1,2-Dibenzamidobenzene Inhibitors of Human Factor Xa

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Received June 24, 1999

High-throughput screening of a combinatorial library of diamidophenols yielded lead compounds with the ability to inhibit human factor Xa (fXa) at micromolar concentrations (e.g. compound **4**, fXa apparent $K_{ass} = 0.64 \times 10^6$ L/mol). SAR studies in this novel structural series of fXa inhibitors showed that the phenolic hydroxyl group was not essential for activity. The best activity was found in substituted 1,2-dibenzamidobenzenes in which the phenyl group of one benzoyl group (A-ring) was substituted in the 4-position with relatively small lipophilic or polarizable groups such as methoxy, vinyl, or chloro and the phenyl group of the other benzoyl group (B-ring) was substituted in the 4-position with larger lipophilic groups such as *tert*-butyl or dimethylamino. The central phenyl ring (C-ring) tolerated a wide variety of substituents, but methoxy, methanesulfonamido, hydroxyl, and carboxyl substitution produced slightly higher levels of activity than other substituents when present in combination with favorable B-ring substitution. Methylation of the amide nitrogen atoms was found to greatly decrease activity. Compound **12** is the highest affinity fXa inhibitor in this group of compounds, having fXa apparent $K_{ass} = 25.5 \times 10^6$ L/mol, about 40× more active than the original lead. This lead series does not show potent inhibition of human thrombin. A model for the binding of these ligands to the fXa active site is proposed. The model is consistent with the observed SAR and can serve to guide future SAR studies.

Introduction

Thromboembolic diseases continue as a leading cause of morbidity and mortality in developed nations. A primary medical strategy to treat and to prevent such diseases has been the use of anticoagulants: heparin and low-molecular-weight heparins for parenteral short-term treatments and vitamin K antagonists such as warfarin for chronic oral therapy. However, there are serious and well-documented liabilities associated with the chronic use of warfarin,[1] and there has been a consequent worldwide pharmaceutical discovery effort to discover safer and more effective anticoagulant compounds which could be used as chronic oral therapy. Initially, a large effort focused on the target thrombin on the basis that direct inhibitors of the fibrinogen-clotting/platelet-activating protease could produce antithrombotic effects in all types of thrombotic disease. Thus far, however, an orally effective thrombin inhibitor has not been successfully developed[2] and the discovery focus to resolve this large unmet medical need has shifted to the serine protease factor Xa.

Factor Xa (fXa) produces thrombin by activating prothrombin during blood clotting whether coagulation is triggered by tissue factor or by blood-contact mechanisms.[3,2a] Accordingly, fXa inhibitors have the potential to be effective in all types of coagulation-based thromboembolic processes by means of repression of thrombin generation. Potential advantages over thrombin inhibitors include the indirect repression of many moles of generated thrombin per fXa inhibitor molecule, rather than the 1:1 stoichiometry necessary for direct thrombin inhibition, and the avoidance of direct interference with multiple thrombin-mediated activities (platelet aggregation, protein C activation, factor XIII activation, factors V and VIII feedback activation).[4] Natural and recombinant fXa inhibitor proteins and small molecular weight reversible fXa inhibitors have been shown to be anticoagulant and antithrombotic in animal models.[5]

The overall development of inhibitors for fXa has to some extent built upon the effort and success for α-thrombin. A comparison of their active site binding regions[12,14] reveals that they both have the relatively deep S1 or "specificity" pocket. The interior of the S1 pocket is fairly hydrophobic except for the presence of the acidic carboxyl side chain of Asp189 at the base. It is this acidic group that is usually found forming a strong salt bridge with a basic amino acid like arginine or lysine or with other positively charged moieties such as benzamidine. Both enzymes possess the S3 binding site made up of Gly216. Additionally, both have a hydrophobic "distal" S4 region; however the structure and character of this area differ somewhat between the two enzymes. In α-thrombin the S4 area is a broad solvent-exposed hydrophobic region, made up of the side

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10.1021/jm990326m CCC: $19.00
Published on Web 02/23/2000

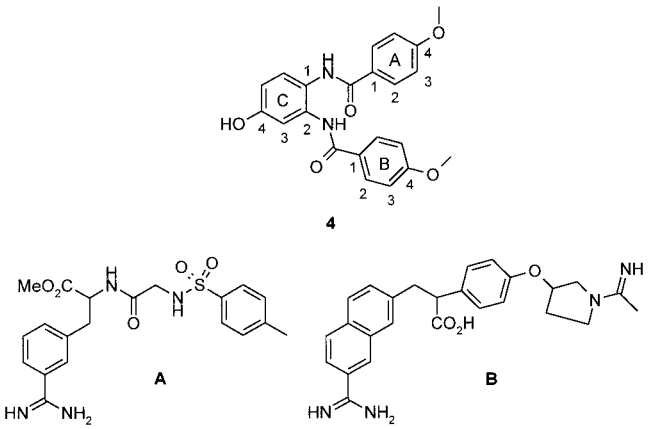


Figure 1. Structures of fXa inhibitors **4**, Tenstop (**A**), and DX-9065a (**B**).

chains of Leu99, Trp215, and Ile174. In fXa the S4 region (also known as the "aryl" binding region) is somewhat more structured, being made up of the aromatic side chains of residues Tyr99, Trp215, and Phe174. Finally, fXa does not possess an equivalent to the small hydrophobic S2 pocket found in α-thrombin.

Several structural types of small molecule fXa inhibitors have been reported. The earliest inhibitors were peptides, modeled on the conservation of Gly-Arg at the cleavage site of prothrombin by fXa. An example of one of these early peptide inhibitors[6] is compound **A** in Figure 1. In this compound a benzamidine is linked by a glycine residue to an arylsulfonamide. Far more potent peptide fXa inhibitors have been made since then with the aid of combinatorial chemistry.[5h] The prototype nonpeptide inhibitor is DX-9065a[5d,h] (compound **B** in Figure 1). An X-ray crystal structure of fXa with **B** bound in its active site[7] shows that that the naphthamidine group binds in the specificity pocket (S1) while the pyrrolidine imine group binds in the aryl binding site (S4). The central group connecting the S1 and S4 binding groups in **B** is a 4-ethylphenoxy moiety. Recently series have been reported in which a propyl[8] group or an amidopropyl[9] group connects the S1 and S4 binding moieties. Still other fXa inhibitor types have been reviewed.[10] The 1,2-dibenzamidobenzene structures reported here provide a novel structure on which to build fXa inhibitors.

We discovered, during high-volume screening, the 1,2-dibenzamidobenzene **4** (Figure 1) which reversibly inhibited human fXa (apparent $K_{ass} = 0.64 \times 10^6$ L/mol). We have now explored a variety of related structures. We have modeled some of these structures in the active site of fXa and we have proposed a mode of binding that is consistent with the observed SAR. Tests against the related serine protease thrombin suggest that these compounds selectively inhibit fXa.

Chemistry

The combinatorial library that produced the lead compound **4** was prepared by solid-phase methods.[11] After the lead compound was found, we used the same methods to prepare additional quantities of **4** and **23** as shown in Scheme 1.

Early in the SAR we prepared compound **2**, the deshydroxy version of the lead compound **4**, by the route shown in Scheme 2. The activity of the deshydroxy compound was found to be essentially the same as that of the lead compound as shown in Table 1. This finding allowed us to explore A- and B-ring SAR without having to include the C-ring hydroxyl group. The A-, B-, and C-ring designations are defined in Scheme 4 and in Table 1.

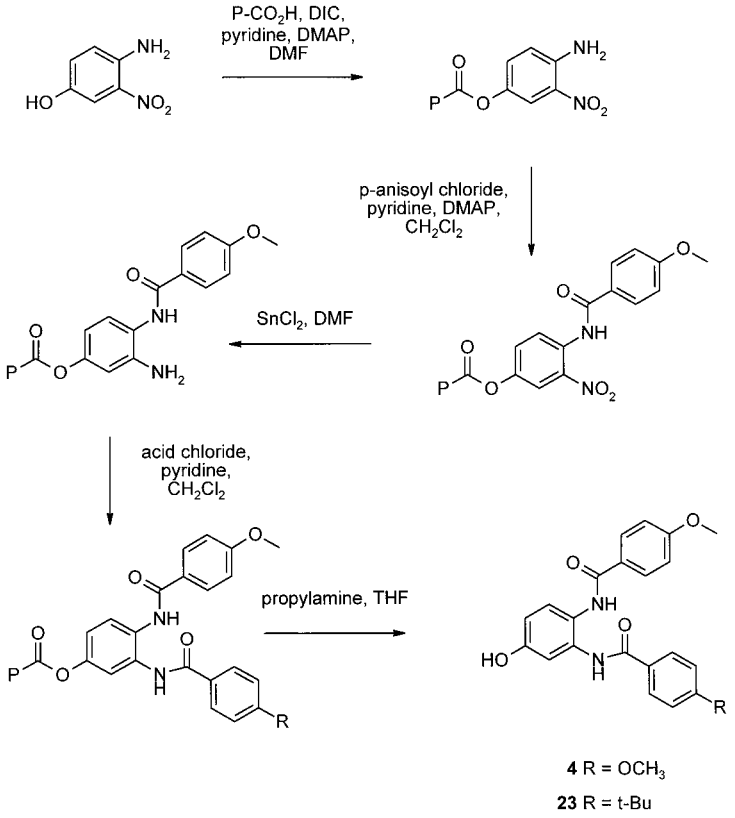
N-Methylation of the monomethylbisamide **10** provided the dimethylbisamide **11** as shown in Scheme 3. Compounds with different substitution on the A- and B-rings were prepared either from the appropriate diamines as shown in Scheme 4 or from the nitroamines as shown in Scheme 5.

Molecular Modeling

Upon confirmation of the lead compound **4** as an inhibitor of fXa, we sought to place our ligand design program on a structure-based foundation. At the time, the only available experimental X-ray structure of human fXa was the des(1−45) coordinate set of Padmanabhan et al.[12] Although not complexed with a small molecule inhibitor, we felt this provided a relatively accurate description of the active site (2.2 Å resolution) from which to begin to propose binding modes for the series lead. An expectation (but not a requirement) for a competitive enzyme inhibitor is that it occupy many of the well-defined binding pockets within an active site. In the case of the current series this consideration would have the lead compound **4** occupy simultaneously the fXa S1 and S4 binding pockets. Shown in Figure 2 is an energy-minimized molecular model of a proposal for how the lead **4** binds to the active site of fXa. This binding mode is somewhat based upon the results from a parallel computational study we performed for various amidine analogues.[13] Details regarding the specific molecular modeling procedures utilized for the current study are reported within the Experimental Section.

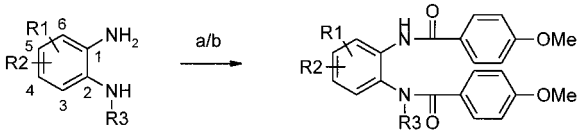
In the model of **4** bound in the fXa active site (shown in Figure 2), the two arms of the inhibitor (A- and B-rings, respectively) lie flat within each of the S1 and S4 sites. The central phenol ring bridges the two arms at almost 90° to each other, itself mostly solvent exposed. This central ring resides near the side of the opening to the S1 pocket. The *p*-methoxybenzoyl group of the A-ring very well complements the shape and the mostly hydrophobic character of the S1 pocket. The position of the A-ring buries the methyl of the *p*-methoxy group favorably in a small hydrophobic hole found on the backside of the S1 pocket, formed by the side chains of Tyr228, Ala190, and Val213. As in α-thrombin,[14] this hole in fXa is normally occupied by a water molecule which in this case would be expelled. The corresponding *p*-methoxybenzoyl group of the B-ring extends down into the more solvent-exposed hydrophobic S4 region. The *p*-methoxy group of this chain is positioned in front of the side chain of Trp215 and almostly directly between the aromatic rings of Phe174 and Tyr99. Due to the low barrier of rotation for this CO single bond (∼2.0 kcal/mol, CHARMm force field) and the yet available space within the S4 region, some rotation about this methoxy group bond was observed during a molecular dynamics simulation of the active site complex. The energy-minimized structure shown in Figure 2 has the NH of the A-ring amide bond simultaneously hydrogen bonded to the backbone carbonyls of Gly216 and Gly218. During molecular dynamics simulations of this complex, a more

Scheme 1[a]



[a] P-CO_2H = 4-carboxypolystyrene resin.

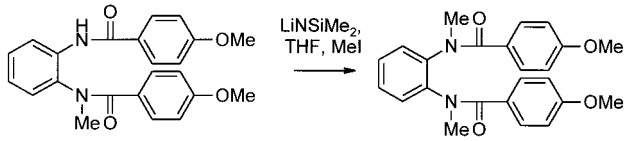
Scheme 2[a]



	R1	R2	R3
1	4-OCH_3	H	H
2	H	H	H
3	6-OCH_3	3-OCH_3	H
5	4-CH_3	H	H
6	4-O-p-anisoyl	H	H
7	4-OH	H	H
8	4-Cl	H	H
9	4-CO_2H	H	H
10	H	H	CH_3

[a] (a) Acid chloride, CH_2Cl_2, aq NaOH; (b) acid chloride, CH_2Cl_2, pyridine.

Scheme 3



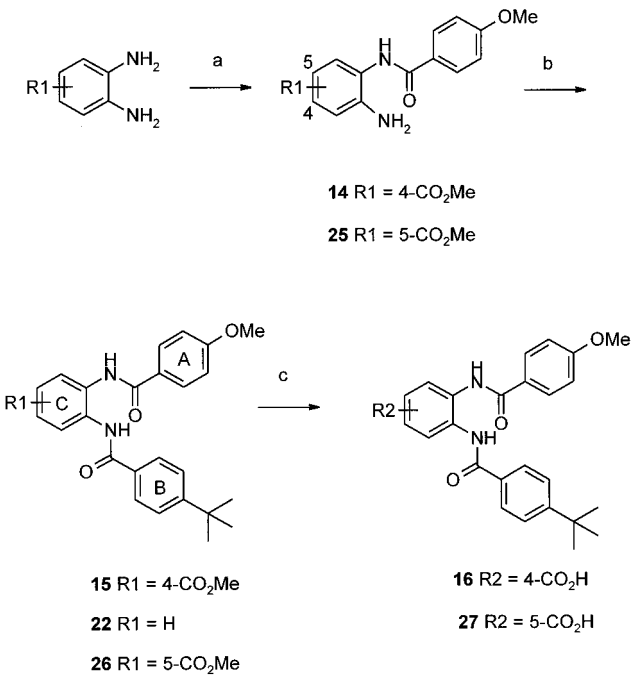
10 **11**

realistic hydrogen-bonding arrangement arises in that the interaction involving the A-ring dynamically exchanges between the two protein acceptor carbonyl oxygens. Although not seen in the minimized structure, during the simulation the B-ring carbonyl group can periodically form a hydrogen bond to the backbone NH of Gly218 (2.5 Å distance in Figure 2). The C-ring hydroxyl group is shown here extending into the solvent sphere, not interacting with the protein. One would expect this group to possibly interact with the guanidinium of Arg143. Although this interaction was not observed during the dynamics simulation of **4**, this could be due to the relatively short simulation time (~ 50 ps) never allowing the two groups to come into contact. However, due to the symmetry of the ligand the two arms could be interchanged placing the hydroxyl group in closer proximity of the positively charged Arg143 side chain. In any case though this interaction would be drastically modulated due to it being solvent exposed and therefore not expected to be significant. Finally, no direct interaction of the ligand with the catalytic triad is observed in the proposed model of **4** with fXa.

Results and Discussion

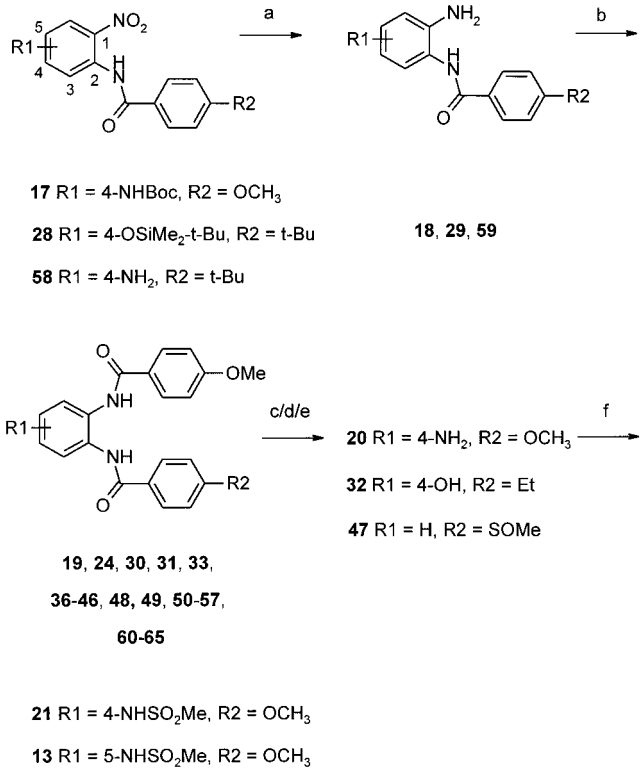
The test results appearing in Table 1 show that the central ring (C-ring) can tolerate substitution at any position. The fXa inhibitory activity only varies by a factor of 5 with the variety of substitutions considered. This insensitivity to C-ring substitution alone is consistent with the proposed structural model of the lead **4** bound to the fXa active site. Figure 2 illustrates that generally the C-ring positions 3−6 point into the solvent and therefore substitutions at these positions need not

Scheme 4[a]



[a] (a) Acid chloride, pyridine, CH_3CN; (b) acid chloride, Et_3N, CH_3CN; (c) NaOH, water, THF, MeOH.

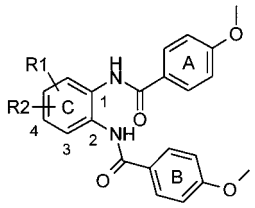
Scheme 5[a]



[a] (a) H_2, Pd−C, THF; (b) acid chloride, pyridine; (c) TFA, CH_2Cl_2; (d) Bu_4NF, THF; (e) MCPBA, $CHCl_3$; (f) $MeSO_2Cl$, CH_2Cl_2, 2,6-di-*tert*-butylpyridine.

have strong interactions with the protein. The similar observed activity of the original 4-OH lead compound **4** and the C-ring unsubstituted analogue **2** allowed A- and B-ring SAR to be studied in C-ring unsubstituted compounds (Tables 2 and 4−6), simplifying the chemistry.

Table 1. Effects of Various C-Ring Substituents on fXa Inhibition by 1,2-Di(4-methoxybenzamido)benzenes



compd	R1	R2	fXa K_{ass}[a] ($\times 10^6$ L/mol)	fIIa K_{ass}[a] ($\times 10^6$ L/mol)	*n* (fXa/fIIa)
1	4-OMe	H	1.25 ± 0.18	−	3
2	H	H	0.84 ± 0.35	0.02 ± 0.00	6/3
3	6-OMe	3-OMe	0.77	0.01	2
4	4-OH	H	0.64 ± 0.21	0.02 ± 0.01	5/4
5	4-Me	H	0.45 ± 0.36	0.02	3/2
7	3-OH	H	0.45	0.01	1
8	4-Cl	H	0.42	−	1
9	4-CO_{2H}	H	0.32	0.02	2/1

[a] K_{ass} represents the apparent association constant as measured by the methods of Smith et al.[2k] K_{ass} values are expressed as mean ± standard deviation when $n \geq 3$ and average when $n = 2$. The precision of single determinations (±std error) is ±12.9%. The precision of mean values is ±7.3%. Information about the statistical analysis that produced these estimates is included in the Experimental Section. $K_{ass} \approx 1/K_i$. A more detailed discussion of K_{ass} and its relationship to K_i is given in the Experimental Section.

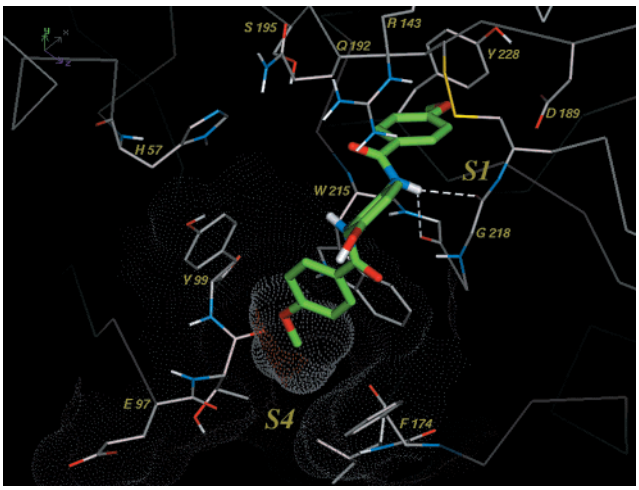
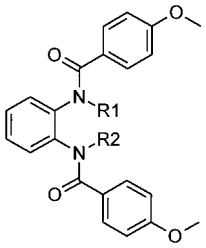


Figure 2. Proposed energy-minimized binding model of the lead compound **4** complexed with the active site of fXa. The orientation is such that Asp189 appears in the upper right-hand corner, Ser195 near the top central, and Glu97 in the lower left-hand corner. The molecular surface of the S4 region is highlighted in small white dots, while the surface for the B-ring substituent (4-methoxy) is shown in large dots. The illustrated portion of the ligand surface in contact with the S4 pocket is colored white, while the exposed portion is colored orange. Hydrogen bonds between **4** and the active site for this energy-minimized structure are shown as dashed lines. All aliphatic hydrogens and waters have been removed for clarity. D = Asp, E = Glu, F = Phe, G = Gly, H = His, Q = Gln, R = Arg, S = Ser, W = Trp, Y = Tyr.

Methylation of one or both of the amide nitrogens greatly decreased fXa affinity as shown in Table 2. As illustrated by the active site binding model, these NH groups are involved in at least one hydrogen bond to the protein, stabilizing the enzyme−inhibitor complex. Incorporation of methyl groups in either the A- or B-ring amides would eliminate these interactions. *N*-Methylation will also change the conformational preference

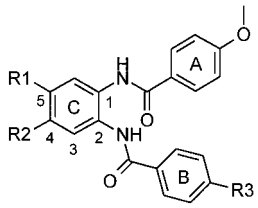
Table 2. Effects of *N*-Methylation on fXa Inhibition by 1,2-Di(4-methoxybenzamido)benzenes



compd	R1	R2	fXa K_{ass}[a] ($\times 10^6$ L/mol)	fIIa K_{ass}[a] ($\times 10^6$ L/mol)	*n* (fXa/fIIa)
2	H	H	0.84 ± 0.35	0.02 ± 0.00	6/3
10	Me	H	0.02	0.00	1
11	Me	Me	0.00	0.00	1

[a] K_{ass} represents the apparent association constant as measured by the methods of Smith et al.[2k] K_{ass} values are expressed as mean ± standard deviation when $n \geq 3$. The precision of single determinations (±std error) is ±12.9%. The precision of mean values is ±7.3%. Information about the statistical analysis that produced these estimates is included in the Experimental Section. $K_{ass} \approx 1/K_i$. A more detailed discussion of K_{ass} and its relationship to K_i is given in the Experimental Section.

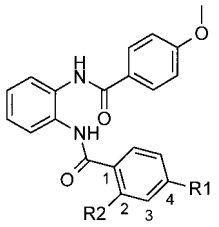
Table 3. Effects of B-Ring Substituents and C-Ring Hydroxylation on fXa Inhibition by A-Ring 4-Methoxydibenzamidobenzenes



compd	R1	R2	R3	fXa K_{ass}[a] ($\times 10^6$ L/mol)	fIIa K_{ass}[a] ($\times 10^6$ L/mol)	*n* (fXa/fIIa)
2	H	H	OMe	0.84 ± 0.35	0.02 ± 0.00	6/3
4	H	OH	OMe	0.64 ± 0.21	0.02 ± 0.01	5/4
12	H	OH	NMe_2	25.54	0.05	1
13	$MeSO_2NH$	H	*t*-Bu	13.00	0.13	1
16	H	CO_2H	*t*-Bu	12.80	0.07	1
21	H	$MeSO_2NH$	*t*-Bu	7.65	0.11	1
22	H	H	*t*-Bu	7.31	0.05	2/1
23	H	OH	*t*-Bu	6.57 ± 1.6	0.04 ± 0.02	3
24	H	H	*i*-Pr	4.91	0.08	1
27	CO_2H	H	*t*-Bu	3.99	0.08	1
30	OH	H	*t*-Bu	3.56	0.05	1
32	H	OH	Et	2.68	0.04	1

[a] K_{ass} represents the apparent association constant as measured by the methods of Smith et al.[2k] K_{ass} values are expressed as mean ± standard deviation when $n \geq 3$ and average when $n = 2$. The precision of single determinations (±std error) is ±12.9%. The precision of mean values is ±7.3%. Information about the statistical analysis that produced these estimates is included in the Experimental Section. $K_{ass} \approx 1/K_i$. A more detailed discussion of K_{ass} and its relationship to K_i is given in the Experimental Section.

Table 4. Effects of B-Ring Substituents on fXa Inhibition by A-Ring 4-Methoxydibenzamidobenzenes



compd	R1	R2	fXa K_{ass}[a] ($\times 10^6$ L/mol)	fIIa K_{ass}[a] ($\times 10^6$ L/mol)	*n*
33	NMe_2	H	16.88 ± 0.07	0.05 ± 0.01	3
36	CMe_2OMe	H	2.35	0.02	1
37	SMe	H	1.63	0.02	1
38	O-*i*-Pr	H	1.19	0.04	1
39	Ph	H	1.10	0.00	1
40	O-*t*-Bu	H	0.82	0.01	1
41	OMe	Cl	0.71	0.03	1
42	SO_2NMe_2	H	0.66	0.00	1
43	OEt	H	0.64	0.00	1
44	SO_2Me	H	0.53	0.00	1
45	OMe	OMe	0.52	0.02	1
46	OPr	H	0.44	0.00	1
47	SOMe	H	0.43	0.00	1
48	OPh	H	0.29	0.00	1
50	OBu	H	0.08	0.00	1
51	$COCF_3$	H	0.01	0.00	1
52	OC_6H_{13}	H	0.00	0.00	1

[a] K_{ass} represents the apparent association constant as measured by the methods of Smith et al.[2k] K_{ass} values are expressed as mean ± standard deviation when $n \geq 3$ and average when $n = 2$. The precision of single determinations (±std error) is ±12.9%. The precision of mean values is ±7.3%. Information about the statistical analysis that produced these estimates is included in the Experimental Section. $K_{ass} \approx 1/K_i$. A more detailed discussion of K_{ass} and its relationship to K_i is given in the Experimental Section.

of the bisamides to disfavor the active site binding conformation and possibly also induce repulsive steric interactions with the active site.

Tables 3 and 4 show the effects of replacing one of the 4-methoxy groups of the di(4-methoxybenzoyl)-benzenes with larger groups. A particularly sharp increase in fXa affinity was observed when methoxy was replaced by *N*,*N*-dimethyl or *tert*-butyl. Replacing a 4-methoxy group in compound **4** with *N*,*N*-dimethyl in compound **12** produced a 40× increase in affinity. A 20× gain in affinity is seen in the analogous deshydroxy compounds **2** and **33**. Similar replacement of 4-methoxy by *tert*-butyl gave a 10× increase in affinity in the hydroxy compounds (**4** and **23**) and a 9× increase in the deshydroxy compounds (**2** and **22**). This general increase in activity for both of these B-ring 4-position substitutions can be attributed to the increase in ligand surface area in contact with the hydrophobic S4 binding region. This difference is evident when comparing Figures 2−4, where the B-ring substituent contact surface area (large white dots) and exposed surface area (large orange dots) are highlighted for analogues **4**, **12,** and **23,** respectively. These larger substituents may also stabilize the ligand in the active site, possibly making potential interactions with the C-ring hydroxyl group more effective. During a molecular dynamics simulation of the complex, the *tert*-butyl group in **23** was observed to undergo slow rotation within the S4 pocket, while no similar motion was observed for the *N*,*N*-dimethyl group in an equivalent simulation of **12**. The further increase in activity for the *N*,*N*-dimethyl substitution (**12**) compared to *tert*-butyl (**23**) can be attributed to the *N*,*N*-dimethyl group minimizing the solvent-exposed hydrophobic surface area and much more rigidly positioning the attached methyl groups directly over the aromatic side chains of Tyr99 and Phe174.

Other B-ring substitutions reported in Tables 3 and 4 exhibit a variety of effects on fXa inhibition. Smaller alkyl groups such as isopropyl and ethyl (**24** and **32**, Table 3) produced smaller increases in affinity over their

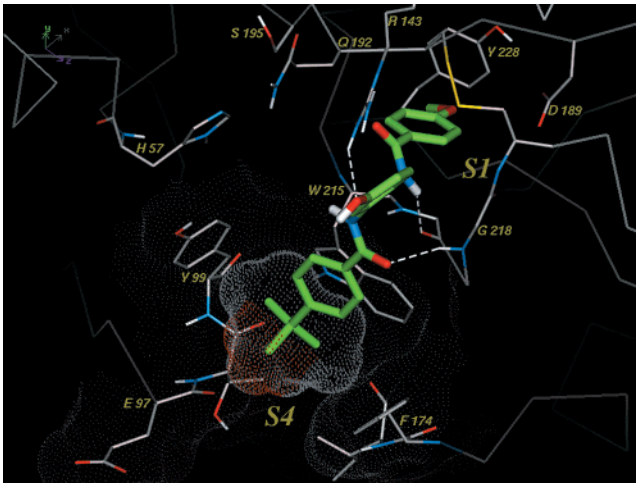


Figure 3. Proposed energy-minimized binding model of compound **23** complexed with the active site of fXa. The orientation and display features are the same as in Figure 2. D = Asp, E = Glu, F = Phe, G = Gly, H = His, Q = Gln, R = Arg, S = Ser, W = Trp, Y = Tyr.

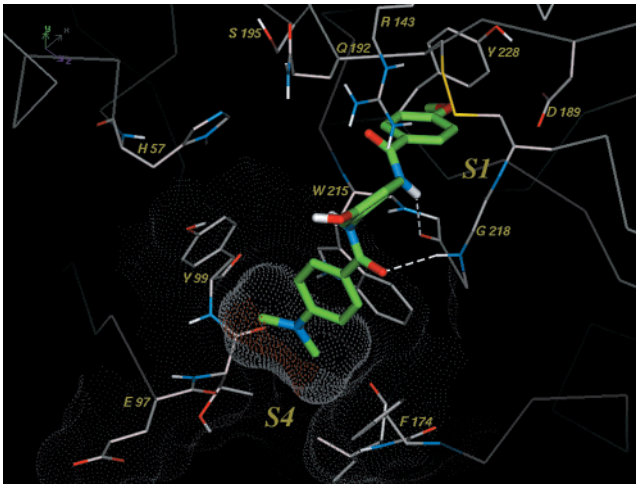
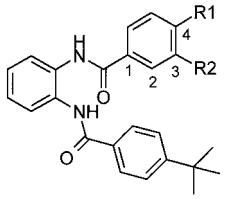


Figure 4. Proposed energy-minimized binding model of compound **12** complexed with the active site of fXa. The orientation and display features are the same as in Figure 2. D = Asp, E = Glu, F = Phe, G = Gly, H = His, Q = Gln, R = Arg, S = Ser, W = Trp, Y = Tyr.

methoxy analogues (**2** and **4**, Table 1). Inserting an oxygen atom between *tert*-butyl or isopropyl and the B-ring decreases affinity, possibly by inducing a less favorable binding conformation. Compound **40** (Table 4) is 9× less active than **22** (Table 3), and **38** (Table 4) is 4× less active than **24** (Table 3). The variety of B-ring 4-substituents shown in Tables 3 and 4 produces a >2500× range of activities, showing the sensitivity of the SAR to structural variations at this position. Addition of small substituents at the 2-position of the B-ring (compounds **41** and **45**) had no effect on affinity.

The SAR is sensitive to changes in substitution on the A-ring, as can be seen by the >300× range of activities in Table 5. In the proposed binding complex model this ring resides within the S1 region and positions the 4-methoxy group into a small hydrophobic pocket formed by the side chains of Ala90, Val213, and Tyr228. A similar interaction of aromatic substituents with a related serine protease S1 pocket was reported in a series of peptide thrombin inhibitors.[15] Only 4-vinyl (**53**) and 4-chloro (**54**) were more active than 4-methoxy

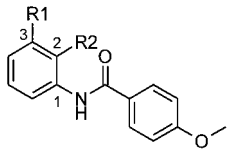
Table 5. Effects of A-Ring Substituents on fXa Inhibition by B-Ring 4-*tert*-Butyldibenzamidobenzenes



compd	R1	R2	fXa K_{ass}[a] (×10^6 L/mol)	fIIa K_{ass}[a] (×10^6 L/mol)	*n*
53	$CHCH_2$	H	3.05	0.01	1
54	Cl	H	2.92	0.05	1
55	H	$CHCH_2$	0.56	0.00	1
56	F	H	0.51	0.00	1
57	H	F	0.40	0.00	1
60	H	H	0.38	0.07	2
61	CH_3	H	0.28	0.00	2
62	H	OCH_3	0.02	0.00	1
63	CH_2CH_3	H	0.01	0.00	1
64	OCF_3	H	0.00	0.00	1

[a] K_{ass} represents the apparent association constant as measured by the methods of Smith et al.[2k] K_{ass} values are expressed as mean ± standard deviation when $n \geq 3$ and average when $n = 2$. The precision of single determinations (±std error) is ±12.9%. The precision of mean values is ±7.3%. Information about the statistical analysis that produced these estimates is included in the Experimental Section. $K_{ass} \approx 1/K_i$. A more detailed discussion of K_{ass} and its relationship to K_i is given in the Experimental Section.

Table 6. Effect of 1,3- versus 1,2-Substitution in Di(4-methoxybenzamido)benzenes



compd	R1	R2	fXa K_{ass}[a] (×10^6 L/mol)	fIIa K_{ass}[a] (×10^6 L/mol)	*n* (fXa/fIIa)
2	H	4-anisoylNH	0.84 ± 0.35	0.02 ± 0.00	6/3
65	4-anisoylNH	H	0.00	0.00	1

[a] K_{ass} represents the apparent association constant as measured by the methods of Smith et al.[2k] K_{ass} values are expressed as mean ± standard deviation when $n \geq 3$ and average when $n = 2$. The precision of single determinations (±std error) is ±12.9%. The precision of mean values is ±7.3%. Information about the statistical analysis that produced these estimates is included in the Experimental Section. $K_{ass} \approx 1/K_i$. A more detailed discussion of K_{ass} and its relationship to K_i is given in the Experimental Section.

(**2**), possibly due in part to less conformational flexibility. The size constraints on the A-ring 4-substituent appear to be severe. The ethyl (**63**) and trifluoromethoxy (**64**) compounds are much less active than **2** although their 4-substituents are only slightly larger than the methoxy group of **2**. Moving the 4-vinyl or 4-methoxy group of **53** or **2** to the 3-position in **55** or **62** decreased affinity, presumably by introducing unfavorable contacts in the S1 pocket. Compound **65** (Table 6) with 1,3-oriented benzamido groups was devoid of fXa inhibitory activity.

Members of the new series behave as competitive inhibitors of fXa. For example compound **2** showed classical competitive inhibition of fXa by Lineweaver–Burke analysis with a K_i of 0.68 ± 0.05 μM ($n = 3$) from Dixon plots.

Only two of the compounds presented (**13** and **21**) demonstrated apparent K_{ass} values with human throm-

bin as high as 0.1×10^{-6} L/mol. The ratio of thrombin inhibition to fXa inhibition for **13** and **21** is about 1/100. The remainder of the compounds generally show thrombin inhibitory activity ≤ 1/100 of their fXa inhibitory activities.

Conclusions

The 1,2-bisamidophenyl compounds described above provide a novel lead structure type for the development of human fXa inhibitors. This series differs from previously described small molecule inhibitors of fXa by using a 1,2-bisamidophenyl group to establish the relative spacing and orientation between the S1 pocket binding group (A-ring) and the S4 pocket binding group (B-ring). In addition to orienting and spacing the A- and B-rings favorably for S1 and S4 pocket binding, the bisamidophenyl unit appears to be able to hydrogen bond to active site residues to favor specific binding. The hundred-fold selectivity for fXa inhibition over thrombin inhibition observed in this series is encouraging, suggesting that fXa inhibitors built on this novel structure have the potential to discriminate between fXa and closely related serine proteases. More detailed data on the specificity of later members of this series are reported by Wiley et al.[13]

Experimental Section

Organic Chemistry. Preparations of final products are included in the Experimental Section. Preparations of intermediates are included in the Supporting Information. All reactions were run under an atmosphere of dry nitrogen unless noted. All solvents and reagents were used as acquired from commercial sources without purification. Nuclear magnetic resonance spectra were recorded at 300 MHz on a GE QE-300 spectrophotometer in the solvent indicated. Chemical shifts are reported in parts per million relative to tetramethylsilane. Infrared spectra were recorded on a Nicolet DX10 FT-IR spectrometer. Melting points were recorded on a Thomas-Hoover melting point apparatus and are uncorrected. Field-desorption (FD) mass spectra were recorded on a VG Analytical 70SE instrument, electrospray ionization (ESI) mass spectra were recorded on a Sciex API 100 instrument, and fast atom bombardment (FAB) mass spectra were recorded on a VG Analytical ZAB2-SE instrument. Elemental analyses were performed by the Physical Chemistry Department at Lilly Research Laboratories on a Control Equipment Corp. 440 elemental analyzer and are within 0.4% of theory unless otherwise noted. Analytical HPLC were performed on a Hitachi L-6200 instrument over a Vydac C_{18} analytical column, eluting with mixtures of CH_3CN in water, buffered with 0.1% TFA.

Molecular Modeling. The coordinate set for the protein structure used in this investigation was the human fXa, X-ray structure of Padmanabhan et al.[12] (Brookhaven PDB file 1hcg). The supplied chymotrypsinogen residue numbering[14] was maintained. All computational construction of ligands, preparation of the protein and protein−ligand complexes, and subsequent graphical analysis were performed with QUANTA, version 96.[16] All energy minimization and molecular dynamics were performed using CHARMm, version 23.2.[16,17]

The protein was initially prepared by building and regularizing coordinates for all atoms in residues 146−151 (undefined in 1hcg) in an orientation generally pointing away from the active site. All hydrogens were added to the protein and crystallographic waters and refined using the HBUILD procedure. The protein was then completely solvated by centering a 8 Å sphere of TIPS3P water on each surface-exposed residue. The ligand binding region was further solvated using a 20 Å sphere of TIPS3P water, centered at a point central to the active site, approximately 6 Å beyond the Cα of Trp215. For this solvated system, the hydrogen positions were initially energy minimized while all non-hydrogen atoms were fixed rigidly in space. This was followed by spatially constrained energy minimization of the entire system by imposing on all non-hydrogen atoms harmonic constraints that decreased in stages from 100 to 50 kcal/mol·Å^2 in increments of 10 kcal/mol·Å^2. The resulting solvated protein system coordinate set was used as the starting structure for all subsequent protein−ligand complexes constructed. All energy minimizations were done using the ABNR algorithm and taken to convergence (gradient tolerance of 0.01 kcal/mol·Å). For all energy minimizations and molecular dynamics simulations, the nonbond interactions were evaluated using a 13 Å nonbond list, updated by the heuristic testing algorithm. For these calculations a force shift function for the electrostatics and a shift function for the van der Waals smoothed the nonbond interactions to zero at a distance of 12 Å. A constant dielectric of 1.0 was used. All calculations were performed on Silicon Graphics R4400 workstations.

The 3D structure of compound **4** was constructed in the ChemNote facility, using default atom types and smoothing assigned charges over all C and aliphatic H atoms to give a total sum of 0.0. The overall initial active site conformation and orientation were taken from that derived in a parallel study of various related amidine-substituted analogues.[13] Compound **4** was positioned by flexibly superimposing it onto the same bisamide phenyl structure of the related analogue possessing the derived active site binding mode.

The structure of **4** was then reinserted into the active site of the fully solvated fXa protein starting structure, and all waters having an oxygen within 2.0 Å of any ligand atom were deleted. The resulting complex was then processed by energy minimization where the ligand, all protein residues having an atom within 12 Å, and all waters within 20 Å of the active site center were unconstrained, while the remainder of the system was rigidly fixed in place. The final energy-minimized structure for **4** is shown in Figure 2 where aliphatic hydrogens and waters have been removed for clarity. A subsequent molecular dynamics simulation was initiated from this energy-minimized structure utilizing the same constraint regime. The simulation utilized a time step of 1 fs and consisted of 3 ps heating (0−300 °C in increments of 10 °C, reassigning velocities every 100 steps), 10 ps equilibration (checking the system temperature every 100 steps and rescaling velocities to correspond to 300 °C if the average deviation is more than ±10 °C), and 40 ps production. During the equilibration stage for each system investigated, velocity rescaling was required only once or twice and only within the first 2 ps. The final coordinates from each stage were saved, as well as from every 20th time step during the production dynamics.

All other analogues investigated were constructed from the energy-minimized fXa complex of **4**, using the 3D Editor. Each of these were also processed by energy minimization and molecular dynamics in the same manner as described.

Materials. Human fXa and human α-thrombin were purchased from Enzyme Research Laboratories (South Bend, IN). Chromogenic *p*-nitroanilide peptide protease substrates were purchased from Midwest Biotech (Fishers, IN): Bz-Ile-Glu-Gly-Arg-pNA (for fXa) and Bz-Phe-Val-Arg-pNA (for thrombin).

Binding Affinity for fXa (and for Thrombin). The binding affinities for human fXa (and for thrombin) were measured as apparent association constants (K_{ass}) derived from protease inhibition kinetics as described previously.[18,2k] The apparent K_{ass} values were obtained in a high-volume protocol using automated dilutions of inhibitors ($n = 3$ for each of 4−8 inhibitor concentrations) into 96-well plates and chromogenic substrate hydrolysis rates determined at 405 nm using a Thermomax plate reader from Molecular Devices (San Francisco, CA). The assay protocol was: 50 μL buffer (0.06 M tris, 0.3 M NaCl, pH 7.4), 25 μL inhibitor test solution (in MeOH), 25 μL human fXa (32 nM in 0.03 M tris, 0.15 M NaCl, 1 mg/mL HSA), finally 150 μL substrate (0.3 mM in water) added within 2 min to start hydrolysis. The final fXa concentration

was 3.2 nM. Free [fXa] and bound [fXa] were determined from linear standard curves on the same plate by use of SoftmaxPro software for each inhibitor concentration and apparent K_{ass} calculated for each inhibitor concentration which produced hydrolysis inhibition between 20% and 80% of the control (3.2 nM fXa): apparent $K_{ass} = [E:I]/[E_f][I_f] = [E_b]/[E_f][I^o - I_b]$. This method allows affinity determinations for tight binding inhibitors as well as for weak binding enzyme inhibitors[21] and has allowed the generation of a large protease inhibitor SAR database.[19] This system of affinity measurement was designed to: (1) validly assess a very large number of samples and (2) determine affinity with tight binding inhibitors where classical K_i methods fail.[20,21] Algebraic solutions for the equation $K_{ass} = [E:I]/[E_f][I_f] = [E_b]/[E_f][I^o - I_b]$ account for the free and bound inhibitor concentrations. Alternatively the whole data set can be graphically analyzed as a linearized solution to the same K_{ass} equation: $I^o/(1 - a) = [1/(\text{apparent } K_{ass})(a)] + E^o$, where a = fraction of free enzyme.[2k] This equation was also derived by Henderson[20] and Beith[21] for study of tight binding inhibitors, where classical methods fail to satisfactorily produce K_i determinations. Application of our method has allowed the accumulation of a large database of apparent K_{ass} values (the K_{ass} values obtained at the single appropriate substrate concentration with each protease of interest) which are self-consistent for each protease and which can be used to assess selectivity by directly relating the various K_{ass} values for respective proteases. Apparent K_{ass} values can be corrected by determining the effect of substrate concentration.[2k,20,21] Corrected K_{ass} values = $1/K_i$. Approximate K_i values = 1/(apparent K_{ass}). The variability of mean apparent K_{ass} values determined at the single substrate concentration was ±15%. The assay system K_m was measured as 0.347 ± 0.031 mM (n = 4), and V_{max} was 13.11 ± 0.76 μM/min with 3.2 nM fXa. A single apparent K_{ass} determination uses 6−8 inhibitor concentrations (in triplicate) bracketing the IC_{50} effect concentration, which allows an estimation regarding the repeatability of the single apparent K_{ass} result. Statistical treatment of our SAR database using a random effects analysis of variance[22] led to estimates that the precision (1 standard error) for a single K_{ass} determination is 12.9% and the precision for a multiple determination (n = 3) is 7.3%. The same general method was used for evaluating protease selectivity of the fXa inhibitors by determining apparent K_{ass} values with appropriate chromogenic protease substrates: for human thrombin, 5.9 nM enzyme was used with 0.2 mM Bz-Phe-Val-Arg-pNA. For classical K_i determinations Dixon plots were generated with the same protocol using four substrate concentrations (0.112, 0.224, 0.448, and 0.896 mM), and the type of inhibition was confirmed with Lineweaver−Burke graphs.

4-Methoxy-*N*^{1},*N*^{2}-bis(4-methoxybenzoyl)-1,2-benzenediamine (1). To a solution of 4-methoxy-1,2-benzenediamine dihydrochloride (3.60 g, 20 mmol) in CH_2Cl_2 (400 mL) was added 0.5 N aq NaOH (168 mL), and the resulting mixture was cooled in an ice−water bath. *p*-Anisoyl chloride (7.2 g, 42 mmol) was added slowly with vigorous stirring. The mixture was allowed to warm slowly to room temperature and stirred for 18 h. The organic layer was separated and washed with dil aq HCl, water, and saturated aq NaCl. The title compound, 5.0 g (48%), crystallized from the CH_2Cl_2 solution: mp 238−239 °C; ^{1}H NMR (DMSO-d_6) δ 3.78 (s, 3H), 3.82 (s, 6H), 6.93 (dd, J = 9, 3 Hz, 1H), 7.05 (d, J = 8 Hz, 4H), 7.31 (d, J = 3 Hz, 1H), 7.45 (d, J = 9 Hz, 1H), 7.90 (d, J = 8 Hz, 2H), 7.93 (d, J = 8 Hz, 2H), 9.87 (s, 1H), 9.92 (s, 1H). Anal. ($C_{23}H_{22}N_2O_5$) C, H, N.

***N*^{1},*N*^{2}-Bis(4-methoxybenzoyl)-1,2-benzenediamine (2).** To a solution of *o*-phenylenediamine (2.16 g, 19.8 mmol) in CH_2Cl_2 (200 mL) was added 0.5 N aq NaOH (84 mL), and the resulting mixture was cooled in an ice−water bath. *p*-Anisoyl chloride (6.2 g, 40 mmol) was added slowly with vigorous stirring. The mixture was allowed to warm slowly to room temperature and stirred for 18 h. The organic layer was separated and washed with dil aq $NaHCO_3$ solution, dil aq HCl, and water. The organic layer was dried (sodium sulfate), filtered, and concentrated in vacuo to provide 5.2 g (70%) of the title compound. A sample was crystallized from CH_2Cl_2: mp 205−206 °C; ESMS $[M + H]^+$ 377.37 calcd $C_{22}H_{20}N_2O_4$ 377.41; ^{1}H NMR (DMSO-d_6) δ 3.82 (s, 6H), 7.05 (d, 4H), 7.27 (dd, 2H), 7.63 (dd, 2H), 7.93 (d, 4H), 9.98 (s, 2H). Anal. ($C_{22}H_{20}N_2O_4$) C, H, N.

3,6-Dimethoxy-*N*^{1},*N*^{2}-bis(4-methoxybenzoyl)-1,2-benzenediamine (3). To a stirred solution of 3,6-dimethoxy-1,2-benzenediamine (2.0 mmol) and pyridine (6.1 mL, 75 mmol) in dichloromethane (30 mL) was added 4-anisoyl chloride (4.9 mmol). After 12 h, the mixture was diluted with dichloromethane and washed with 1 N aq citric acid, saturated aq NaCl solution, saturated aq $NaHCO_3$ solution, dried ($MgSO_4$), filtered, and concentrated in vacuo. The resulting solid was suspended in Et_2O, sonicated, filtered and dried in vacuo to give 555 mg (65%) of the title compound: ^{1}H NMR (DMSO-d_6) δ 3.75 (s, 6H), 3.78 (s, 6H), 6.98 (d, J = 9.0 Hz, 4H), 6.99 (s, 2H), 7.84 (d, J = 9.0 Hz, 4H), 9.28 (br s, 2H); MS (FD) *m/e* 435.9 (M^+). Anal. ($C_{24}H_{24}N_2O_6$) C, H, N.

***N*^{1},*N*^{2}-Bis(4-methoxybenzoyl)-4-hydroxy-1,2-benzenediamine (4). Procedure 1.** A mixture of $SnCl_2 \cdot 2H_2O$ (5.0 g, 10.0 mmol) and resin bound nitroamide[11] (600 mg, 1.0 mmol based on a substitution of 2 mequiv) in DMF (20 mL) was stirred for 5 h. The resin was filtered and washed several times with DMF, twice with a solution of Et_3N/DMF (10%) and several times with DCM. The resin was dried under vacuum for a few hours prior to the next step.

To a suspension of the above resin (600 mg, 1.0 mmol) in dichloromethane (20 mL) were added pyridine (1.3 mL, 15.0 mmoL) and a solution of *p*-methoxybenzoyl chloride (1.7 g, 10.0 mmol) in dichloromethane (4 mL). The mixture was stirred for 18 h, drained and the resin washed several times with DMF followed by several washes with dichloromethane. The resin was dried under vacuum for a few hours prior to the next step.

Propylamine (3 mL, excess) was added to a suspension of the resin (~600 mg, 1.0 mmol) in THF (15 mL). The mixture stirred for 12 h. The residue obtained after concentration of the solution was triturated in dichloromethane to afford 250 mg (63%) of pale beige solid. Crystallization of the residue from dichloromethane/MeOH gave 180 mg of the title product: mp 225−229 °C; ^{1}H NMR (DMSO-d_6) δ 3.81 (s, 6H), 6.66 (d, 1H), 7.04 (d, 4), 7.16 (s, 1H), 7.30 (d, 1H), 7.89 (dd, 4H), 9.57 (s, 1H), 9.81 (s, 2H). Anal. ($C_{22}H_{20}N_2O_5$) C, H, N.

Procedure 2. Into 25 mL CH_2Cl_2 was dispersed 0.406 g (1 mmol) 4-methoxy-*N*^{1},*N*^{2}-bis(4-methoxybenzoyl)-1,2-benzenediamine. After cooling the solution in an ice bath, 0.284 mL (3 mmol) BBr_3 was added in one portion. After 4 h the reaction mixture was allowed to warm to room temperature over 1 h, diluted with CH_2Cl_2 (75 mL) and washed with water (150 mL) water. The organic layer was dried ($MgSO_4$) and concentrated. The product was purified by flash chromatography (silica, 0% to 20% MeOH in $CHCl_3$), and on cooling in freezer, fractions crystallized, giving 96 mg (24% yield) of the desired compound: ^{1}H NMR (DMSO-d_6) δ 3.80 (s, 6H), 6.66 (d, 1H), 7.05 (d, 4H), 7.18 (s, 1H), 7.30 (d, 1H), 7.89 (d, 2H), 7.95 (d, 2H), 9.57 (br s, 1H), 9.81 (s, 2H); MFD 392 (M^+). Anal. ($C_{22}H_{20}N_2O_5$) C, H, N.

4-Methyl-*N*^{1},*N*^{2}-bis(4-methoxybenzoyl)-1,2-benzenediamine (5). Following the procedure described for the synthesis of compound **3**, **5** was prepared from 4-methyl-1,2-diaminobenzene: 83% yield; ^{1}H NMR (DMSO-d_6) δ 2.34 (s, 3H), 3.82 (s, 6H), 7.06 (d, J = 8.8 Hz, 4H), 7.00−7.10 (m, 1H), 7.45−7.55 (m, 2H), 7.92 (d, J = 8.8 Hz, 2H), 7.93 (d, J = 8.8 Hz, 2H), 9.91 (s, 2H); MS (ESI) *m/e* 391.2 $(MH)^+$. Anal. ($C_{23}H_{22}N_2O_4$) C, H, N.

2,3-Bis[(4-methoxybenzoyl)amino]phenol (7). A solution of 2,3-bis[(4-methoxybenzoyl)amino]phenoxy 4-methoxybenzoate (7.75 g, 14.7 mmol) in MeOH (100 mL) was cooled to ice−water bath temperature and 5 N aq NaOH solution (3.0 mL) was added. The reaction mixture was allowed to warm to room temperature and stirred for 72 h. The reaction mixture was concentrated in vacuo and the resulting solid was dissolved in CH_2Cl_2 and washed with dil aq HCl, water, and saturated NaCl solution. The organic layer was dried (sodium sulfate), filtered, and concentrated in vacuo. Recrystallization

of the residue from Et_2O/hexane gave 2.3 g (40%) of the title product: mp 208−209 °C; ^{1}H NMR (DMSO-d_6) δ 3.82 (s, 3H), 3.84 (s, 3H), 6.79 (d, 1H), 7.04 (dd, 4H), 7.17 (t, 1H), 7.24 (d, 1H), 7.83 (d, 2H), 7.99 (d, 2H), 9.62 (bs, 3H). Anal. ($C_{22}H_{20}N_2O_5$) C, H, N.

4-Chloro-*N*^{1},*N*^{2}-bis(4-methoxybenzoyl)-1,2-benzenediamine (8). Following the procedure described for the synthesis of compound **3**, **8** was prepared from 4-chloro-1,2-diaminobenzene: 86% yield; ^{1}H NMR (DMSO-d_6) δ 3.82 (s, 6H), 7.06 (d, J = 9.0 Hz, 4H), 7.32 (dd, J = 2.6, 8.8 Hz, 1H), 7.65 (d, J = 8.8 Hz, 1H), 7.78 (d, J = 2.6 Hz, 1H), 7.85−7.95 (m, 4H), 9.97 (s, 1H), 10.00 (s, 1H); MS (ESI) *m/e* 409.2 $(MH)^+$. Anal. ($C_{22}H_{19}ClN_2O_4$) C, H, N.

3,4-Bis[(4-methoxybenzoyl)amino]benzoic Acid (9). A solution of *p*-anisoyl chloride (5.64 g, 33 mmol) in CH_2Cl_2 (40 mL) was dropped into pyridine (100 mL) containing 4.56 g (30 mmol) 3,4-diaminobenzoic acid, cooled by an ice bath. Reaction mixture was allowed to warm gradually to room temperature. After 72 h, CH_2Cl_2 (200 mL) was added, forming a precipitate, which was collected and washed with CH_2Cl_2. The product was recrystallized from a concentrated $CHCl_3$−MeOH solution, giving 148 mg (1.2% yield) of the desired compound: ^{1}H NMR (DMSO-d_6) δ 3.81 (s, 6H), 7.05 (d, 4H), 7.82 (m, 2H), 7.90 (m, 4H), 8.19 (s,1H), 10.07 (s, 1H), 10.08 (s, 1H), 12.9 (br s, 1H); MS (FD) *m/e* (420 (M^+). Anal. ($C_{23}H_{20}N_2O_6$) C, H, N.

***N*^{1}-Methyl-*N*^{1},*N*^{2}-bis(4-methoxybenzoyl)-1,2-benzenediamine (10).** Using the procedure described for the preparation of compound **3**, compound **10** was prepared from *N*^{1}-methyl-1,2-benzenediamine: 95% yield; ^{1}H NMR (DMSO-d_6) δ 3.25 (s, 3H), 3.70 (s, 3H), 3.85 (s, 3H), 6.72 (br d, J = 8.0 Hz, 2H), 7.0−7.1 (m, 4H), 7.2−7.3 (m, 3H), 7.52 (d, J = 8.0 Hz, 1H), 7.90 (d, J = 9.0 Hz, 2H), 9.68 (s, 1H); MS (FD) *m/e* 390.0 (M^+). Anal. ($C_{23}H_{22}N_2O_4$) C, H, N.

***N*^{1},*N*^{2}-Dimethyl-*N*^{1},*N*^{2}-bis(4-methoxybenzoyl)-1,2-benzenediamine (11).** To a stirring solution of compound **10** (0.5 g, 1.28 mmol) in THF (5 mL) at 0 °C was added a 0.5 M solution of lithium bis(trimethylsilyl)amide in THF (2.4 mL, 1.2 mmol), followed by iodomethane (0.5 mL, 6.4 mmol). The cold bath was removed and after stirring overnight, the solvent was removed in vacuo and the residue was partitioned between EtOAc and water. The organic phase was washed twice with 1 M citric acid, once with brine, twice with saturated aq $NaHCO_3$, and once again with brine. The organic phase was then dried with $MgSO_4$, filtered and concentrated in vacuo. The residue was dissolved in a small amount of $CHCl_3$ and chromatographed over silica gel, eluting with a gradient of 30% EtOAc in hexanes through 70% EtOAc in hexanes. The product containing fractions were combined and concentrated in vacuo to give 0.5 g (98%) of a white foam: ^{1}H NMR (DMSO-d_6) δ 3.72 (br s, 12 H), 6.7−7.4 (br m, 12 H); MS (FD) *m/e* 404.1 (M^+). Anal. ($C_{24}H_{24}N_2O_4$) C, H, N.

***N*^{2}-[4-(Dimethylamino)benzoyl]-4-hydroxy-*N*^{1}-(4-methoxybenzoyl)-1,2-benzenediamine (12).** A solution of 4-(dimethylamino)benzoic acid and thionyl chloride in CH_2Cl_2 was refluxed 4 h. Volatile solvents were removed in vacuo to yield 1.10 g of 4-(dimethylamino)benzoyl chloride. This material was used in subsequent reactions without purification.

To a mixture of 4-*tert*-butyldimethylsilyloxy-*N*^{1}-(4-methoxybenzoyl)-1,2-benzenediamine (200 mg, 1.20 mmol) and 4-(dimethylamino)benzoyl chloride (200 mg) in CH_2Cl_2 (5 mL) were added excess *N*-methylmorpholine and a catalytic amount of 4-(dimethylamino)pyridine. The mixture was stirred 16 h at ambient temperature then was partitioned between EtOAc and saturated $NaHCO_3$. The organic portion was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was taken up in EtOAc and hexane added until cloudy. The mixture was sonicated causing a precipitate to form. The solid silyl ether was collected by filtration then dissolved in 3 mL THF. The solution was treated with 1 mL 5 N HCl and allowed to stand for 60 h then neutralized with saturated $NaHCO_3$ solution. Hexane was added and the mixture sonicated. The resultant solid was collected by filtration and dried under vacuum to yield the title bisamide phenol: ^{1}H NMR (DMSO-d_6) δ 2.98 (s, 6H), 3.82 (s, 3H), 6.63 (dd, J = 2.8, 8.5, 1H), 6.73 (d, J = 8.7, 2H), 7.05 (d, J = 8.7, 2 H), 7.19 (d, J = 3.0, 1H), 7.28 (d, J = 8.7, 1H), 7.77 (d, J = 8.7, 2H), 7.92 (d, J = 8.7, 2H), 9.49 (s, 1H), 9.61 (s, 1H), 9.85 (s, 1H); IR 1606, 1504, 1292, 1264, 1175 cm^{-1}; MS (ion spray) *m/e* 406 (M + 1). Anal. ($C_{23}H_{23}N_3O_4$) C, H; N: calcd, 10.36; found, 9.72.

***N*^{2}-(4-*tert*-Butylbenzoyl)-*N*^{5}-methylsulfonyl-*N*^{1}-(4-methoxybenzoyl)-1,2,5-benzenetriamine (13).** *N*^{2}-(4-*tert*-Butylbenzoyl)-*N*^{1}-(4-methoxybenzoyl)-1,2,5-benzenetriamine trifluoroacetate (230 mg, 0.55 mmol) was dissolved in CH_2Cl_2 (50 mL) and 2,6-di-*tert*-butylpyridine (247 μL, 1.1 mmol) and methylsulfonyl chloride (47 μL, 0.61 mmol) were added. The reaction was stirred at room temperature under nitrogen for 8 h. More methylsulfonyl chloride (47 μL, 0.61 mmol) and 2,6-di-*tert*-butylpyridine (247 μL, 1.1 mmol) were added. The reaction was stirred for an additional 16 h. Additional 2,6-di-*tert*-butylpyridine (1 mL, 4.45 mmol) was added and the reaction was stirred for 2 more h. The reaction was concentrated in vacuo and the residue was dissolved in EtOAc and washed with 1 N HCl (2 × 20 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated. The crude residue was purified by flash column chromatography (1:1 CH_2Cl_2/EtOAc) to give the desired product (160 mg, 59%): ^{1}H NMR (DMSO-d_6) δ 1.30 (s, 9H), 3.03 (s, 3H), 3.82 (s, 3H), 7.06(d, J = 9.0, 2H), 7.11 (dd, J = 2.6, 8.7, 1H), 7.55 (m, 4H), 7.86 (d, J = 8.7, 2H), 7.93 (d, J = 8.7, 2H), 9.83 (s, 1H), 9.94 (s, 1H), 9.99 (s, 1H); IR 3284, 3242, 1657, 1612, 1501, 1388, 1335, 1286, 1257, 1156 cm^{-1}; MS *m/e* 495.31. Anal. ($C_{26}H_{29}N_3O_5S$) C, H, N.

3-[(4-*tert*-Butylbenzoyl)amino]-4-[(4-methoxybenzoyl)-amino]benzoic Acid (16). Using the procedure described in for the preparation of compound **27**, methyl 3-[(4-*tert*-butylbenzoyl)amino]-4-[(4-methoxybenzoyl)amino]benzoate (1.00 mmol) yielded, after acidification of the aq layer, 318 mg (71%) of the title compound as a crystalline solid: ^{1}H NMR (DMSO-d_6) δ 1.28 (s, 9H), 3.80 (s, 3H), 7.05 (d, 2H), 7.52 (d, 2H), 7.81 (s, 1H), 7.89 (d, 1H), 7.94 (d, 1H), 8.19 (s, 1H), 10.11 (s, 1H), 10.19 (s, 1H); IR (KBr) 1645, 1690, 3256 cm^{-1}; MS (FD) *m/e* 446 (M^+). Anal. ($C_{26}H_{26}N_2O_5$) C, H, N.

***N*^{2}-(4-*tert*-Butylbenzoyl)-*N*^{4}-methylsulfonyl-*N*^{1}-(4-methoxybenzoyl)-1,2,4-benzenetriamine (21).** The *N*^{2}-(4-*tert*-butylbenzoyl)-*N*^{1}-(4-methoxybenzoyl)-1,2,4-benzenetriamine (230 mg, 0.55 mmol) was dissolved in CH_2Cl_2 (50 mL) and 2,6-di-*tert*-butylpyridine (247 μL, 1.1 mmol) and methylsulfonyl chloride (47 μL, 0.61 mmol) were added. The reaction was stirred at room temperature under nitrogen for 8 h. More 2,6-di-*tert*-butylpyridine (247 μL, 1.1 mmol) and methylsulfonyl chloride (47 μL, 0.61 mmol) were added. After stirring for 2 more h, the reaction was then concentrated in vacuo. The residue was dissolved in EtOAc and washed with 1 N HCl (2 × 20 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash column chromatography (1:1 EtOAc/CH_2Cl_2) to give the pure product (204 mg, 75%): ^{1}H NMR (DMSO-d_6) δ 1.30 (s, 9H), 3.03 (s, 3H), 3.82 (s, 3H), 7.06 (d, J = 9.0, 2H), 7.11 (dd, J = 2.4, 8.9, 1H), 7.56 (m, 4H), 7.87 (d, J = 8.7, 2H), 7.93 (d, J = 9.0, 2H), 9.83 (s, 1H), 9.90 (s, 1H), 10.05 (s, 1H); IR 1653, 1608, 1510, 1327, 1255, 1156 cm^{-1}; MS (FD) *m/e* 495.45. Anal. ($C_{26}H_{29}N_3O_5S$) C, H, N.

***N*^{1}-(4-Methoxybenzoyl)-*N*^{2}-(4-*tert*-butylbenzoyl)-1,2-benzenediamine (22).** Using the procedure described for the preparation of 3,6-dimethoxy-*N*^{1},*N*^{2}-bis(4-methoxybenzoyl)-1,2-benzenediamine **(3),** 4-anisoyl chloride (2.2 mmol) and *N*^{1}-(4-*tert*-butylbenzoyl)-1,2-benzenediamine (1.8 mmol) yielded 441 mg (61%) of the title compound: ^{1}H NMR (DMSO-d_6) δ 1.30 (s, 9 H), 3.83 (s, 3 H), 7.07 (d, J = 9.0 Hz, 2 H), 7.27 (m, 2 H), 7.54 (d, J = 8.5 Hz, 2 H), 7.64 (m, 2 H), 7.88 (d, J = 8.5 Hz, 2 H), 7.94 (d, J = 8.5 Hz, 2 H), 7.88 (d, J = 8.5 Hz, 2 H), 7.94 (d, J = 8.5 Hz, 2 H), 10.00 (br s, 2 H); MS (FD) *m/e* 402.3 (M^+). Anal. ($C_{25}H_{26}N_2O_3$) C, H, N.

***N*^{1}-(4-Methoxybenzoyl)-*N*^{2}-(4-*tert*-butylbenzoyl)-4-hydroxy-1,2-benzenediamine (23).** Using 4-*tert*-butylbenzoyl chloride and the procedure described for the preparation of compound **4** yielded 174 mg (40%) of the title compound a white solid: mp 234−235 °C; ^{1}H NMR (MeOD) δ 1.25 (s, 9H), 3.76 (s, 3H), 6.64 (dd, 1H), 6.90 (d, 2H), 7.09 (d, 1H), 7.24 (d,

1H), 7.44 (d, 2H), 7.73−7.83 (m, 5H). Anal. ($C_{25}H_{26}N_2O_4 \cdot 1/3H_2O$) C, H, N.

***N*¹-(4-Methoxybenzoyl)-*N*²-(4-isopropylbenzoyl)-1,2-benzenediamine (24).** To a mixture of 4-isopropylbenzoic acid (1.65 mmol) and pyridine (2.1 mmol) in toluene (15 mL) was added thionyl chloride (2.1 mmol). After heating at 80 °C for 3 h, the reaction mixture was cooled and concentrated in vacuo to give 4-isopropylbenzoyl chloride. A solution of this material (1.65 mmol) in CH_2Cl_2 (15 mL) was added to a mixture of *N*¹-(4-methoxybenzoyl)-1,2-benzenediamine (399 mg, 1.65 mmol) and pyridine (1.65 mmol) in CH_2Cl_2 (15 mL) cooled to 0 °C. The reaction mixture was warmed to room temperature and stirred for 1 h. The reaction was partitioned between CH_2Cl_2 (25 mL) and 1 N HCl (10 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo to give 523 mg (82%) of the title compound as a white solid: ^{1}H NMR ($CDCl_3$) δ 1.30 (d, 6H, J = 6.9 Hz), 3.00 (m, 1H), 6.94−6.92 (m, 2H), 7.00 (d, 2H, J = 8.7 Hz), 7.36 (d, 2H, J = 8.1 Hz), 7.46−7.40 (m, 2H), 7.93 (d, 2H, J = 8.4 Hz), 7.99 (d, 2H, J = 9.0 Hz), 9.21 (s, 1H), 9.23 (s, 1H); MS (FD) *m*/*e* 388 (M^+); IR ($CHCl_3$) 1256, 1507, 1608, 1646 cm^{-1}. Anal. ($C_{24}H_{24}N_2O_3$) C, H, N.

3-[(4-Methoxybenzoyl)amino]-4-[(4-*tert*-butylbenzoyl)amino]benzoic Acid (27). To a solution of methyl 3-[(4-methoxybenzoyl)amino]-4-[(4-*tert*-butylbenzoyl)amino]-benzoate (0.487 g, 1.00 mmol) in THF (32 mL) and MeOH (8 mL) was added 5 N aq NaOH (0.6 mL). The resulting mixture was stirred for 16 h, a second portion of 5 N aq NaOH (0.6 mL) added, and the mixture stirred for an additional 16 h. The solvent was concentrated in vacuo and the crude product acidified with dil aq HCl and diluted with EtOAc. The mixture was extracted with saturated aq K_2CO_3 solution. The aq layer was acidified and extracted with EtOAc. The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo. Crystallization of the residue from CH_2Cl_2/hexane provided 376 mg (100%) of the title product: ^{1}H NMR (DMSO-d_6) δ 1.28 (s, 9H), 3.81 (s, 3H), 7.05 (d, 2H), 7.53 (d, 2H), 7.82 (d, 1H), 7.86 (d, 2H), 7.87 (d, 1H), 8.18 (s, 1H), 10.08 (s, 1H), 10.12 (s, 1H); MS (FD) *m*/*e* 446 (M^+); IR (KBr) 1608, 1659, 1687, 2963 cm^{-1}.; Anal. ($C_{26}H_{26}N_2O_5$) H, N; C: calcd, 69.94; found, 70.90.

***N*¹-(4-Methoxybenzoyl)-*N*²-(4-*tert*-butylbenzoyl)-5-hydroxy-1,2-benzenediamine (30).** The *N*¹-(4-methoxybenzoyl)-*N*²-(4-*tert*-butylbenzoyl)-5-*tert*-butyldimethylsilylhydroxy-1,2-benzenediamine (220 mg, 0.41 mmol) was dissolved in THF (20 mL) and the solution was cooled to 0 °C. A 1 M THF solution of tetra-*n*-butylammonium fluoride (0.82 mL, 0.82 mmol) was added and the reaction turned yellow. After stirring for 15 min at 0 °C, the reaction was quenched with water (5 mL). The THF was removed under reduced pressure and the residue was partitioned between EtOAc and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified using flash column chromatography (10% EtOAc/CH_2Cl_2−50% EtOAc/CH_2Cl_2) to give the desired compound (140 mg, 81%): ^{1}H NMR (DMSO-d_6) δ 1.29 (s, 9H), 3.81 (s, 3H), 6.65 (dd, J = 2.4, 8.5, 1H), 7.04 (d, J = 8.7, 2H), 7.17 (d, J = 2.3, 1H), 7.31 (d, J = 9.0, 1H), 7.51 (d, J = 8.3, 2H), 7.87 (t, J = 7.3, 4H), 9.53 (s, 1H), 9.79 (s, 1H), 9.84 (s, 1H); MS *m*/*e* 418.03. Anal. ($C_{25}H_{26}N_2O_4$) C, H; N: calcd, 6.69; found, 5.98.

***N*¹-(4-Methoxybenzoyl)-*N*²-(4-ethylbenzoyl)-4-hydroxy-1,2-benzenediamine (32).** To a solution of *N*¹-(4-methoxybenzoyl)-*N*²-(4-propylbenzoyl)-4-(*tert*-butyldimethylsilyloxy)-1,2-benzenediamine (300 mg, 0.59 mmol) in THF (20 mL) cooled to 0 °C was added a 1 M solution of tetra-*n*-butylammonium fluoride in THF (1.4 mL, 1.4 mmol). After 15 min, the reaction mixture was diluted with water and partitioned with EtOAc. The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was chromatographed (silica gel, 10% EtOAc/90% CH_2Cl_2 to 40% EtOAc/60% CH_2Cl_2) to give 200 mg (87%) of the title compound as a white solid: ^{1}H NMR (DMSO-d_6) δ 1.18 (t, 3 H, J = 7.5 Hz), 2.65 (q, 2 H, J = 7.5 Hz), 3.81 (s, 3 H), 6.65 (dd, 1 H, J = 8.7, 2.6 Hz), 7.04 (d, 2 H, J = 8.7 Hz), 7.21 (d, 1 H, J = 2.6 Hz), 7.29 (d, 1 H, J = 9.0 Hz), 7.33 (d, 2 H, J = 7.9 Hz), 7.81 (d, 2 H, J = 8.3 Hz), 7.92 (d, 2 H, J = 8.7 Hz), 9.53 (s, 1 H), 9.80 (s, 1 H), 9.84 (s, 1 H); MS (FAB) 391.1 (M + 1). Anal. ($C_{23}H_{22}N_2O_4$) C, H, N.

***N*¹-[4-(Dimethylamino)benzoyl]-*N*²-(4-methoxybenzoyl)-1,2-benzenediamine (33).** A mixture of *N*¹-(4-methoxybenzoyl)-1,2-benzenediamine (242 mg, 1.00 mmol), 4-(dimethylamino)benzoic acid (200 mg, 1.24 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (2040 mg, 1.26 mmol), and 1-hydroxybenzotriazole (135 mg, 1.00 mmol) in 3 mL CH_2Cl_2 was stirred 48 h at ambient temperature. The mixture was partitioned between EtOAc and 10% citric acid. The organic portion was washed with water and saturated $NaHCO_3$ then dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified on silica gel with 40% EtOAc in hexane to yield the title compound (77 mg, 20%) as a white powder: ^{1}H NMR ($CDCl_3$) δ 3.07 (s, 6H), 3.87 (s, 3H), 6.86 (d, J = 8.7, 2H), 6.97 (d, J = 8.7, 2H), 7.06 (m, 2H), 7.43 (m, 1H), 7.56 (m, 1H), 7.91 (d, J = 8.7, 2H), 7.96 (d, J = 8.7, 2H), 8.87 (s, 1H), 9.22 (s, 1H); MS (FD) *m*/*e* 389 (M^+). Anal. ($C_{23}H_{23}N_3O_3$) C, H, N.

***N*¹-(4-Methoxybenzoyl)-*N*²-[4-(1-methoxy-1-methylethyl)benzoyl]-1,2-benzenediamine (36).** Using the procedure described for the preparation of compound **24**, *N*¹-(4-methoxybenzoyl)-1,2-benzenediamine (125 mg, 0.52 mmol) was allowed to react with 4-[2-(2-methoxypropyl)]benzoic acid (93 mg, 0.48 mmol) to yield 107 mg (49%) of the title compound as a white solid: ^{1}H NMR ($CDCl_3$) δ 1.58 (s, 6H), 3.13 (s, 3H), 3.90 (s, 3H), 6.92−6.97 (m, 2H), 7.01 (d, 2H, J = 9.0 Hz), 7.46−7.42 (m, 2H), 7.55 (d, 2H, J = 8.4 Hz), 7.97−8.02 (m, 4H), 9.20 (s, 1H), 9.36 (s, 1H); MS (FD) *m*/*e* 418 (M^+). Anal. ($C_{25}H_{26}N_2O_4$) C, H, N.

***N*¹-(4-Methoxybenzoyl)-*N*²-[4-(methylthio)benzoyl]-1,2-benzenediamine (37).** Using the procedure described for the preparation of compound **24**, *N*¹-(4-methoxybenzoyl)-1,2-benzenediamine (772 mg, 3.19 mmol) was allowed to react with 4-(methylthio)benzoic acid (772 mg, 4.59 mmol) to yield 1.13 g (91%) of the title compound as a white solid: ^{1}H NMR ($CDCl_3$) δ 9.37 (s, 1H), 9.18 (s, 1H), 7.95 (d, 2H, J = 10.5 Hz), 7.90 (d, 2H, J = 10.2 Hz), 7.40−7.33 (m, 2H), 7.30 (d, 2H, J = 10.8 Hz), 6.97 (d, 2H, J = 10.5 Hz), 6.85 (m, 2H), 3.87 (s, 3H), 2.52 (s, 3H); MS (FD) 392 (M^+); IR ($CHCl_3$) 1256, 1508, 1599, 1644 cm^{-1}. Anal. ($C_{22}H_{20}N_2O_3S$) C, H, N.

***N*¹-(4-Methoxybenzoyl)-*N*²-[4-(1-methylethoxy)benzoyl]-1,2-benzenediamine (38).** Using the procedure described for the preparation of compound **43**, 4-(1-methylethoxy)benzoic acid (2.00 mmol) yielded, after recrystallization from CH_2Cl_2/hexane, 272 mg (34%) of the title compound: ^{1}H NMR (DMSO-d_6) δ 1.24 (d, 6H), 3.78 (s, 3H), 4.68 (septet, 1H), 6.99 (d, 2H), 7.02 (d, 2H), 7.2 (m, 2H), 7.6 (m, 2H), 7.86 (d, 2H), 7.91 (d, 2H), 9.96 (s, 2H); IR (KBr) 1607, 1648, 3300 cm^{-1}; MS (FD) *m*/*e* 404 (M^+). Anal. ($C_{24}H_{24}N_2O_4$) C, H, N.

***N*¹-(4-Methoxybenzoyl)-*N*²-(4-phenylbenzoyl)-1,2-benzenediamine (39).** Using a procedure similar to that described for the preparation of compound **3**, 4-phenylbenzoic acid (200 mg, 1.01 mmol) yielded 75 mg (18%) of the title compound: ^{1}H NMR (DMSO-d_6) δ 3.83 (s, 3H), 7.08 (d, J = 9.0, 2H), 7.31 (m, 2H), 7.43 (m, 1H), 7.52 (t, J = 7.3, 2H), 7.68 (m, 2H), 7.76 (d, J = 7.2, 2H), 7.85 (d, J = 8.3, 2H), 7.97 (d, J = 9.0, 2H), 8.05 (d, J = 8.3, 2H); MS (FD) *m*/*e* 422 (M^+). Anal. ($C_{27}H_{22}N_2O_3$) C, H, N.

***N*¹-(4-Methoxybenzoyl)-*N*²-(4-*tert*-butoxybenzoyl)-1,2-benzenediamine (40).** The title compound was prepared from 4-*tert*-butoxybenzoyl chloride using the methods described for the synthesis of compound **43** to give 0.231 g (28%) crystallized from CH_2Cl_2−hexane: ^{1}H NMR (DMSO-d_6) δ 1.35 (s, 9H), 3.79 (s, 3H), 7.03 (d, 2H), 7.09 (d, 2H), 7.15 (m, 2H), 7.6 (m, 2H), 7.86 (d, 2H), 9.90 (d, 2H), 9.93 (s, 1H), 9.99 (s, 1H); MS (FD) *m*/*e* 418 (M^+). Anal. ($C_{25}H_{26}N_2O_4$) C, H, N.

***N*¹-(2-Chloro-4-methoxybenzoyl)-*N*²-(4-methoxybenzoyl)-1,2-benzenediamine (41).** Using the procedure described for compound **45**, 2-chloro-4-methoxybenzoyl chloride (410 mg, 2.42 mmol) yielded 770 mg (77%) of the title compound: ^{1}H NMR δ (DMSO-d_6) 3.81 (s, 3H), 3.82 (s, 3H),

6.98−7.15 (m, 4H), 7.22−7.31 (m, 2H), 7.60−7.70 (m, 3H), 7.95 (d, 2H), 9.80 (bs, 1H), 10.02 (bs, 1H). Anal. ($C_{22}H_{19}ClN_2O_4$) C, H, N.

***N*¹-(4-Methoxybenzoyl)-*N*²-[4-(dimethylaminosulfonyl-)benzoyl]-1,2-benzenediamine (42).** Using the procedure described for the preparation of compound **24**, N^1-(4-methoxybenzoyl)-1,2-benzenediamine (534 mg, 2.21 mmol) was allowed to react with 4-(dimethylaminosulfonyl)benzoic acid (534 mg, 2.33 mmol) to yield 349 mg (35%) of the title compound: ^{1}H NMR ($CDCl_3$) δ 2.76 (s, 6H), 3.90 (s, 3H), 6.97 (m, 2H), 7.02 (d, 2H, J = 9.0 Hz), 7.32 (d, 1H, J = 9.6 Hz), 7.53 (d, 1H, J = 9.3 Hz), 7.89 (d, 2H, J = 8.4 Hz), 7.96 (d, 2H, J = 8.7 Hz), 8.15 (d, 2H, J = 8.4 Hz), 8.90 (s, 1H), 9.79 (s, 1H); MS (FD) *m/e* 453 (M^+); IR ($CHCl_3$) 1166, 1257, 1508, 1607, 1652 cm^{-1}. Anal. ($C_{23}H_{23}N_3O_5S$) C, H, N.

***N*¹-(4-Methoxybenzoyl)-*N*²-(4-ethoxybenzoyl)-1,2-benzenediamine (43).** To a mixture of 4-ethoxybenzoic acid (0.332 g, 2.00 mmol) and a few drops of *N*,*N*-dimethylformamide in CH_2Cl_2 (50 mL) cooled to 0 °C was added oxalyl chloride (0.21 mL, 2.2 mmol). After 30 min reaction the mixture was warmed to room temperature and was stirred for an additional 10 min. The mixture was concentrated in vacuo, and the residue was dissolved in CH_2Cl_2 (10 mL). The resulting solution was added in two portions to a mixture of N^1-(4-methoxybenzoyl)-1,2-benzenediamine (0.455 g, 2.00 mmol) and Et_3N (0.281 mL, 2.00 mmol) in CH_2Cl_2 (40 mL) cooled to 0 °C. After 4 h, the mixture was allowed to warm to room temperature and was stirred for an additional 12 h. The reaction was quenched with cold dil aq HCl (50 mL), diluted with hexane, and shaken in a separatory funnel. The organic layer was washed with cold dil aq HCl and saturated aq $NaHCO_3$ solution. The solution was dried ($MgSO_4$), filtered, and concentrated in vacuo. Recrystallization of the residue from CH_2Cl_2/hexane provided 317 mg (41%) of title compound: ^{1}H NMR (DMSO-d_6) δ 1.37 (t, 3H), 3.82 (s, 3H), 4.10 (q, 2H), 7.05 (d, 2H), 7.08 (d, 2H), 7.3 (m, 2H), 7.6 (m, 2H), 7.86 (d, 4H), 9.97 (s, 2H); IR (KBr) 1606, 1646, 3259 cm^{-1}; MS (FD) *m/e* 390 (M^+). Anal. ($C_{23}H_{23}N_2O_4$) H, N; C: calcd, 70.75; found, 66.03.

***N*¹-(4-Methoxybenzoyl)-*N*²-(4-methylsulfonylbenzoyl)-1,2-benzenediamine (44).** Using the procedure described for the preparation of compound **24**, N^1-(4-methoxybenzoyl)-1,2-benzenediamine (399 mg, 1.65 mmol) and 4-methylsulfonylbenzoic acid (463 mg, 2.31 mmol) yielded 591 mg (84%) of the title compound as a white solid: ^{1}H NMR ($CDCl_3$) δ 3.08 (s, 3H), 3.88 (s, 3H), 7.00 (d, 2H, J = 8.7 Hz), 7.32−7.12 (m, 3H), 7.71 (d, 1H, J = 8.4 Hz), 7.91 (d, 2H, J = 8.7 Hz), 8.04 (d, 2H, J = 8.4 Hz), 8.15 (d, 2H, J = 8.4 Hz), 8.51 (s, 1H), 9.75 (s, 1H); MS (FD) *m/e* 424 (M^+); IR (KBr) 757, 1155, 1437, 1509, 1659, 3300 cm^{-1}. Anal. ($C_{22}H_{20}N_2O_5S$) C, H, N.

***N*¹-(2,4-Dimethoxybenzoyl)-*N*²-(4-methoxybenzoyl)-1,2-benzenediamine (45).** To a solution N^1-(4-methoxybenzoyl)-1,2-benzenediamine hydrochloride (558 mg, 2.08 mmol) in CH_2Cl_2 (100 mL) was added 0.5 N aq NaOH (8 mL), and the resulting mixture was cooled in an ice−water bath. 2,4-Dimethoxybenzoyl chloride (0.40 g, 2.0 mmol) was added slowly with vigorous stirring. The mixture was allowed to warm slowly to room temperature and stirred for 18 h. The organic layer was separated and washed with dil aq $NaHCO_3$ solution, dil aq HCl, and water. The organic layer was dried (sodium sulfate), filtered, and concentrated in vacuo to provide 0.52 g (64%) of the title compound: ^{1}H NMR δ (DMSO-d_6) 3.58 (s, 3H), 3.82 (s, 3H), 3.88 (s, 3H), 6.61 (d, 1H), 6.68 (dd, 1H), 7.0−7.4 (m, 5H), 7.95−8.20 (m, 4H), 9.92 (s, 1H), 10.12 (s, 1H). Anal. ($C_{23}H_{22}N_2O_5$) C, H, N.

***N*¹-(4-Methoxybenzoyl)-*N*²-[4-(propyloxy)benzoyl]-1,2-benzenediamine (46).** The title compound was prepared from 4-propyloxybenzoyl chloride using the methods described for the synthesis of compound **43** to give 0.224 g (28%) of a crystalline title compound from CH_2Cl_2−hexane: ^{1}H NMR (DMSO-d_6) δ 0.96 (t, 3H), 1.74 (hextet, 2H), 3.83 (s, 3H), 3.99 (t, 2H), 3.99 (t, 2H), 7.05 (d, 4H), 7.27 (m, 2H), 7.65 (m, 2H), 7.94 (d, 4H), 9.59 (s, 2H); MS (FD) *m/e* 404 (M^+). Anal. ($C_{24}H_{24}N_2O_4$) C, H, N.

***N*¹-(4-Methoxybenzoyl)-*N*²-[4-(methylsulfinyl)benzoyl]-1,2-benzenediamine (47).** To a solution of N^1-(4-methoxybenzoyl)-N^2-[4-(methylthio)benzoyl]-1,2-benzenediamine (417 mg, 0.60 mmol) in $CHCl_3$ (20 mL), cooled to 0 °C was added *m*-chloroperoxybenzoic acid (346 mg, 1.16 mmol). After 30 min, the reaction mixture was warmed to room temperature and calcium hydroxide (123 mg, 1.66 mmol) was added. After 15 min, the reaction mixture was filtered and the filtrate concentrated in vacuo. The residue was chromatographed (silica gel, 50% EtOAc/50% hexanes to 80% EtOAc/20% hexanes) to give 360 mg (83%) of the title compound as a white solid: ^{1}H NMR ($CDCl_3$) δ 2.77 (s, 3H) 3.89 (s, 3H), 6.91 (m, 2H), 7.00 (d, 2H, J = 8.7 Hz), 7.45 (m, 1H), 7.32 (m, 1H), 7.75 (d, 2H, J = 8.7 Hz), 7.97 (d, 2H, J = 8.7 Hz), 8.13 (d, 2H, J = 8.7 Hz), 9.12 (s, 1H), 9.79 (s, 1H); MS (FD) 408 (M^+); IR ($CHCl_3$) 1257, 1508, 1607, 1651, 3008 cm^{-1}. Anal. ($C_{22}H_{20}N_2O_4$) C, H, N.

***N*¹-(4-Methoxybenzoyl)-*N*²-(4-phenoxybenzoyl)-1,2-benzenediamine (48).** The N^1-(4-methoxybenzoyl)-1,2-benzenediamine (200 mg, 0.826 mmol), 4-phenoxybenzoic acid (177 mg, 0.826 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (316 mg, 1.65 mmol), and DMAP (10 mg, 0.083 mmol) were combined in CH_2Cl_2 (2 mL) and stirred for 18 h. The mixture was then diluted with additional CH_2Cl_2, washed with 1 N NaOH, and with 1 N HCl. The organic layer was dried over sodium sulfate, filtered, and concentrated in vacuo to provide the desired product (294 mg, 0.67 mmol, 81%) as a foam which solidified: ^{1}H NMR ($CDCl_3$) δ 3.89 (s, 3H), 6.75 (m, 2H), 7.05 (m, 6H), 7.21 (m, 1H), 7.32 (m, 2H), 7.41 (t, J = 7.8, 2H), 8.00 (d, J = 7.2, 4H), 9.50 (s, 1H), 9.61 (s, 1H); IR 1646, 1607, 1505, 1245 cm^{-1}; MS *m/e* 438.70. Anal. ($C_{27}H_{22}N_2O_4$) H, N; C: calcd, 73.96; found, 72.22.

***N*¹-(4-Butoxybenzoyl)-*N*²-(4-methoxybenzoyl)-1,2-benzenediamine (50).** The title compound was prepared from 4-butoxybenzoyl chloride using the methods described for the synthesis of compound **43** to give 0.277 g of crystalline product (33%) from CH_2Cl_2−hexane: ^{1}H NMR (DMSO-d_6) δ 0.982 (s, 3H), 1.44 (hextet, 2H), 1.71 (quintet, 2H), 3.82 (s, 3H), 4.03 (q, 2H), 7.04 (d, 2H), 7.06 (d, 2H), 7.25 (t, 1H), 7.28 (t, 1H), 7.54 (m, 2H), 7.91 (d, 2H), 7.93 (d, 2H), 8.89 (s, 2H); MS (FD) *m/e* 418 (M^+). Anal. ($C_{25}H_{26}N_2O_4$) C, H, N.

***N*¹-(4-Methoxybenzoyl)-*N*²-[4-(trifluoroacetyl)benzoyl]-1,2-benzenediamine (51)**. The title compound was prepared from 4-trifluoroacetylbenzoyl chloride using the methods described for the synthesis of compound **43** to give 0.511 g (58%) crystallized from CH_2Cl_2−hexane: ^{1}H NMR (DMSO-d_6) δ 3.80 (s, 3H), 7.03 (d, 2H), 7.28 (m, 2H), 7.64 (m, 2H), 7.92 (d, 2H), 8.15 (s, 4H), 9.89 (s, 1H), 10.32 (s, 1H); MS (FD) *m/e* 442 (M^+). Anal. ($C_{23}H_{17}F_3N_2O_4$) C, H, N.

***N*¹-[4-(Hexyloxy)benzoyl]-*N*²-(4-methoxybenzoyl)-1,2-benzenediamine (52).** The title compound was prepared from 4-hexyloxybenzoyl chloride using the methods described for the synthesis of compound **43** to give 0.415 g (46%) of the title compound as crystals from CH_2Cl_2−hexane: ^{1}H NMR (DMSO-d_6) δ 0.84 (t, 3H), 1.30 (m, 4H), 1.41 (quintet, 2H), 1.73 (quintet, 2H), 3.82 (s, 3H), 4.03 (t, 2H), 7.05 (d, 2H), 7.07 (d, 2H), 7.74 (m, 2H), 7.78 (d, 2H), 7.79 (d, 2H), 9.59 (s, 2H); MS (FD) *m/e* 446 (M^+). Anal. ($C_{27}H_{30}N_2O_4$) C, H, N.

***N*²-(4-*tert*-Butylbenzoyl)-*N*¹-(4-vinylbenzoyl)-1,2-benzenediamine (53).** Using the procedure described for the preparation of compound **44**, 4-vinylbenzoic acid (0.67 mmol) yielded 210 g (79%) of the title compound as a white amorphous solid: ^{1}H NMR (DMSO-d_6) δ 1.30 (s, 9 H), 5.40 (d, 1 H, J = 13.5 Hz), 5.99 (d, 1 H, J = 21.0 Hz), 6.81 (dd, 1 H, J = 21.3, 13.2 hz), 7.31−7.27 (m, 2 H), 7.54 (d, 2 H, J = 10.5 Hz), 7.88 (d, 2 H, J = 10.2 Hz), 7.94 (d, 2 H, J = 10.2 Hz), 10.01 (s, 1 H), 10.07 (s, 1 H); MS (FD) *m/e* 398 (M^+). Anal. ($C_{26}H_{26}N_2O_2$) C, H, N.

***N*¹-(4-*tert*-Butylbenzoyl)-*N*²-(4-chlorobenzoyl)-1,2-benzenediamine (54).** To a solution of N^1-(4-*tert*-butylbenzoyl)-1,2-benzenediamine (100 mg, 0.37 mmol) in 3 mL CH_2Cl_2 was added 4-chlorobenzoyl chloride (95 μL, 0.74 mmol) and excess K_2CO_3. The mixture was stirred 30 min then a 1:1 solution of THF and 5 N NaOH was added. The resultant mixture was stirred an additional 20 min and diluted with Et_2O. The

mixture was washed twice with water, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was sonicated with hexane causing a precipitate to form which was collected by filtration and dried under vacuum to yield 100 mg (66%) of the title compound: ^{1}H NMR ($CDCl_3$) δ 1.37 (s, 9H), 6.95 (m, 2H), 7.33 (d, J = 9.4, 1H), 7.50 (d, J = 8.7, 3H), 7.53 (d, J = 8.3, 2H), 7.91 (d, J = 8.7, 2H), 7.95 (d, J = 8.7, 2H), 9.01 (s, 1H), 9.48 (s, 1H); IR 1651, 1600, 1505, 1319, 1271, 1092 cm^{-1}; MS (FD) *m/e* 406 (M^+). Anal. ($C_{24}H_{23}ClN_2O_2$) C, H, N.

***N*^{2}-(4-*tert*-Butylbenzoyl)-*N*^{1}-(3-vinylbenzoyl)-1,2-benzenediamine (55).** To a solution of 3-vinylbenzoic acid (200 mg, 1.35 mmol) in THF (10 mL) was added thionyl chloride (241 mg, 2.02 mmol) and pyridine (214 mg, 2.7 mmol). The reaction was heated at 80 °C for 2 h and cooled to room temperature. *N*^{1}-(4-*tert*-Butylbenzoyl)-1,2-benzenediamine (362 mg, 1.35 mmol) was added. After stirring for 2 h, the reaction mixture was diluted with CH_2Cl_2 and washed once with saturated aq copper sulfate solution, once with saturated aq NaCl solution, dried ($MgSO_4$), filtered, and concentrated in vacuo. Chromatography (silica gel, 10% EtOAc/90% CH_2Cl_2) provided 200 mg (37%) of the title compound as a white solid: ^{1}H NMR (DMSO-d_6) δ 1.32 (s, 9 H), 5.34 (d, 1 H, J = 10.9 Hz), 5.94 (d, 1 H, J = 17.7 Hz), 6.79 (dd, 1 H, J = 10.9, 17.7 Hz), 7.52−7.56 (m, 2 H), 7.29−7.33 (m, 2 H), 7.84 (d, 1 H, J = 7.8 Hz), 7.67−7.70 (m, 2 H), 7.91 (d, 2 H, J = 8.4 Hz), 8.01 (s, 1 H), 10.01 (s, 1 H), 10.09 (s, 1 H); MS (FAB) 399 (M + 1). Anal. ($C_{26}H_{26}N_2O_2$) C, H, N.

***N*^{2}-(4-*tert*-Butylbenzoyl)-*N*^{2}-(4-fluorobenzoyl)-1,2-benzenediamine (56).** Using the procedure described for the preparation of compound **55**, 4-fluorobenzoic acid (0.71 mmol) yielded 260 mg (94%) of the title compound as a white amorphous solid: ^{1}H NMR (DMSO-d_6) δ 1.29 (s, 9 H), 7.30−7.26 (m, 2 H), 7.36 (t, 2 H, J = 8.3 Hz), 7.52 (d, 2 H, J = 8.7 Hz), 7.68−7.61 (m, 2 H), 7.87 (d, 2 H, J = 8.3 Hz), 8.00−8.04 (m, 2 H), 9.95 (s, 1 H), 10.08 (s, 1 H); MS (FD) *m/e* 390. Anal. ($C_{24}H_{23}FN_2O_2$) C, H, N.

***N*^{1}-(3-Fluorobenzoyl)- *N*^{2}-(4-*tert*-butylbenzoyl)-1,2-benzenediamine (57).** The *N*^{2}-(4-*tert*-butylbenzoyl)-1,2-benzenediamine (200 mg, 0.75 mmol) was dissolved in THF (10 mL). Pyridine (121 μL, 1.50 mmol) and 3-fluorobenzoyl chloride (91 μL, 0.75 mmol) were added. After 24 h, the reaction was quenched with saturated aq NH_4Cl. The mixture was poured into a separatory funnel and diluted with CH_2Cl_2. The mixture was washed with saturated aqueous NH_4Cl and the organic layer was dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash column chromatrography (10% EtOAc/CH_2Cl_2) to give the desired product (280 mg, 96%): ^{1}H NMR (DMSO-d_6) δ 1.20 (s, 9H), 7.29 (m, 2H), 7.44 (m, 1H), 7.53 (d, J = 8.3, 2H), 7.67 (m, 5H), 7.88 (d, J = 8.3, 2H), 9.95 (s, 1H); IR 1654, 1588, 1510, 1474, 1444, 1322, 1270 cm^{-1}; MS *m/e* 390.35. Anal. ($C_{24}H_{23}FN_2O_2$) C, H, N.

***N*^{1}-Benzoyl-*N*^{2}-(4-*tert*-butylbenzoyl)-1,2-benzenediamine (60).** Using the procedure described for the preparation of compound **3**, benzoyl chloride (0.80 mmol) and *N*^{1}-(4-*tert*-butylbenzoyl)-1,2-benzenediamine (0.75 mmol) yielded 150 mg (54%) of the title compound: ^{1}H NMR (DMSO-d_6) δ 1.30 (s, 9H), 7.25−7.35 (m, 2H), 7.49−7.60 (m, 5H), 7.66 (dd, J = 4.0, 5.8 Hz, 2H), 7.88 (d, J = 8.3 Hz, 2H), 7.95 (d, J = 6.8 Hz, 2H), 10.01 (s, 1H), 10.08 (s, 1H); MS (FD) *m/e* 372.1 (M^+). Anal. ($C_{24}H_{24}N_2O_2$) C, H, N.

***N*^{1}-(4-Methylphenyl)-*N*^{2}-(4-*tert*-butylbenzoyl)-1,2-benzenediamine (61).** Using the procedure described for the synthesis of compound **3**, 4-toluoyl chloride (1.1 mmol) and *N*^{1}-(4-*tert*-butylbenzoyl)-1,2-benzenediamine (0.93 mmol) yielded 360 mg (100%) of the title compound: ^{1}H NMR (DMSO-d_6) δ 1.30 (s, 9 H), 2.37 (s, 3 H), 7.28 (m, 2 H), 7.33 (d, J = 8.0 Hz, 2 H), 7.54 (d, J = 8.5 Hz, 2 H), 7.66 (m, 2 H), 7.85 (d, J = 8.0 Hz, 2 H), 7.89 (d, J = 8.3 Hz, 2 H), 10.02 (br s, 2 H); MS (FD) *m/e* 386.3 (M^+). Anal. ($C_{25}H_{26}N_2O_2$) C, H, N.

***N*^{1}-(3-Methoxybenzoyl)-*N*^{2}-(4-*tert*-butylbenzoyl)-1,2-benzenediamine (62).** To a stirred solution of *N*^{1}-(4-*tert*-butylbenzoyl)-1,2-benzenediamine (1.8 mmol) and 3-anisic acid (3.6 mmol) in dimethylformamide (20 mL) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.52 g, 2.75 mmol). After 12 h, the solvent was removed in vacuo. The residue was dissolved in EtOAc and washed twice with 1 M aq citric acid, once with water, twice with saturated aq $NaHCO_3$ solution, once with water, and once with saturated aq NaCl solution. The organic phase was dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was triturated with Et_2O, filtered, and dried in vacuo to give 610 mg (84%) of the title compound: ^{1}H NMR (DMSO-d_6) δ 1.30 (s, 9H), 3.78 (s, 3H), 7.15 (dd, J = 1.5, 8.3 Hz, 1H), 7.25−7.35 (m, 2H), 7.44 (t, J = 8.0 Hz, 1H), 7.48−7.52 (m, 2H), 7.55 (d, J = 8.5 Hz, 2H), 7.66−7.77 (m, 2H), 7.92 (d, J = 8.3 Hz, 2H), 10.05 (s, 2H); MS (FD) *m/e* 402.2 (M^+). Anal. for ($C_{25}H_{26}N_2O_3$) C, H, N.

***N*^{1}-(4-*tert*-Butylbenzoyl)-*N*^{2}-(4-ethylbenzoyl)-1,2-benzenediamine (63).** Following the procedure used in the preparation of compound **3**, **63** was prepared from 4-ethylbenzoyl chloride. The product was purified by silica gel chromatography, eluting with a gradient of 10% through 50% EtOAc in hexanes: 54% yield; ^{1}H NMR (DMSO-d_6) δ 1.20 (t, J = 7.5 Hz, 3H), 1.30 (s, 9H), 2.67 (q, J = 7.5 Hz, 2H), 7.25−7.35 (m, 2H), 7.36 (d, J = 8.3 Hz, 2H), 7.55 (d, J = 8.3 Hz, 2H), 7.60−7.70 (m, 2H), 7.87 (d, J = 8.3 Hz, 2H), 7.89 (d, J = 8.3 Hz, 2H), 10.0 (s, 2H); MS (FD) *m/e* 400.4 (M^+). Anal. ($C_{26}H_{28}N_2O_2$) C, H, N.

***N*^{1}-(4-*tert*-Butylbenzoyl)-*N*^{2}-(4-trifluoromethoxybenzoyl)-1,2-benzenediamine (64)**. Following the procedure described for the preparation of compound **62**, **64** was prepared from 4-trifluoromethoxybenzoic acid: 64% yield; ^{1}H NMR (DMSO-d_6) δ 1.29 (s, 9H), 7.25−7.30 (m, 2H), 7.52 (d, J = 8.3 Hz, 4H), 7.60−7.70 (m, 2H), 7.87 (d, J = 8.3 Hz, 2H), 8.07 (d, J = 8.3 Hz, 2H), 9.93 (s, 1H), 10.15 (s, 1H); MS (FD) *m/e* 456 (M^+). Anal. ($C_{25}H_{23}N_2O_3F_3$) C, H, N.

***N*^{1},*N*^{3}-Bis(4-methoxybenzoyl)-1,3-benzenediamine (65).** Into 100 mL CH_2Cl_2 was dissolved 1.08 g (10 mmol) *m*-phenylenediamine. The solution was cooled in an ice bath, and 2.81 mL (20 mmol) Et_3N was added in one portion, followed by 3.42 g (20 mmol) *p*-anisoyl chloride dropwise. Reaction mixture was allowed to warm gradually to room temperature and after 16 h was quenched with cold dil HCl (100 mL). A precipitate formed, which was collected, washed with cold dil HCl, and dried at 50 °C, giving 3.58 g (95% yield) of the desired compound: ^{1}H NMR (DMSO-d_6) δ 3.73 (s, 3H), 7.06 (d, 4H), 7.30 (t, 1H), 7.50 (d, 2H), 8.00 (d, 4H), 8.33 (s, 1H), 10.15 (s, 2H); MS (FD) *m/e* 376 (M^+). Anal. ($C_{22}H_{20}N_2O_4$) C, H, N.

Acknowledgment. We thank the Physical Chemistry Department of the Lilly Research Laboratories for their help in characterizing the compounds reported here.

Supporting Information Available: Experimental procedures for the preparation of compounds **6**, **14**, **15**, **17**−**20**, **25**, **26**, **28**, **29**, **31**, **34**, **35**, **49**, **58,** and **59**. This information is available free of charge via the Internet at http://pubs.acs.org.

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JM990326M