **38** as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) 1.47 (s, 9H), 1.54 (s, 9H), 2.95 (m, 6H), 3.61 (t, J = 6.4 Hz, 2H), 4.22 (s, 2H), 6.91 (s, 1H), 7.11 (d, J = 8.0 Hz, 1H), 7.18 (d, J = 8.2 Hz, 2H), 7.76 (d, J = 8.2 Hz, 2H), 7.96 (d, J = 8.0 Hz, 1H); IR ($CHCl_3$) 1738, 1648, 1611, 1286, 1155 cm^{-1}; MS (FAB) *m/e* 508; mp 165−168 °C. Anal. ($C_{29}H_{37}N_3O_5$) C, H, N.

6-[2-[4-(Aminoiminomethyl)phenyl]ethyl]-3,4-dihydro-1-oxo-2(1*H*)-isoquinolineacetic Acid Mono(trifluoroacetate) (39). Following the procedure outlined for the preparation of **24**, **39** was prepared in 65% yield starting from 0.06 g of **38**: ^{1}H NMR (300 MHz, CD_3OD) 3.01 (m, 6H), 3.66 (t, J = 6.5 Hz, 2H), 4.29, (s, 2H), 7.11 (m, 2H), 7.40 (d, J = 8.3 Hz 2H), 7.70 (d, J = 8.2 Hz, 2H), 7.79 (d, J = 8.4 Hz, 1H); IR (KBr) 3337, 3111, 1650, 1612, 1209, 1180 cm^{-1}; MS (FAB) *m/e* 352.1665 (352.1661 calcd for $C_{20}H_{22}N_3O_3$). Anal. ($C_{22}H_{22}N_3O_5 \cdot 0.25C_4H_{10}O$) C, H, N.

3,4-Dihydro-6-(methoxycarbonyl)-1-oxo-2(1*H*)-isoquinolineacetic Acid 1,1-Dimethylethyl Ester (40). A solution of **29** (5.0 g, 12.2 mmol), DMF (25 mL), palladium(II) acetate (0.082 g, 0.37 mmol), triphenylphosphine (0.19 g, 0.73 mmol), freshly distilled Et_3N (3.4 mL, 24.4 mmol), and anhydrous MeOH (9.9 mL) was stirred under an atmosphere of CO (balloon) at 65 °C for 15 h. The reaction mixture was then allowed to cool to room temperature where it was diluted with H_2O (100 mL). The resulting mixture was extracted with EtOAc, and the combined extracts were dried ($MgSO_4$) and concentrated. The crude material was purified by chromatography (silica gel, 1:1 hexanes/EtOAc) to provide 2.80 g (72%) of **40** as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) 1.47 (s, 9H), 3.10 (t, J = 6.5 Hz, 2H), 3.66 (t, J = 6.5 Hz, 2H), 3.93 (s, 3H), 4.27 (s, 2H), 7.88 (s, 1H), 7.99 (d, J = 8.1 Hz, 1H), 8.14 (d, J = 8.0 Hz, 1H); IR ($CHCl_3$) 1730, 1722, 1654, 1290, 1154 cm^{-1}; MS (FD) *m/e* 319. Anal. ($C_{17}H_{21}NO_5$) C, H, N.

6-Carboxy-3,4-dihydro-1-oxo-2(1*H*)-isoquinolineacetic Acid 1,1-Dimethylethyl Ester (41). A solution of **40** (2.8 g, 8.7 mmol) and THF (87 mL) was treated with aqueous LiOH (87 mL of a 0.1 N solution, 8.7 mmol), and the resulting solution was maintained at room temperature for 12 h. The reaction mixture was then concentrated to half volume and extracted with EtOAc. The remaining aqueous material was acidified to pH 5 with 1 N HCl, and this mixture was extracted with EtOAc. The extracts were concentrated, providing 2.2 g of **41** as an essentially pure clear oil (85%): ^{1}H NMR (300 MHz, $CDCl_3$) 1.43 (s, 9H), 3.15 (t, J = 6.5 Hz, 2H), 3.71 (t, J = 6.4 Hz, 2H) 4.22 (s, 2H), 7.99 (m, 3H); IR ($CHCl_3$) 3109, 1699, 1651, 1154 cm^{-1}; MS (FD) *m/e* 306. Anal. ($C_{16}H_{19}NO_5$) C, H, N.

3,4-Dihydro-1-oxo-6-[[(phenylmethoxy)carbonyl]-amino]-2(1*H*)-isoquinolineacetic Acid 1,1-Dimethylethyl Ester (42). A solution of **41** (0.20 g, 0.66 mmol) and anhydrous toluene (50 mL) was treated with diphenyl phosphorazidate (0.28 mL, 1.31 mmol) and freshly distilled Et_3N (0.18 mL, 1.31 mmol), and the resulting solution was maintained at 85 °C for 2 h. The reaction mixture was then allowed to cool to room temperature where it was treated with benzyl alcohol (0.14 mL, 1.31 mmol) and stirred for an additional hour. The reaction mixture was then concentrated and the crude isolate purified by chromatography (silica gel, 1:1 hexanes/EtOAc) to yield 0.21 g (79%) of **42** as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) 1.45 (s, 9H), 2.96 (t, J = 6.5 Hz, 2H), 3.56 (t, J = 6.5 Hz, 2H), 4.19 (s, 2H), 5.18 (s, 2H), 7.16 (dd, J = 2.0, 8.4 Hz, 1H), 7.30 (m, 5H), 7.50 (s, 1H), 7.60 (s, 1H), 7.95 (d, J = 2.4 Hz, 1H); IR ($CHCl_3$) 3431, 3011, 1738, 1647, 1524 cm^{-1}; MS (FD) *m/e* 410. Anal. ($C_{16}H_{19}NO_5$) C, H, N.

6-Amino-3,4-dihydro-1-oxo-2(1*H*)-isoquinolineacetic Acid 1,1-Dimethylethyl Ester (43). A mixture of **42** (0.20 g, 0.49 mmol), EtOH (20 mL), EtOAc (20 mL), and Pd/C (0.2 g of 10% on carbon) was stirred under an atmosphere of hydrogen (balloon) for 1 h and then filtered and concentrated, giving 1.3 g (95%) of **43** as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) 1.49 (s, 9H), 2.94 (t, J = 6.6 Hz, 2H), 3.58 (t, J = 6.6 Hz, 2H), 4.21 (s, 2H), 6.41 (d, J = 1.72 Hz, 1H), 6.06 (dd, J = 1.7, 8.3 Hz, 1H), 7.89 (d, J = 8.3 Hz, 1H); IR ($CHCl_3$) 3008, 1737, 1640, 1621, 1607, 1154 cm^{-1}; MS (FD) *m/e* 276; mp 138−140 °C. Anal. ($C_{15}H_{20}N_2O_3$) C, H, N.

6-[(4-Cyanobenzoyl)amino]-3,4-dihydro-1-oxo-2(1*H*)-isoquinolineacetic Acid 1,1-Dimethylethyl Ester (44). A solution of **43** (0.125 g, 0.45 mmol), anhydrous dichloromethane (2.5 mL), 4-cyanobenzoic acid (0.066 g, 0.45 mmol), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.095 g, 0.50 mmol), and DMAP (0.01g) was maintained at room temperature for 2 h and then diluted with EtOAc (100 mL). This mixture was washed with H_2O and then concentrated. The crude isolate was purified by chromatography (silica gel, 2:1 hexanes/EtOAc) to give 0.18 g (96%) of **44** as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) 1.47 (s, 9H), 3.10 (t, J = 6.5 Hz, 2H), 3.66 (t, J = 6.57 Hz, 2H), 4.23 (s, 2H), 7.32 (dd, J = 2.1, 8.5 Hz, 1H), 7.80 (d, J = 8.5 Hz, 1H), 7.85 (s, 1H), 8.02 (dd, J = 8.5, 10.5 Hz, 4H), 8.20 (s, 1H); IR ($CHCl_3$)

3010, 2270, 1738, 1647, 1524, 1429 cm^{-1}; MS (FD) *m/e* 405. Anal. ($C_{23}H_{23}N_3O_4$) C, H, N.

6-[[4-[[[(1,1-Dimethylethoxy)carbonyl]amino]-iminomethyl]benzoyl]amino]-3,4-dihydro-1-oxo-2(1*H*)-isoquinolineacetic Acid 1,1-Dimethylethyl Ester (45). Following the procedure employed for the synthesis of **22**, compound **45** was prepared in 36% yield starting from 0.17 g of **44**: ^{1}H NMR (300 MHz, $CDCl_3$) 1.46 (s, 9H), 1.50 (s, 9H), 2.90 (t, J = 6.2 Hz, 2H), 3.55 (t, J = 6.3 Hz, 2H), 4.16 (s, 2H), 7.46 (m, 3H), 7.64 (d, J = 8.2 Hz, 2H), 7.78 (m, 2H), 9.91 (br s, 1H); IR ($CHCl_3$) 2984, 1740, 1538, 1272, 1152 cm^{-1}; MS (FAB) *m/e* 523. Anal. ($C_{28}H_{34}N_4O_6$) C, H, N.

6-[[4-(Aminomethyl)benzoyl]amino]-3,4-dihydro-1-oxo-2(1*H*)-isoquinolineacetic Acid Mono(trifluoroacetate) (46). Following the procedure employed for the synthesis of **24**, **46** was prepared in 76% yield starting from 0.07 g of **45**: ^{1}H NMR (300 MHz, CD_3OD) 3.09 (t, J = 6.6 Hz, 2H), 3.72 (t, J = 6.6 Hz, 2H), 4.32 (s, 2H), 7.67 (m, 1H), 7.80 (br s, 1H), 7.94 (d, J = 8.3 Hz, 3H), 8.16 (d, J = 8.2 Hz, 2H); IR (KBr) 3354, 3007, 1634, 1538, 1196 cm^{-1}; MS (FAB) *m/e* 367. Anal. ($C_{21}H_{19}F_3N_4O_6$) C, H, N.

6-[[(4-Cyanophenyl)amino]carbonyl]-3,4-dihydro-1-oxoisoquinolineacetic Acid 1,1-Dimethylethyl Ester (47). A mixture of **41** (0.20 g, 0.66 mmol) and toluene (5 mL) was treated with oxalyl chloride (0.07 mL, 0.78 mmol) and a catalytic amount of DMF at room temperature. After 1 h, the solution was concentrated to dryness, the crude residue was taken up in CH_2Cl_2 (1 mL), and this solution was treated sequentially with pyridine (1 mL) and 4-cyanoanaline (0.09 g, 0.79 mmol). The resulting mixture was stirred at room temperature for 1 h, diluted with EtOAc (100 mL), and washed with H_2O (3 × 20 mL). The organic material was dried ($MgSO_4$) and concentrated. The crude residue was recrystallized from EtOAc/hexanes, providing 0.26 g (80%) of **47** as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) 1.44 (s, 9H), 3.06 (t, J = 6.5 Hz, 2H), 3.65 (t, J = 6.5 Hz, 2H), 4.21 (s, 2H), 7.69 (m, 4H), 7.91 (m, 3H); IR (KBr) 2222, 1730, 1679, 1529, 1319 cm^{-1}; MS (FD) *m/e* 405; mp 220 °C dec. Anal. ($C_{23}H_{23}N_3O_4$) C, H, N.

6-[[[4-[[[(1,1-Dimethylethoxy)carbonyl]amino]-iminomethyl]phenyl]amino]carbonyl]-3,4-dihydro-1-oxo-2(1*H*)-isoquinolineacetic Acid 1,1-Dimethylethyl Ester (48). Compound **48** was prepared following the general procedure employed for the synthesis of **24**: ^{1}H NMR (300 MHz, $CDCl_3$) 1.45 (s, 9H), 1.54 (s, 9H), 3.04 (m, 2H), 3.62 (t, J = 6.4 Hz, 2H), 4.21 (s, 2H), 7.6−7.8 (m, 7H), 8.02 (m, 1H); IR ($CHCl_3$) 3304, 2978, 1740, 1641, 1602, 1582, 1498 cm^{-1}; MS (FAB) 523. Anal. ($C_{28}H_{34}N_4O_5$) C, H, N.

6-[[[4-(Aminoiminomethyl)phenyl]amino]carbonyl]-3,4-dihydro-1-oxo-2(1*H*)-isoquinolineacetic Acid Mono(trifluoroacetate) (49). Compound **49** was prepared following the general procedure outlined for the preparation of **25**: ^{1}H NMR (300 MHz, CD_3OD) 3.18 (t, J = 6.54 Hz, 2H), 3.75 (t, J = 6.8 Hz, 2H), 4.35 (s, 2H), 7.8−7.9 (m, 4H), 7.9−8.1 (m, 3H); IR (KBr) 3400, 1707, 1666, 1655, 1637, 1611, 1482, 1191 cm^{-1}; MS (FAB) *m/e* 367. Anal. ($C_{21}H_{19}N_4O_6F_3 \cdot 0.5H_2O$) C, H, N.

GPIIb−IIIa ELISA. The ability of the compounds to antagonize the binding of fibrinogen to GPIIb−IIIa was determined by ELISA (enzyme-linked immunoadsorbent assay) utilizing purified human platelet GPIIb−IIIa, biotinylated fibrinogen, alkaline phosphatase-labeled goat antibiotin, and *p*-nitrophenol phosphate as previously described.[72]

Platelet Aggregation Assay. Assessment of functional blockade of GPIIb−IIIa was made using ADP-induced platelet aggregation in human platelet-rich plasma (PRP). Varying concentrations of test compound or vehicle were incubated in human PRP for 1 min prior to the addition of ADP (5 μM), and the aggregation response was followed turbidometrically.[73]

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