From Peptide to Non-Peptide. 2. The *de Novo* Design of Potent, Non-Peptidal Inhibitors of Platelet Aggregation Based on a Benzodiazepinedione Scaffold

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Abstract: Earlier studies of peptides containing the arginine-glycine-aspartic acid (RGD) sequence led to the development of a structural model describing the three-dimensional presentation required for RGD-mediated inhibition of glycoprotein IIbIIIa/fibrinogen binding. We describe here the use of that structural model to design a rigid, non-peptidal lead series that reproduces the topography of the peptide backbone using a benzodiazepinedione scaffold. This scaffold is used to synthesize novel molecules which are highly potent inhibitors of platelet aggregation and which possess improved bioavailability. The importance of shape as a design criterion is demonstrated by constructing molecules that present alternative topographies; these molecules are shown to be significantly less potent.

Introduction

In earlier studies, we defined a conformation of the arginine-glycine-aspartic acid (RGD) sequence that is responsible for inhibiting platelet aggregation via interaction with glycoprotein IIbIIIa (GPIIbIIIa). The structural and chemical requirements for RGD-mediated antagonism were independently explored using NMR studies of a rigid, potent peptide (G4120)[1] and molecular dynamics simulations of an ensemble of flexible active analogs.[2] Both of these approaches suggested that a "cupped" presentation of the RGD sequence was important for potency; the rigidity of G4120 furthermore indicated that a non-peptidal analog with a rigid core could be tolerated by GPIIbIIIa. Rather than use sequential modifications to evolve a non-peptide from a peptide,[3] we elected to design a non-peptidal scaffold to fit the contour and volume of the peptide backbone of G4120. We focused our design on rigid scaffolds that would enable us to decouple the manipulation of functional variables (e.g., positioning and modification of side chains or hydrophobic groups) from the manipulation of overall shape. The structural and functional information obtained from such an approach could subsequently be transferred to alternate frameworks, if necessary.[4]

Materials and Methods

Design Considerations. The specific choice of design targets was governed by the structural studies of cyclic peptides and linear analogs. Although we were confident that the cupped shape of the RGD sequence observed in the solution structure of G4120 was related to its bound-state conformation, we wished to construct a framework that would allow us to explore systematic variations of this shape in order to identify more precisely the dispositions of the side chains. In linear RGD peptides, the aspartic acid cannot be replaced by either a D-Asp[5] or Glu[6] without a complete loss in activity, suggesting that this residue constitutes a critical recognition element. We therefore wanted to incorporate into our scaffold the ability to reproduce the pseudoaxial presentation of the Asp side chain in G4120. By contrast, we observed in linear analogs that diverse "side chains" could be used to deliver the guanidine. We also wanted to expore the possible role of a hydrogen bond acceptor to mimic the Gly amide oxygen and provide for the attachment of hydrophobic groups in regions corresponding to the cysteine and tyrosine side chains of G4120.

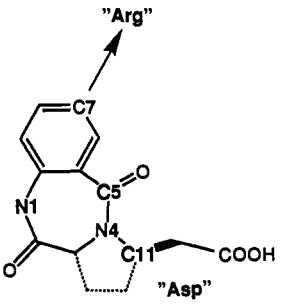

Figure 1. Pyrrolo[1,4]benzodiazepine-2,5-dione scaffold indicating the numbering scheme used throughout the text.

Crystallographic and model-built structures of a number of rigid, pharmaceutically tolerated compounds were evaluated as potential scaffolds using the above criteria. This evaluation focused our design on compounds derived from a fused 6/7 (benzapine) framework, which is found in a number of known drugs such as diazepam[7] and anthramycin.[8] This framework maintains a cupped shape due to the fusion of the aromatic and seven-membered rings. The aromatic ring affords a number of positions for probing the "Arg" side chain vector, while the hybridization and stereochemistry within the seven-membered ring can be altered to provide subtle variations in shape and electrostatic profile. Incorporating a third ring allows precise control of the "Asp" side-chain presentation.

Further analysis lead to the specific design of a series of molecules containing a pyrrolo[1,4]benzodiazepine-2,5-dione framework (Figure

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(1) McDowell, R. S.; Gadek, T. R. *J. Am. Chem. Soc.* **1992**, *114*, 9245.
(2) McDowell, R. S.; Gadek, T. R.; Barker, P. L.; Burdick, D. J.; Chan, K. S.; Quan, C. L.; Struble, M.; Thorsett, E. D.; Tischler, M.; Tom, J. Y. K.; Webb, T. R.; Burnier, J. P. *J. Am. Chem. Soc.*, previous paper in this issue.
(3) Dutta, A. S. *Adv. Drug. Res.* **1991**, *21*, 145.
(4) Hirschmann, R.; Sprengeler, P. A.; Kawasaki, T.; Leahy, J. W.; Shakespeare, W. C.; Smith, A. B., III. *J. Am. Chem. Soc.* **1992**, *114*, 9699.
(5) Pierschbacher, M. D.; Ruoslahti, E. *J. Biol. Chem.* **1987**, *262*, 17294.
(6) Pytela, R.; Pierschbacher, M. D.; Ruoslahti, E. *Proc. Natl. Acad. Sci. U.S.A.* **1985**, *82*, 5766.
(7) Sternbach, L. H.; Reeder, E. *J. Org. Chem.* **1961**, *26*, 4936.
(8) Leimgruber, W.; Batcho, A. D.; Schemler, F. *J. Am. Chem. Soc.* **1965**, *87*, 5793.

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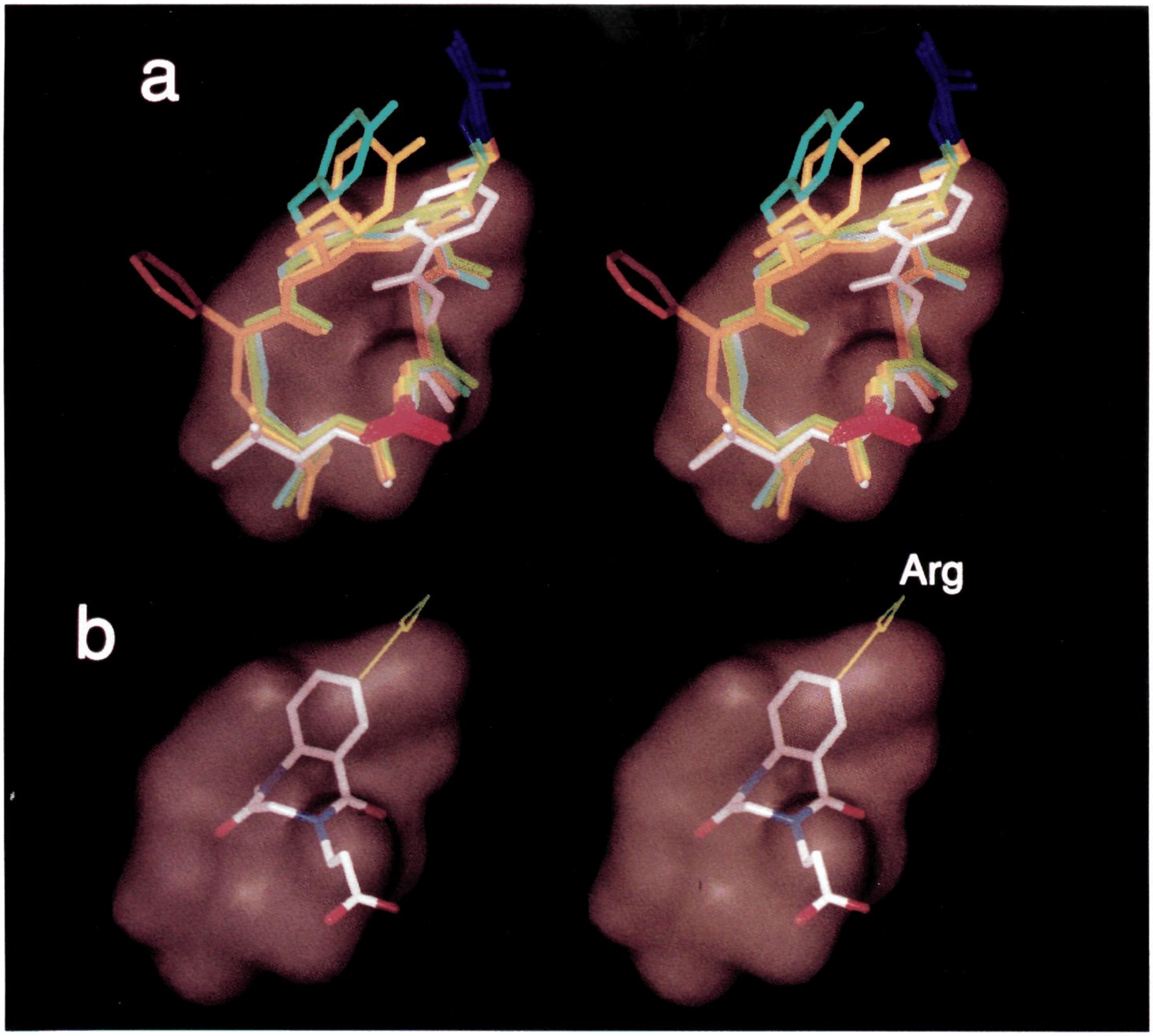


Figure 2. (a) Consensus structural alignment of active cyclic RGD peptides taken from ensemble dynamics studies.[2] Analogs are color-coded according to the following scheme: **5**, white; **6**, cyan; **7**, yellow; **8**, orange; **9**, green. The Arg guanidine and Asp carboxylate are colored blue and red, respectively. The volume occupied by the cyclic backbone and Cβ atoms is also shown; this volume represents an allowed space which could be occupied by a rigid scaffold. (b) Benzodiazepinedione scaffold superimposed on the consensus volume described above.

1). Precise control of the Asp side-chain presentation was achieved by fusing a third ring onto the benzodiazepinedione nucleus; the 3*R*,11*R* stereoisomer of the tricyclic series reproduces the Asp side-chain geometry observed in G4120. The torsional profile of the N4–C11 bond of the bicyclic series was calculated using MM2[9] and contains two local minima of approximately equal energy, one of which was similar to the desired angle enforced by the 3*R*,11*R* tricyclic compound.

The benzodiazepinedione framework satisfies the primary design criteria enumerated above and provides a synthetically versatile platform for subsequent structural modification and medicinal optimization. The benzodiazepinedione nucleus is quite rigid since 6 of the atoms in the seven-membered ring participate in conjugated systems. This rigidity enforces the desired "cupped shape" while maintaining an overall volume which lies conservatively within the consensus volume for active RGD analogs (Figures 2 and 3).[2] The Arg and Asp side chains are appropriately presented from C7 and C11, respectively. An initial comparison with the solution structure of G4120 suggested using a propyl linkage to deliver the guanidine from the aromatic ring of the benzodiazepinedione, which provides additional sites that can be synthetically targeted for alternate Arg side-chain attachments. The amide oxygen at C5 provides a good overlap with the Gly-Asp amide oxygen in G4120. The amide nitrogen at N1 can be readily alkylated to alter the physicochemical profile of the molecule and to explore additional potential binding interactions.

Variation of Structural Features. The structural hypotheses underlying our design of the benzodiazepinediones were further explored by altering critical structural features of the framework. By analogy to earlier peptide studies, these alterations were predicted to reduce activity. Studies of linear peptide analogs had revealed that the placement of rigid and flexible regions along the "Arg-Gly" portion of the molecule directly affected potency by influencing the spatial disposition of the charged residues.[2] A corresponding series of benzodiazepinedione analogs were therefore prepared in which the length of the tether connecting the Asp carboxylate to N4 was modified and compensating adjustments in the length of the Arg side chain were made in order to maintain a consistent "atom count" between the guanidine and carboxylate groups.

The cupped shape of the benzodiazepinediones results from the fusion of the two rings; because this shape had been shown to be important for peptides,[1] we reasoned that monocyclic analogs lacking the seven-membered ring would be less potent. A significant loss in activity was observed when an extended RGD conformation was induced by embedding the epitope in a cyclic hexapeptide.[2] The analogous modification of the non-peptidal framework was achieved by contracting the diazepinedione to a planar quinazolinone.

(9) Allinger, N. L.; Yuh, Y. H. *QCPE* **13**, 395.

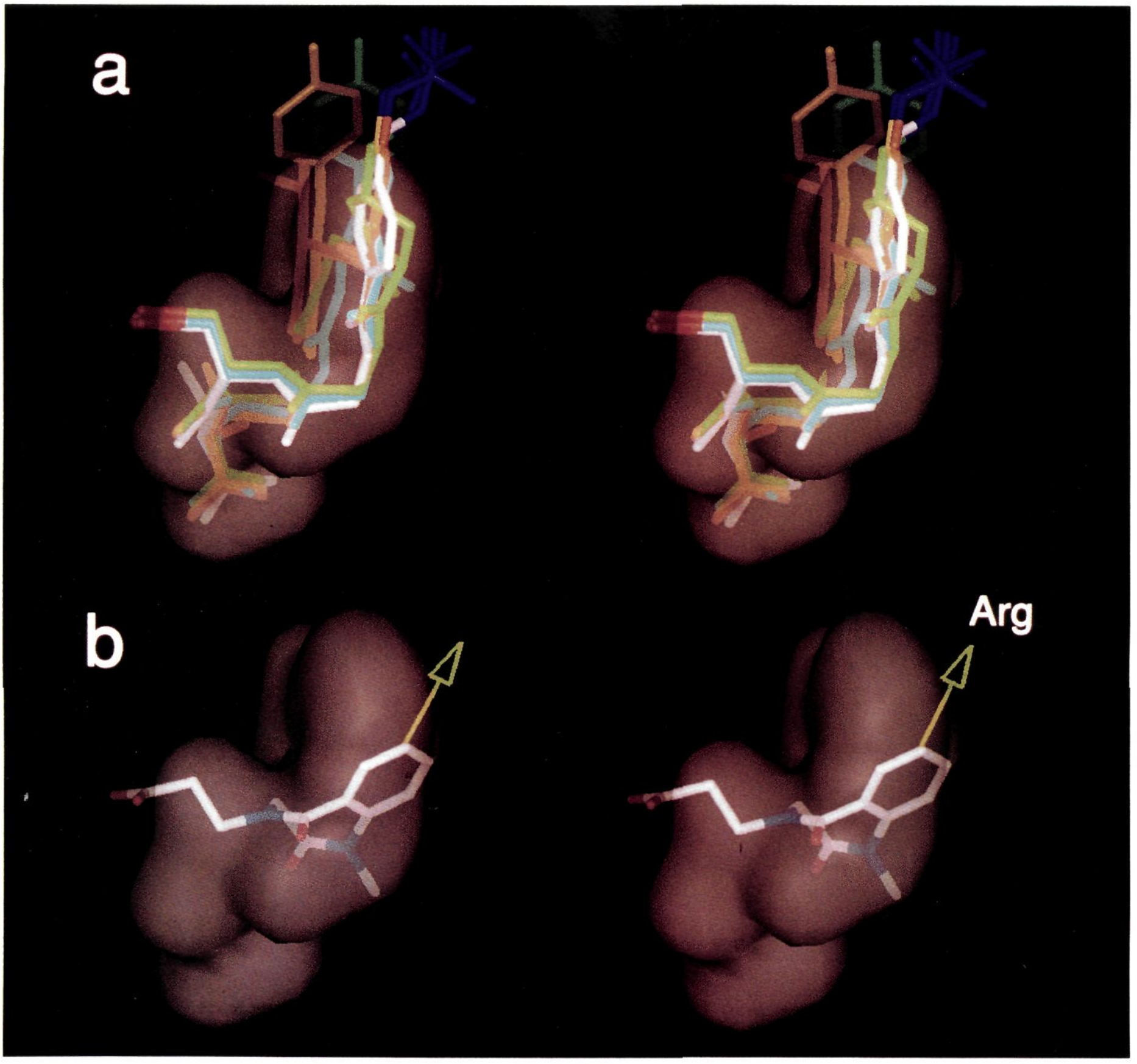


Figure 3. (a) "Sideways" view of the consensus alignment of RGD peptides described in Figure 2a, illustrating the cupped shape of the RGD epitope. (b) Corresponding view of the benzodiazepine scaffold.

Synthesis. The retrosyntheses of the tricyclic pyrrolobenzodiazepinediones **1** and bicyclic analogs **2** are illustrated in Figure 4. Although the initial tricyclic analogs were prepared by introducing the alkylguanidine group earlier in the synthesis (*vide infra*), subsequent analogs were prepared from a common 7-iodo intermediate. This intermediate facilitated the attachment of diverse Arg side chains to the aromatic ring using a palladium-catalyzed coupling.[10,11]

The bi- and tricyclic benzodiazepinediones were prepared starting from 6-iodoisatoic anhydride **6** and an appropriately substituted α-amino acid (Figure 4A). A more efficient route used in later syntheses of the bicyclic 7-iodobenzodiazepinediones started with the same iodoisatoic anhydride and formed the seven-membered ring in a triply convergent manner from β-alanine ethyl ester and α-bromoacetyl bromide (Figure 4B).

Assays. Compounds were evaluated for potency using both ELISA and platelet aggregation assays as previously described.[2]

Results

Synthesis. The preparation of the requisite α-amino acid derivatives **7** and **8** is shown in Scheme 1. The proline derivative **10** was prepared by reducing the vinylogous carbamate **9** with sodium cyanoborohydride. The resulting mixture of *cis* and *trans* isomers (1:1) was separated by column chromatography. The glycine adduct **11** was synthesized in 95% yield from glycine *tert*-butyl ester and ethyl acrylate. Deprotection of compounds **10** and **11** with hydrogen chloride cleanly provided the α-amino acids **7** and **8**, respectively.

Condensation of **7**-*cis* with 6-(*N*-boc-3-aminopropyl)isatoic anhydride gave the tricycle **12** in 34% yield (Scheme 2).[12,13] The *trans* isomer of **7** provided only scant amounts of the tricyclic product. Fortunately, epimerization of **12** at the 3 position under basic conditions yielded the two diastereoisomers of **13**, which were separable by HPLC (Scheme 2). The corresponding guanidino acids **1a,b** were prepared using formamidinosulfonic acid **14**.[14]

(10) Tsuji, J. *Organic Synthesis with Palladium Compounds*; Springer-Verlag: Berlin, 1980.
(11) Heck, R. F. *Palladium Reagents in Organic Synthesis*; Academic Press: London, 1985.
(12) Kaneko, T.; Wong, H.; Doyle, T. W. *Tetrahedron Lett.* **1983**, *24*, 5165.
(13) Kim, D. H. *J. Heterocycl. Chem.* **1975**, *12*, 1323.
(14) Kim, K.; Lin, Y.-T.; Mosher, H. S. *Tetrahedron Lett.* **1988**, *29*, 3183.

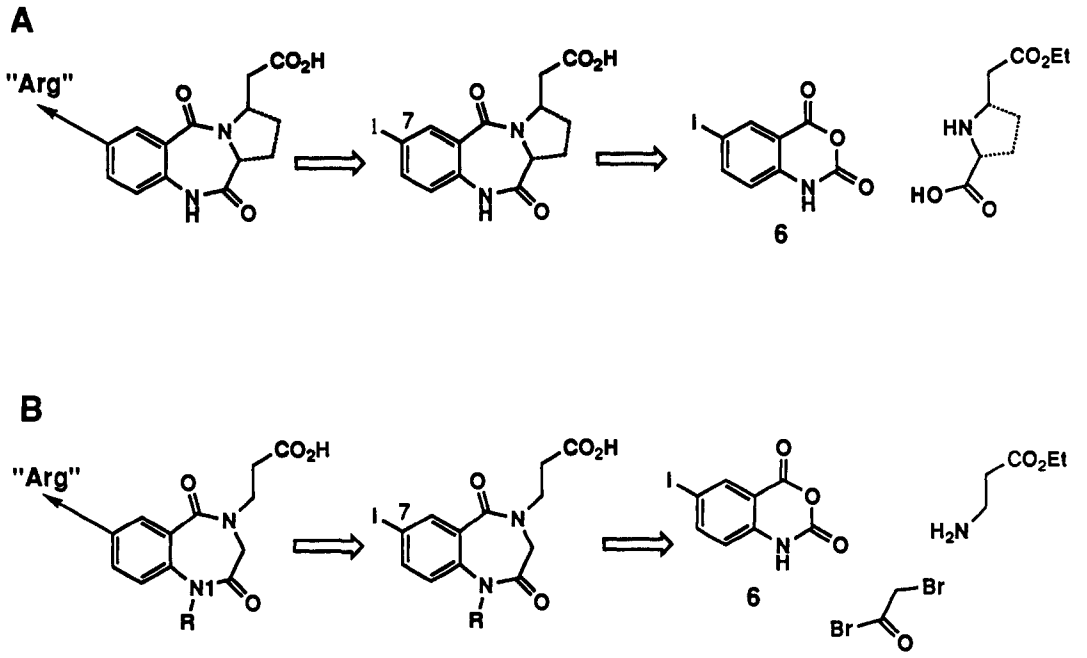
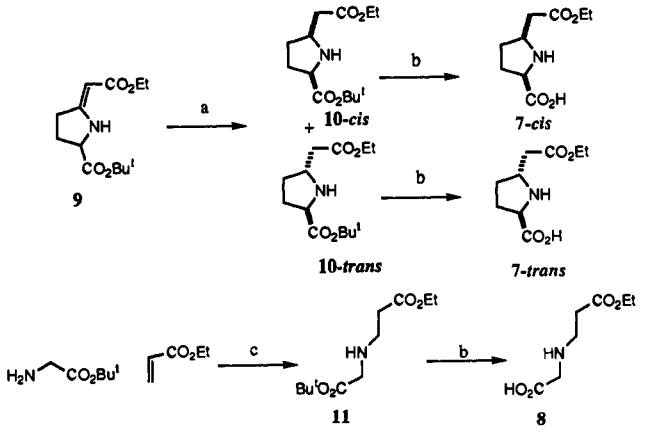


Figure 4. (a) Retrosynthetic approach used in the preparation of the tricyclic pyrrolo[1,4]benzodiazepine-2,5-diones and (b) retrosynthetic approach used in preparing the bicyclic analogs.

Scheme 1. Synthesis of α-Amino Acids **7** and **8**[a]



[a] (a) $NaCNBH_4$, EtOH, AcOH; (b) HCl/dioxane; (c) EtOH.

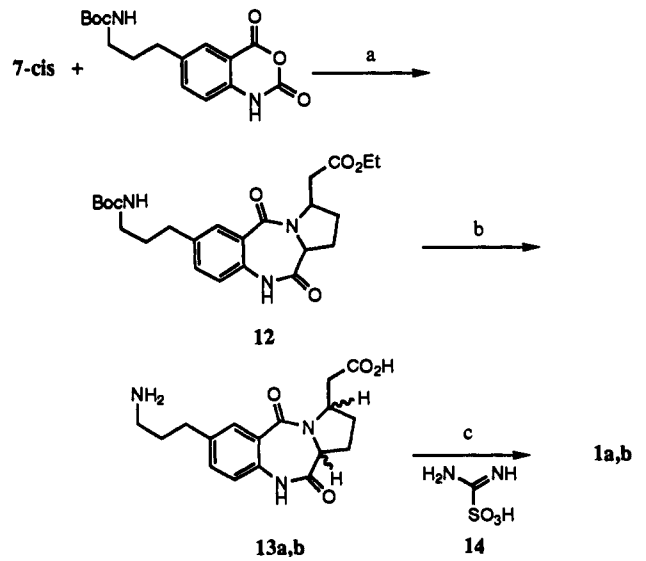
The bicyclic compound **15** was similarly prepared from 6-(*N*-boc-3-aminopropyl)isatoic anhydride and the glycine derivative **8**. In spite of the poor yield (6%), the material was converted to its corresponding guanidino acid **2a** without complication (Scheme 3).

Benzodiazepinediones methylated at N1 were optimally prepared in a five-step procedure starting with *N*-methylanthranilic acid (Scheme 4). Iodination followed by reaction with phosgene yielded the isatoic anhydride **16**. Subsequent reaction of **16** with an amino acid ethyl ester hydrochloride,[15] followed by acylation with α-bromoacetyl bromide and base-promoted ring closure provided compounds **17** (n = 0–2), the direct precursors to compounds **2b–g** and **3**.

The preparation of the aryl iodides required for the synthesis of compounds **4** and **5** is shown in Scheme 5. Reaction of **6** with β-alanine ethyl ester afforded **18**, which was alkylated with *p*-chlorobenzyl chloride to give **19**. Subsequent acylation and ring closure afforded **20**. Analogs lacking the seven-membered ring were also prepared from **19** and either formic–acetic anhydride or acetyl chloride to give **21a** and **21b**, respectively. The quinazolinone **22** and benzoyl derivative **23** were prepared using standard methods (Scheme 5).

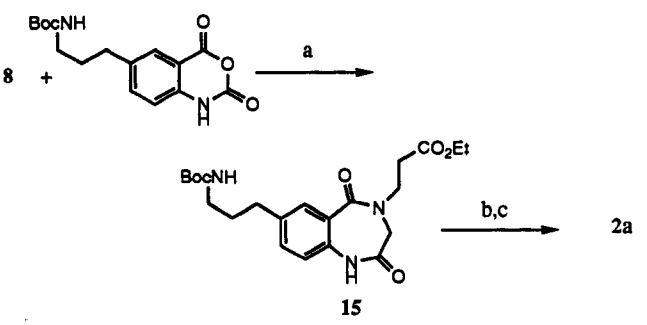
(15) Venuti, M. C. *Synthesis* **1982**, 266.

Scheme 2. Synthesis of Pyrrolobenzodiazepinediones **1a,b**[a]



[a] (a) Pyridine, pyridine·HCl, reflux; (b) i. HCl/EtOAc, ii. NaOH, MeOH; (c) 5% $KHCO_3$.

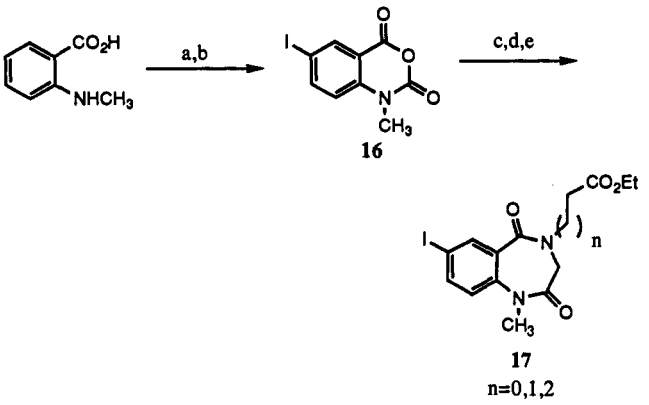
Scheme 3. Synthesis of Benzodiazepinedione **2a**[a]



[a] (a) Pyridine, pyridine·HCl, reflux; (b) i. HCl/EtOAc, ii. NaOH, MeOH; (c) **14**, 5% $KHCO_3$.

The aryl iodides **17** and **21–23** were elaborated to their corresponding guanidino acids **2c–f**, **4**, and **5** via a palladium-catalyzed alkynyl–aryl coupling, followed by deprotection of the

Scheme 4[a]



[a] (a) ICl; (b) $COCl_2$, K_2CO_3; (c) β-alanine ethyl ester hydrochloride, Et_3N, DMAP, DMF; (d) α-bromoacetyl bromide, CH_2Cl_2, H_2O; (e) $CsCO_3$, DMF.

resulting alkyne (or reduced alkyl derivative) and guanidinylation with **14**. A representative example, illustrating the methods used in preparing compound **2e**, is shown in Scheme 6.

The amidino acid **2g** was prepared by coupling **17b** with 4-cyanophenylacetylene.[16] The aryl nitrile **24** was converted to the amidino ester by standard methods (Scheme 7).

All compounds were purified by HPLC and characterized by ^1H NMR and high-resolution mass spectrometry (FAB). Characterization data are available as supplementary material.

Optimization of Designed Analogs. While the tricyclic compounds **1a** and **1b** were inactive, the analogous bicyclic molecule, **2a**, possessed sufficient potency to merit further development (Table 1). Addition of a methyl group to N1 resulted in a slight increase in activity, which was further enhanced by rigidifying the guanidine linkage with an acetylene group. Extension of this linkage by the sequential addition of methylene groups resulted in a molecule (**2e**) that was only 10-fold less potent than G4120 in platelet aggregation. Further extension (**2f**) reduced the potency, indicating that the spatial disposition of the guanidine and carboxylate moieties in **2e** was nearly optimal for this framework. A recent report of non-peptidal GPIIbIIIa antagonists describes the use of a phenylamidine surrogate to replace the alkylguanidine of arginine.[17] Incorporation of the surrogate resulted in a compound (**2g**) that is more potent than G4120 in platelet aggregation.

Current efforts are focused on improving the oral bioavailability of these compounds by formulating prodrugs and by introducing functionality at N1 that alters the overall physicochemical properties of the molecules without perturbing the binding epitope. Work is also in progress to explore whether the inactivities of **1a** and **1b** result from an inappropriate presentation of the Asp side chain or from unfavorable van der Waals contacts between the five-membered ring and GPIIbIIIa.

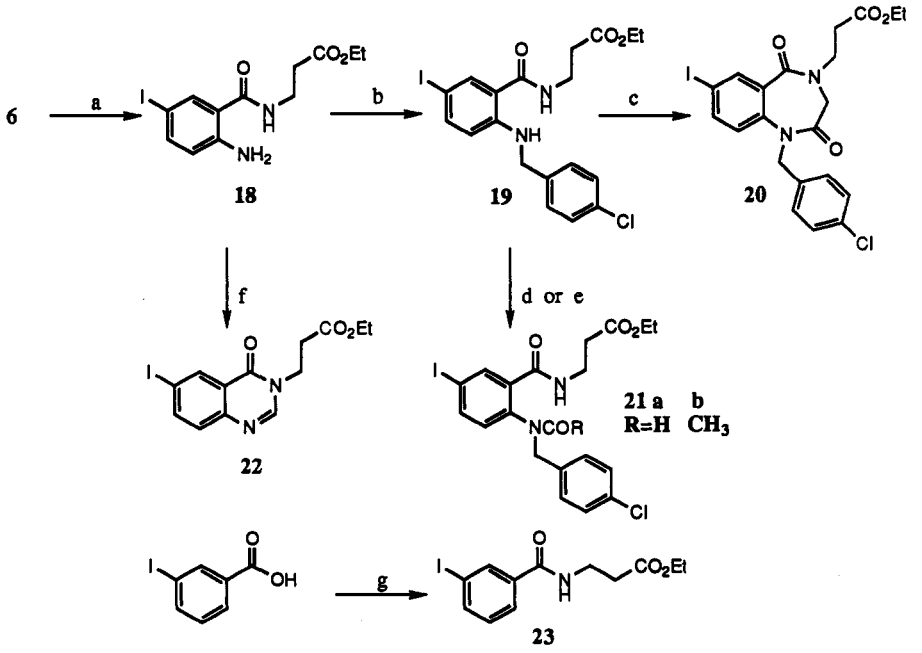
Variation of Structural Features. The consequences of varying the placement of the benzodiazepinedione core are shown in Table 2. While molecule **3a** is only 2-fold less active than **2e**, analogs **3c** and **3e** are inactive despite an equivalent atom count between the guanidine and carboxylate groups. These findings parallel the results observed when the placement of the Arg-Gly amide group was varied in linear analogs of GRGDV.[2] The inactivity of analogs **3b** and **3d** further illustrates the exquisite sensitivity of the placement of the Asp carboxylate with respect to the "cup" of the benzodiazepinedione. A similar sensitivity is observed in linear and cyclic peptides, in which the conservative substitution of Glu for Asp is not tolerated.

A dramatic reduction in activity results when the seven-membered ring is contracted to a six-membered ring, thereby "flattening" the scaffold (**4**, Table 3). As with the peptides, enforcing an extended orientation of the binding determinants causes a concomitant loss in activity. Analogs lacking the seven-membered ring (**5b–d**, Table 3) are predictably less potent than the fused analog **5a**.

Discussion

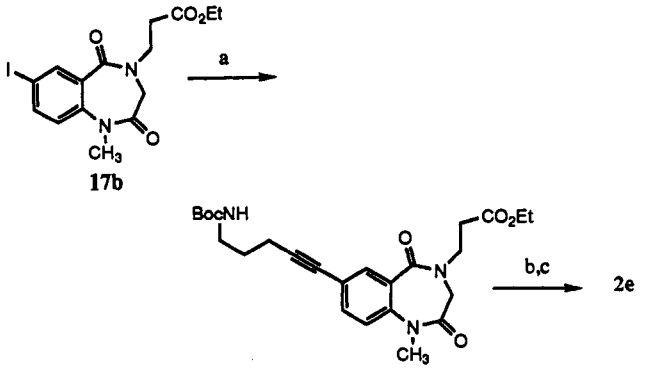
Reflecting the degree of interest in GPIIbIIIa/fibrinogen antagonists as antithrombotic agents, a number of other non-peptidal RGD mimetics have recently been disclosed. These molecules have been discovered using approaches that range from screening of compound libraries[17,18] to the design of constrained analogs of local peptide conformation.[19,20] As the diversity of these analogs continues to grow, it will be instructive to compare their structural similarities or dissimilarities to assess the uniqueness of the topography represented by the benzodiaz-

Scheme 5. Synthesis of Aryl Iodides **20–23**[a]



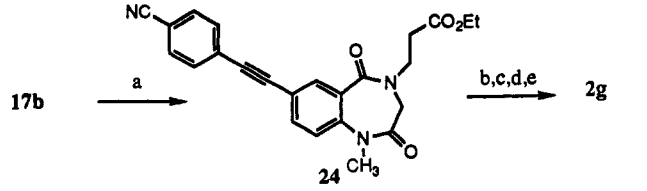
[a] (a) β-Alanine ethyl ester hydrogen chloride, DMF, Et_3N, DMAP; (b) *p*-chlorobenzyl chloride, DMF, 2,6-lutidine, 100 °C; (c) i. α-bromoacetyl bromide, CH_2Cl_2, H_2O, ii. $CsCO_3$, DMF; (d) AcOCHO, Ac_2O; (e) AcCl, CH_2Cl_2, H_2O; (f) $(EtO)_3CH$, heat; (g) i. $(COCl)_2$, PhH, catalyst DMF, ii. β-alanine ethyl ester hydrogen chloride, CH_2Cl_2, Et_3N, DMAP.

Scheme 6. Synthesis of Benzodiazepinedione **2e**[a]



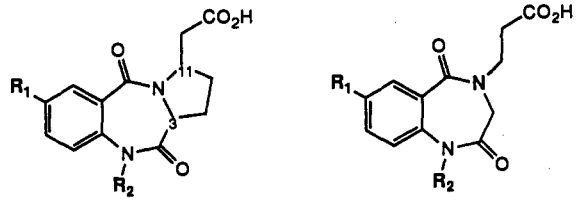
[a] (a) *N*-Boc-5-aminopent-1-yne, $Pd(Ph_3P)_2Cl_2$, CuI, Et_3N, EtOAc; (b) i. HCl/EtOAc, ii. NaOH, MeOH; (c) **14**, 5% $KHCO_3$.

Scheme 7. Synthesis of the Benzamidine Benzodiazepinedione **2g**[a]

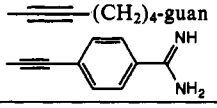


[a] (a) 4-Cyanophenylacetylene, $Pd(Ph_3P)_2Cl_2$, CuI, Et_3N, EtOAc; (b) H_2S, pyridine, Et_3N; (c) MeI, CH_2Cl_2; (d) NH_4OAc, MeOH; (e) NaOH, MeOH.

Table 1. Activities of Nonpeptidic GPIIbIIIa Antagonists[a]



1a,b **2a-g**

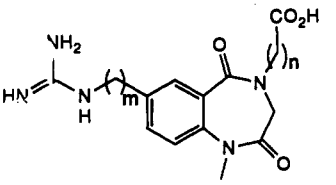
molecule	R_1	R_2	IC_{50} (μM) ELISA	IC_{50} (μM) PRP
1a[b]	$-(CH_2)_3$-guan	H	>100.0	nd
1b[b]	$-(CH_2)_3$-guan	H	>100.0	nd
2a	$-(CH_2)_3$-guan	H	0.714	nd
2b	$-(CH_2)_3$-guan	CH_3	0.466	nd
2c	$-\equiv-CH_2$-guan	CH_3	0.170	23.6
2d	$-\equiv-(CH_2)_2$-guan	CH_3	0.140	15.6
2e	$-\equiv-(CH_2)_3$-guan	CH_3	0.026	3.2
2f	$-\equiv-(CH_2)_4$-guan	CH_3	0.060	6.4
2g		CH_3	0.011	0.12

[a] The guanidine moiety is represented using the abbreviation guan. [b] Molecules **1a** and **1b** are diastereomerically pure racemates of unknown configuration at positions 3 and 11.

epinedione series. The binding of RGD peptides to GPIIbIIIa involves a significant change in receptor conformation,[21,22] suggesting that GPIIbIIIa may accommodate alternate presentations of the RGD epitope.

The high biological activity observed for larger, flexible RGD-containing molecules such as kistrin and echistatin indicates that

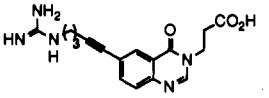
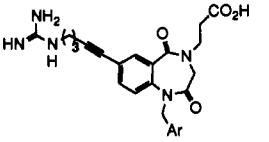
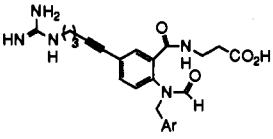
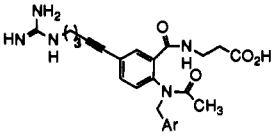
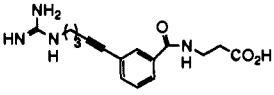
Table 2. Variations in Asp Side-Chain Length



3a-e

molecule	*m*	*n*	ELISA IC_{50} (μM)
3a	5	2	0.055
3b	5	1	>100.0
3c	6	1	>100.0
3d	5	3	>100.0
3e	4	3	>100.0

Table 3. Variations in Molecular Shape[a]

molecule	structure	ELISA IC_{50} (μM)
4		10.80
5a		0.009
5b		0.16
5c		1.67
5d		1.00

[a] In the structures, Ar represents a *p*-chlorophenyl ring.

rigidity *per se* may not absolutely be required for potency.[23] The comparable level of activity of G4120 indicated, however, that a compact framework that enforced a cupped RGD presentation would yield a potent inhibitor of GPIIbIIIa/fibrinogen binding. In principle, therefore, our design of non-peptidal GPIIbIIIa antagonists could have proceeded either by a systematic modification of the linear RGD sequence itself or by the "scaffolding" approach described herein. We pursued the latter strategy in order to generate a lead series in which critical functional determinants could be independently optimized without affecting conformation.

Reproducing the cupped RGD backbone of G4120 using the benzodiazepinedione framework has rapidly led to the discovery of platelet aggregation inhibitors that are comparable to the most

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potent compounds known. Unlike the peptides, this series has demonstrated oral bioavailability, as measured by *ex vivo* platelet aggregation assays. The optimizations of *in vitro* potency and *in vivo* bioavailability were significantly aided by the presence of a rigid scaffold. The structural considerations that framed the design of the benzodiazepinedione scaffold were validated by studies showing that the cyclic peptides and their benzodiazepinedione counterparts exhibit parallel topographical requirements: potency is reduced when the structural features that induce a cupped presentation of the epitope are removed; enforcing a "flat" presentation virtually eliminates activity. Extending the comparison to include an atom-by-atom mapping of G4120 and the benzodiazepinediones was not considered, since neither the NMR structure of G4120 nor the ensemble dynamics calculations indicated an unambiguous placement of the Arg guanidine group.

The RGD epitope represents an ideal target for structure-based design because it is spatially compact and dominated by electrostatic interactions. We started with a structural model derived from NMR studies of potent cyclic peptides and molecular dynamics simulations of related active analogs which yielded a self-consistent picture of how these analogs share a common presentation of the binding determinants. The essential topographical features of this model were reproduced in the context of a known bioavailable scaffold, generating a novel lead series for medicinal chemistry. The optimization of that series toward a preclinical candidate will be reported in future publications. In principle, a similar strategy can be used to design nonpeptidal analogs of other peptide or protein epitopes that are reducible to a few key interactions and for which a detailed structural model can be derived.

Experimental Section

The detailed experimental protocol for one example of each method used in the preparation of compounds **1–5** is described in supplementary material. General methods are also provided for aryl coupling and elaboration of the protected amino acids to the corresponding guanidino acids.

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Supplementary Material Available: Syntheses, separation conditions, and characterization data for example intermediates used in the preparation of compounds **1–5** (37 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.