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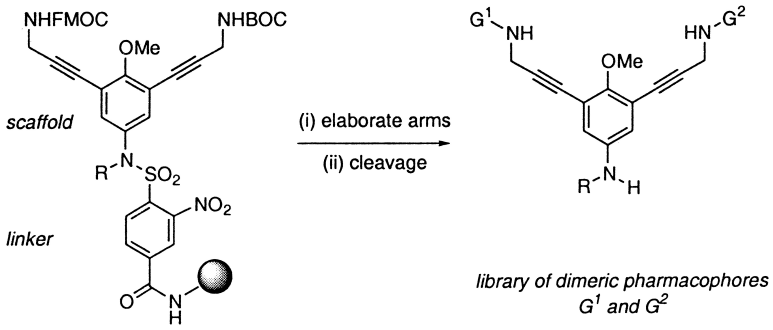

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A Rigid Linker-Scaffold for Solid-Phase Synthesis of Dimeric Pharmacophores

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Bifunctional linker-scaffolds (compounds **1**−**3**) were designed to meet several criteria for solid-phase syntheses of bivalent ligands. They have two amine-functionalized arms that can be differentially protected. Elaboration of these arms could give ligand-pharmacophore dimers wherein the two active components are held reasonably rigidly at around 10 Å separation. Their bifunctional design also enables reactions of libraries with libraries to amplify diversity in a truly combinatorial fashion. Molecules **1**−**3** are also designed so that cleavage of the linker liberates the scaffold entity into solution under conditions that create only byproducts that should not interfere with biological assays. Thus they contain 2-nitrobenzene sulfonamide components that cleave in the presence of good nucleophiles. In the event, the linker-scaffolds **1**−**3** were prepared (Schemes 1 and 2). The *N*-benzyl system **2** was shown to have good stability to the types of conditions that might be used to functionalize the scaffold arms and to be sufficiently labile to the cleavage nucleophile (vide infra). The nucleophiles generally used to cleave nitrobenzene sulfonamides either generate undesirable byproducts (thiophenol or alkane thiols) or proved to be insufficiently reactive for the required solid-phase transformations (*n*-propylamine). However, sodium sulfide was investigated as a new alternative and shown to be a highly reactive cleavage agent that gives only volatile byproducts and sodium hydroxide. It is suggested that sodium sulfide is a highly desirable nucleophile for cleavage of 2-nitrobenzene sulfonamides, in general. The linker-scaffolds **1**−**3** were used to prepare a small library of bivalent ligands targeted to a protein receptor having charged cavities separated by approximately 10 Å. These systems were made from guanidine, pyridinium, carboxylic acid, and sulfonic acid constituents (Tables 1 and 2).

Protein−protein interactions[1] generally feature important contact points ("hot-spots") that involve only a small number of amino acid residues. These hot-spots typically occupy discontinuous sites that may be separated by 10 Å or more.[2−4] Nature exploits this situation in several ways. Using only 20 amino acid side chains (including hydrogen), a near-infinite number of hot-spot combinations and orientations can be created on a rigid protein tertiary structure. This diversification provides an excellent evolutionary basis to refine a protein so that it will only interact selectively with another. Combinations of hot-spots also enhance the kinetic and thermodynamic factors in favor of binding, as is true for any multivalent ligand.[5,6] Furthermore, discontinuous hot-spots can interact with two or more proteins simultaneously, leading to dimerization events that activate regulatory biological networks.[7]

It is extremely difficult to find monomeric compounds that disrupt or mimic protein−protein interactions. Synthetic polypeptides that will do this have been identified by phage display methods,[8−12] though it could be argued that these are not monomeric compounds but oligomers containing more than one hot-spot. Huge high throughput screening efforts using small molecule libraries have a very low percentage hit rate, and some of the compounds that emerge from these screens are remarkably symmetrical, implying that they may bind two protein sites (or sites on two proteins) simultaneously.[13,14] Overall, it is hard to find synthetic components that mimic individual protein hot-spots, and it is probably necessary to mimic more than one to disrupt or mimic a particular protein−protein interaction.

Small pharmacophores separated by a scaffold system have considerable potential in several branches of medicinal chemistry, including protein−protein interactions. The diverse applications of synthetic dimers of FK506 (i.e., FK1012 and the hydrogenated forms of this)[15−20] illustrate the value of being able to control dimerization processes in signal transduction and related areas. NMR studies have been used to prove that two small molecules that bind a protein weakly can be combined into bivalent systems that exhibit greater affinity.[21−25] Dimers of vancomycin are emerging as potentially valuable targets for medicinal chemistry,[26−29] serotonin dimers have been prepared as selective 5-HT agonists,[30] and dimeric DNA intercalating molecules have widely appreciated therapeutic potential.[31−37] In general, synthetic bivalent ligands can bind one receptor more effectively than the monomeric constituents, and they are able to initiate biological processes by cross-linking two receptor units.

If appropriate linker-scaffolds were available, remarkably efficient solid-phase syntheses of bivalent systems could be designed. This is due to the numerical[38] and practical advantages of combining libraries on a supported bifunctional scaffold. In an illustrative strategy, a library of *n* compounds could be attached to one arm of the scaffold, one compound per well in *n* different wells, and then the resin could be

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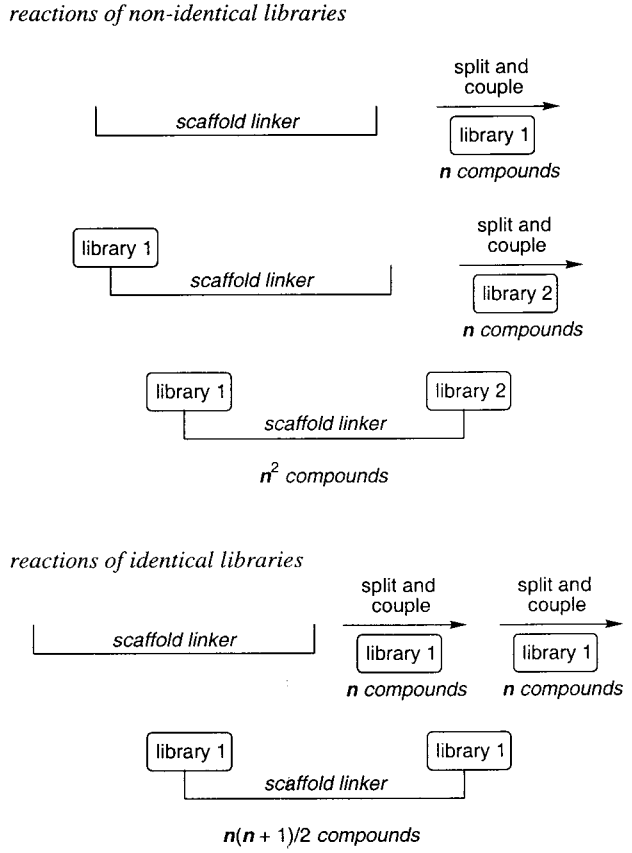
divided again and coupled using the second arm. If a different library also coincidentally having *n* components were used in this second coupling, then n^2 samples could be prepared, one per well. If instead the same library were used twice, then there are somewhat less possible combinations, as illustrated below, but still the resulting library would be much larger than the one it was made from. In general, if large numbers of the constituent pharmacophores are not accessible, then syntheses of bivalent systems can produce large, and potentially very interesting, libraries from a small number of components. This concept is the opposite of convergence in total syntheses. Convergent syntheses are designed to increase the number of fragments that are eventually combined to produce a single desired product. Reactions of libraries with libraries as outlined here increase the number of products that can be made from a given number of fragments. The term *divergence* is therefore appropriate.



Several different scaffolds[39] for solid-phase syntheses have been designed, but typically for purposes other than reactions of libraries with libraries to form bivalent systems. For instance, several reports describe scaffolds to increase resin loading by attaching Y-shaped structures, including dendric wedges, to supports.[40−44] Most of these systems are based on symmetrical, and conformationally flexible, aliphatic polyamines,[45−47] though some carbohydrate-based systems have been developed.[48,49] Incorporation of aliphatic polyamines can be an advantage for targets in medicinal chemistry that are known to respond to these,[45] but it is not ideal for production of libraries wherein pharmacophores should be held apart by a rigid spacer. Systems designed for solid-phase syntheses of molecular tweezers for molecular recognition tend to be more rigid,[50−52] but the systems prepared so far are symmetrical ones for preparation of homodimers. A few rigid, differentially functionalized scaffolds have been prepared, but they are either relatively hindered and/or unreactive, making solid-phase coupling reactions less efficient than is desirable.[53,54] The most relevant prior research in this area involves scaffolds that do not have custom-made cleavable linkers, either flexible amines or carbohydrate scaffolds.

Approaches to solution-phase syntheses of libraries of bivalent systems tend to be inappropriate for preparation of pure heterodimers without tedious purification procedures. For instance, symmetrical anhydrides have been used to give homodimers or statistical mixtures of homo- and heterodimeric products in solution via amide bond forming reactions.[55−57] Alkene metathesis reactions have also been used to give pure homodimers or statistical mixtures of homo- and heterodimers, but these methods also entail complications with respect to double bond isomerism.[18,38] More recently, dialdehydes have been coupled with oxime monomers to form relatively simple mixtures of dimers in solution.[58] Unlike solid-phase syntheses, these approaches are not particularly amenable to sequential couplings to two reactive groups to give single hetero- and homodimers that are free of byproducts generated in deprotection steps.

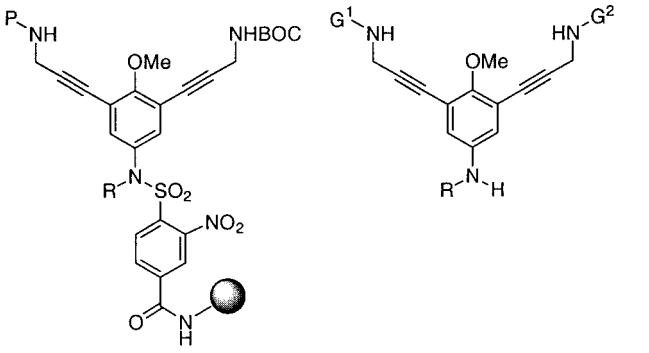
Ideal scaffolds for solid-phase reactions of libraries with libraries to give dimers have several fundamental requirements. There must be a means to introduce constituents of a library on one arm of the scaffold without perturbing the other. Conversely, there must also be a way to introduce a library on the second arm without affecting the library supported on the first. The distance between the scaffold arms should be flexible enough that the molecular conformation can adjust to match the receptor surface, but not so flexible that the entropic advantage of binding dimers is lost. A strategy for removing the side-chain protecting groups before the products are liberated from the resin should be in place, otherwise the products will be contaminated with byproducts from the side-chain-cleavage reactions. Similarly, the reagents used to free the dimers from the resin should be easily removed or biologically innocuous, otherwise it will be necessary to purify each compound before screening. In summary, an ideal scaffold for combinations of libraries-with-libraries should allow the following:

- functionalization of two orthogonally protected reactive groups on scaffold arms,
- moderately rigid pharmacophore separation that could be varied by chemical modification,
- a resin-to-scaffold functional group attachment that is stable to the coupling steps and cleavage of side-chain protecting groups, and
- cleavage of the functionalized scaffold while giving only byproducts that are easily removed and/or are unlikely to interfere with biological assays.

To the best of our knowledge, there is no published linker-scaffold design that satisfies these criteria.

This paper describes a synthesis of linker-scaffolds **1**−**3**. An illustrative application of these materials in a library synthesis is also given. Compounds **1**−**3** have orthogonally

protected arms that can hold pharmacophores at a separation of approximately 10 Å. The critical functionality is the nitrobenzene sulfonamide that is tolerant to various coupling conditions. The normal conditions for S_NAr cleavage of nitrobenzene sulfonamides (e.g. using sodium thiophenoxide)[59,60] would give noxious byproducts that would not be compatible with biological assays. However, this paper also introduces sodium sulfide as a new reagent for cleavage of this functional group without generation of byproducts that will perturb data from biological assays. These linker-scaffolds therefore fulfill most of the criteria outlined above.



	P	R
1a	FMOC	Me
1b	BOC	Me
2a	FMOC	Bn
2b	BOC	Bn
3a	FMOC	MeO_2CCH_2
3b	BOC	MeO_2CCH_2

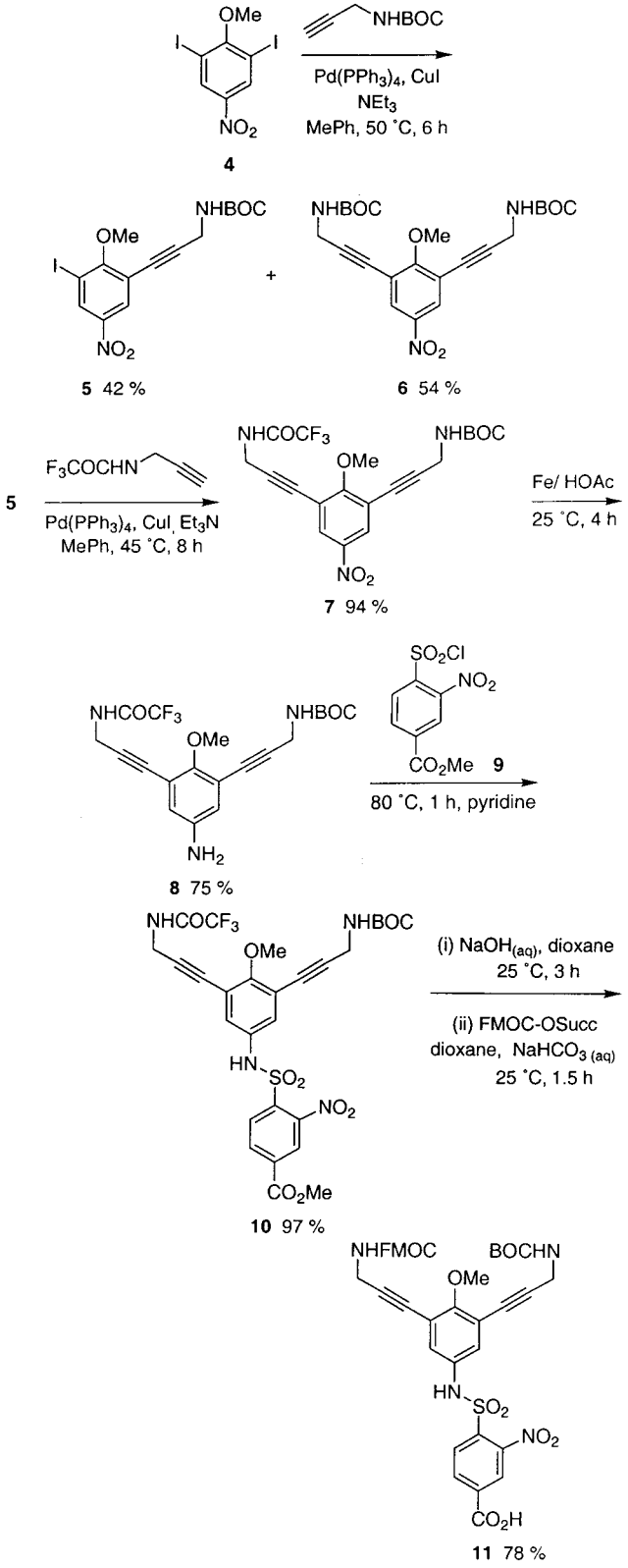
libraries
A G^1 and G^2 positively charged
B G^1 positive, G^2 negative
C G^1 and G^2 negative

Results and Discussion

Synthesis of the Linker-Scaffold Systems. Scheme 1 outlines the route that was used to obtain the skeleton of systems **1**−**3**. 3,5-Diiodo-4-methoxynitrobenzene **4**[61] was reacted with 1.1 equiv of *N*-BOC-protected propargylamine in a Sonogashira coupling to give a mixture of the mono- and di-substituted products **5** and **6**. It was difficult to increase the selectivity for the monosubstituted product **5** in this reaction, and alternative routes using bromoiodo arenes gave low yields for the second Sonogashira coupling involving the aryl bromide component. Fortunately, however, the two arylalkynes were chromatographically separable, and both are useful for preparing linker-scaffold systems. A second coupling to **5**, this time using *N*-trifluoroacetyl propargylamine, gave the differentially protected nitrobenzene **7** that was then reduced to the corresponding arylamine **8**. 4-(Methoxycarbonyl)-2-nitrobenzene sulfonyl chloride **9** was prepared by a modification of the literature procedure,[62] involving preparation of a benzyl sulfide via an S_NAr reaction, then oxidative chlorination to give the SO_2Cl functionality. Combination of this sulfonyl chloride with the arylamine **8** gave the sulfonamide **10**. Treatment of **10** with aqueous hydroxide removed the *N*-trifluoroacetate and hydrolyzed the methyl carboxylate. The crude material was reacted with FMOC-*O*-succinimide to give the desired acid **11**. This is a key starting material for preparation of heterodimeric libraries.

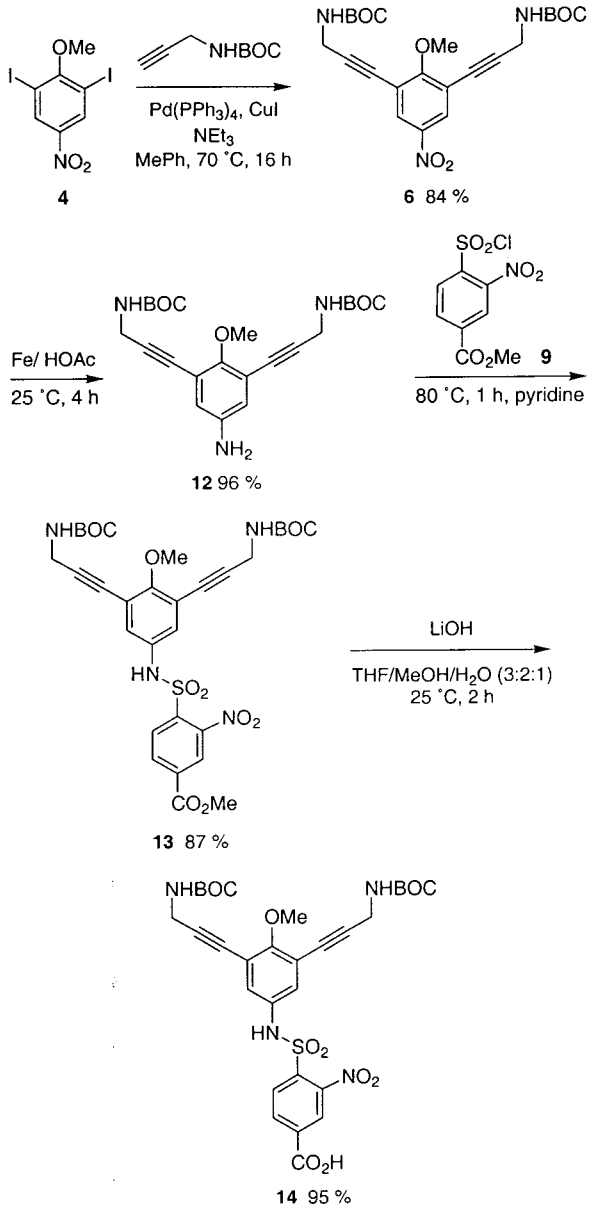
Homodimeric libraries can be made using a similar, but symmetrical, linker-scaffold **14**. This material was prepared via a route that is analogous to the one described above, as shown in Scheme 2.

Scheme 1. Synthesis of the Unsymmetrical Linker-Scaffolds

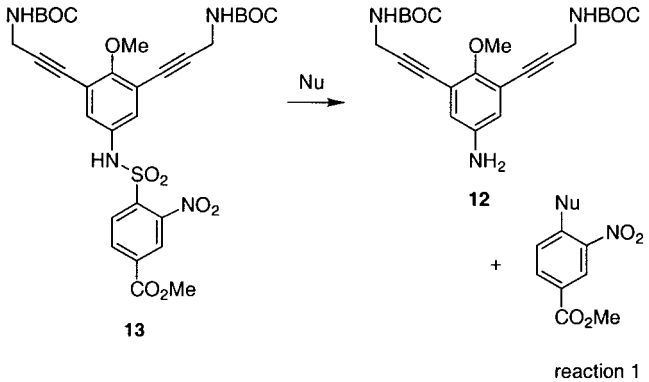


Cleavage of the Linkers. The symmetrical sulfonamide **13** was used in solution to test potential cleavage conditions for the solid-phase work. Qualitative experiments showed that this compound reacted only slowly with *n*-propylamine (CH_2Cl_2) and with (α-thio)acetic acid/NEt_3 (DMF). Thiophenol and potassium carbonate in DMF cleaved **13** as indicated

Scheme 2. Synthesis of the Symmetrical Linker-Scaffolds



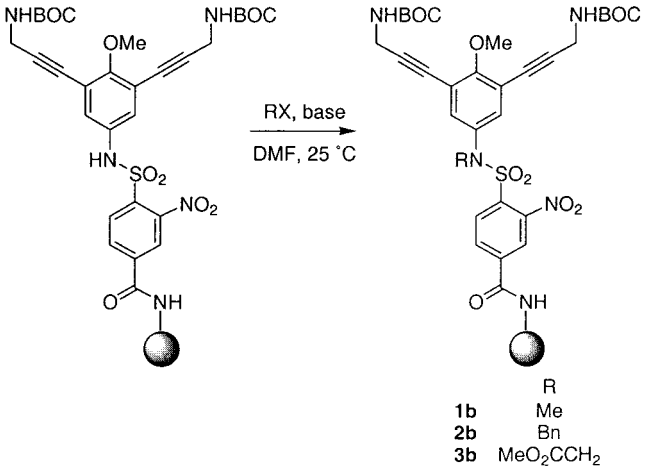
in reaction 1. However, this transformation was relatively slow at 25 °C, and we later found that it was hard to drive to completion on a solid support. These observations were predictable since the sulfonamide N*H* tends to be deprotonated under basic conditions, and this deactivates the system toward S_NAr reactions.[63]



reaction 1

The data described above confirmed that it was important to N-alkylate the sulfonamide functionality before cleavage of the linker. Such alkylation steps can also be regarded as an opportunity to introduce further diversification into a library, hence strategically and practically it was desirable to alkylate the sulfonamide *after* attachment to the resin. Consequently, samples of the symmetrical system **14** were coupled to aminomethyl polystyrene resin (from NovaBiochem) by activating the acid with a carbodiimide in the presence of *N*-hydroxybenzotriazole. This coupling was performed with approximately 1.5 equiv of the linker-scaffold relative to the functional groups on the resin, and continued until a negative ninhydrin test was observed.[64] Resin loadings were determined by removal of the BOC protecting groups (50% TFA/CH_2Cl_2), coupling with excess FMOC glycine, then quantitative detection of the liberated FMOC byproducts via UV spectroscopy.[65]

It was found that the alkylation of the sulfonamide nitrogen was best performed before the amine arms of the scaffold were functionalized. Briefly, if the sulfonamide was not alkylated first, then unwanted competing reactions occurring at the sulfonamide N*H* were frequently observed. Methyl, benzyl, and carbomethoxymethylene {(CH_2CO_2Me)} alkylating groups were chosen for further studies. It was anticipated that the methyl substituent would provide alkylation with minimal steric encumbrance, the benzyl substituent would be more hindered, and the carbomethoxymethylene-substituted system would electronically activate the sulfonamide toward cleavage. The on-resin alkylation reactions are depicted in reaction 2.



reaction 2

The aryl diynes that form when the sulfonamide is cleaved are fluorescent. This characteristic provided a useful qualitative test for rupture of the linker. For instance, when the *tert*-butyloxycarbonyl protecting groups were removed from the supported linker system **1b** (giving an intermediate trifluoroacetate salt), and BOC-protected amino acids were coupled immediately, then no fluorescence was observed in solution. However, the outcome was different when the intermediate trfluoroacetate salt was treated with triethylamine prior to coupling. In that case, addition of the amine caused liberation of fluorescent material into solution. This led us to conclude that, under basic conditions, the free amines of the scaffold arms were causing observable

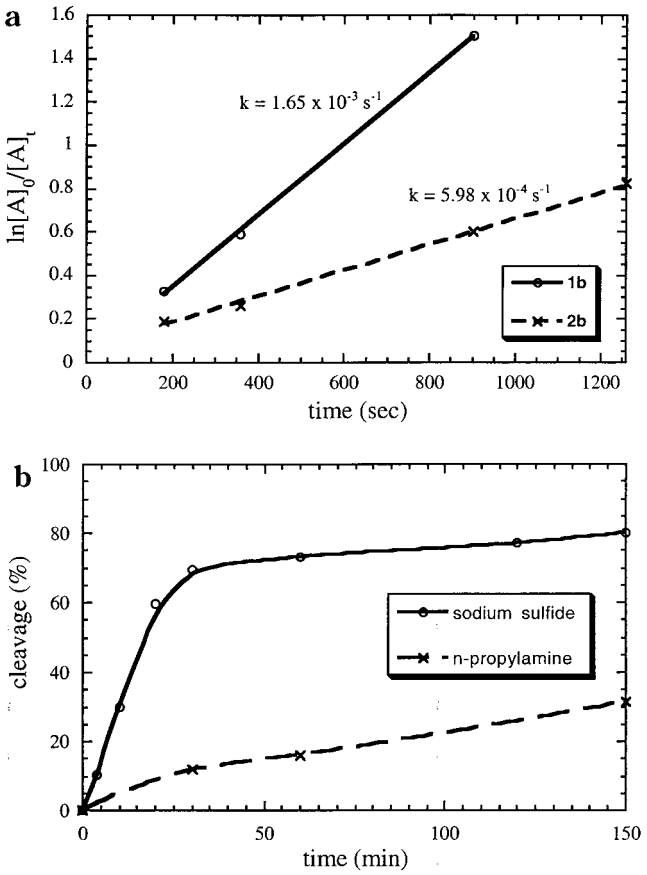


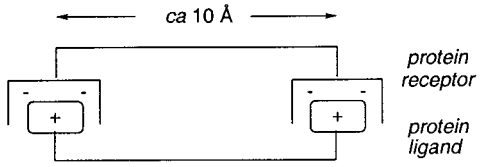
Figure 1. Cleavage of linker-scaffolds: (a) systems **1b** and **2b** with *n*-propylamine; (b) system **2b** cleaved with saturated sodium sulfide in DMF and with 20% *n*-propylamine in dichloromethane.

cleavage of the *N*-methyl sulfonamide groups in other supported molecules in an "intraresin" reaction. Parallel experiments with the supported *N*-benzyl sulfonamide system **2b**, however, did not liberate observable fluorescent material on the time scale of this experiment (up to 1 h), implying that **2b** was more stable than the *N*-methyl system **1b**.

Quantitative experiments were performed to test the stability of the linkers to 20% *n*-propylamine in dichloromethane, as a model for the undesirable self-cleavage of the diamine under basic conditions as described above. To do this, the rate of liberation of diyne arylamines from the supported systems **1b**, **2b**, and **3b** was monitored by HPLC. The data for system **3b** was difficult to interpret due to side products that formed in the reaction. However, comparison of the initial cleavage rates for the *N*-methyl and *N*-benzyl systems **1b** and **2b**, respectively, showed that **1b** was cleaved approximately 2.8 times as fast (Figure 1a). These observations indicate that the *N*-benzyl system **2** was the most robust of the three, sulfonamide **1** was more vulnerable to premature cleavage reactions, and **3** gave unwanted byproducts.

A goal of these studies was to cleave the linkers using reagents that would only give byproducts that were either highly volatile and/or unlikely to interfere with biological assays. In principle, *n*-propylamine would fulfill this requirement. However, the quantitative experiments described above indicated that cleavage of systems **1**−**3** by *n*-propylamine was unacceptably slow. Consequently, it was necessary to investigate other cleavage reagents. The reagents typically used for rupture of nitrobenzene sulfonamides, i.e., sodium thiophenylate and α-thioacetate,[59,60,66] give noxious byproducts that are difficult to remove and could interfere with biological assays. After considerable experimentation, we found that sodium sulfide in DMF is a highly effective reagent for the cleavage process. A quantitative comparison of the rate of cleavage of **1b** with sodium sulfide and with *n*-propylamine (Figure 1b) indicates that the former reaction had near optimal conversion in approximately 50 min, whereas the latter reaction under the same conditions was only 60% complete after 210 min. Moreover, hydrolysis of excess sodium sulfide gives only hydrogen sulfide and sodium hydroxide. Though toxic, hydrogen sulfide is easily and completely removed by evaporation and/or lyophilization of the solvent media. The aqueous buffers typically used in biological assays will conveniently neutralize small amounts of sodium hydroxide; consequently both the byproducts formed from sodium sulfide-mediated cleavage are relatively innocuous.

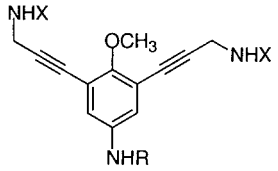
Application of the Linker-Scaffolds in a Synthesis of an Illustrative Library. A small library was prepared to address a typical scenario in protein−protein interactions. Many targets involve two discontinuous hot-spots consisting of negatively charged cavities interacting with positively charged side-chains, as illustrated below. We set out to design a library that could support positively and negatively charged pharmacophores at a spacing of around 10 Å.



A library of dimers with two groups that are positively charged at physiological pH was prepared to test against this target. Dimers that include one or two negatively charged pharmacophores were made to be included in the screen as control substrates.

Homodimers in the library were prepared in good yield from the symmetrical *N*-benzyl sulfonamide **2b**. A few compounds were also made using the *N*-methyl and *N*-carboxymethylene systems **1b** and **3b**, but in other cases (not shown) the yields obtained from these were unsatisfactory, presumably due to the stability issues described above. Conditions for these transformations are summarized in reaction 3. All the steps were performed to generate one compound per well. Guanidine functional groups were introduced from a small library of carbodiimides **15** prepared via several solution-phase methods that have already been described in a publication from our group (reaction 4).[67] The carbodiimides were then reacted with the unmasked scaffold system until a negative ninhydrin test was obtained, after which the products could be cleaved from the resin using a saturated solution of the sodium sulfide in DMF. Some symmetrical diacids were made by coupling deprotected forms of the linker-scaffold systems **1b**, **2b**, and **3b** with a small library of anhydrides. Similarly, some dipyridinium homodimers were made by reaction of the linker-scaffold systems with *N*-methyl 2-chloropyridinium iodide. Some data for the compounds prepared are given in Table 1.

Table 1. Homodimers



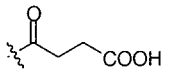
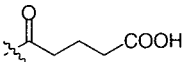
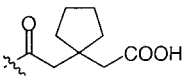
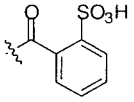
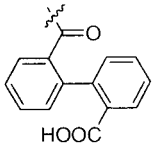
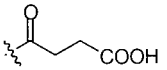
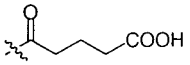
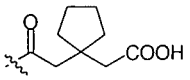
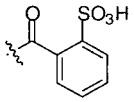
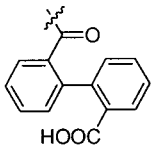
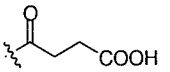
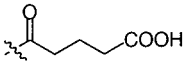
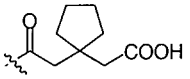
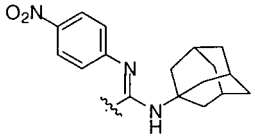
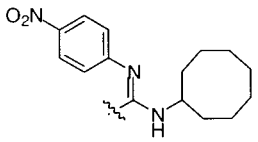
compound	R	X	HPLC purity[a] (%)	yield (%)
16	CH_3		95	65
17	CH_3		86	53
18	CH_3		97	58
19	CH_3		100	49
20	CH_3		92	52
21	Bn		100	70
22	Bn		96	61
23	Bn		100	55
24	Bn		92	68
25	Bn		100	48
26	$CH_2CO_2CH_3$		99	51
27	$CH_2CO_2CH_3$		97	33
28	$CH_2CO_2CH_3$		95	53
29	CH_3		86	49
30	CH_3		96[b]	38

Table 1. (Continued)

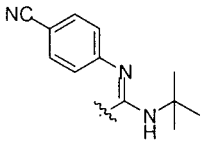
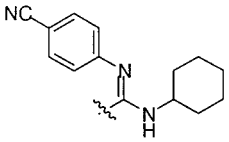
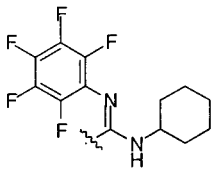
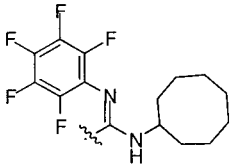
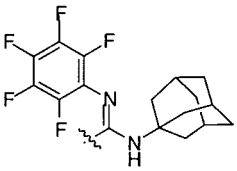
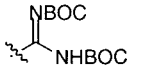
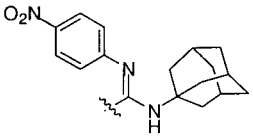
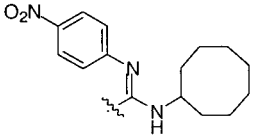
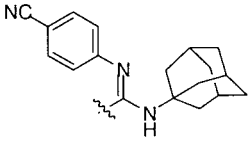
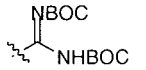
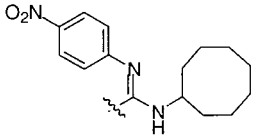
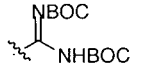
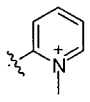
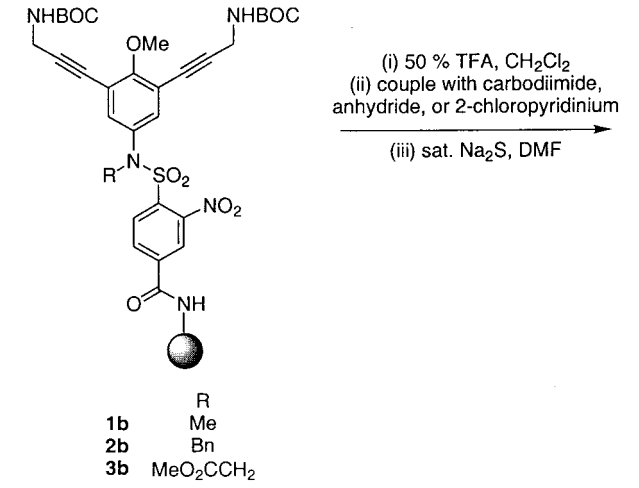
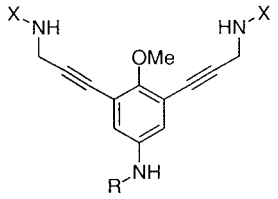
compound	R	X	HPLC purity[a] (%)	yield (%)
31	CH_3		88	35
32	CH_3		86[b]	40
33	CH_3		86	69
34	CH_3		85	33
35	CH_3		85	47
36	CH_3		96	87
37	Bn		94	64
38	Bn		88	62
39	Bn		92	46
40	Bn		100	59
41	$CH_2CO_2CH_3$		94[b]	35
42	$CH_2CO_2CH_3$		81	56
43	CH_3		97	78

Table 1 (Continued)

compound	R	X	HPLC purity[a] (%)	yield (%)
44	Bn		99	86
45	$CH_2CO_2CH_3$		99	42

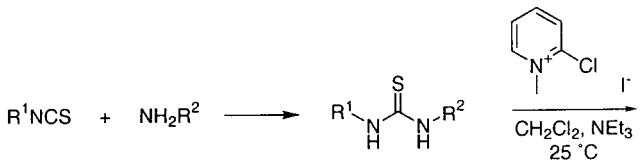
[a] Purity was based on the peak area of HPLC traces of crude products at 254 nm; molecular ions were detected for all compounds via MALDI-MS. The yields are based on the amount of recovered product, using an estimated loading 0.28 mmol/g of resin. [b] Purity of product after being passed through a short silica plug.

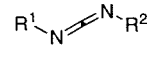




homodimers (Table 1)

reaction 3

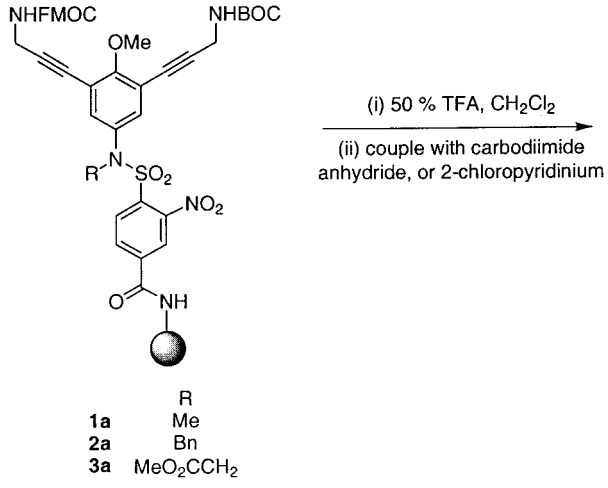


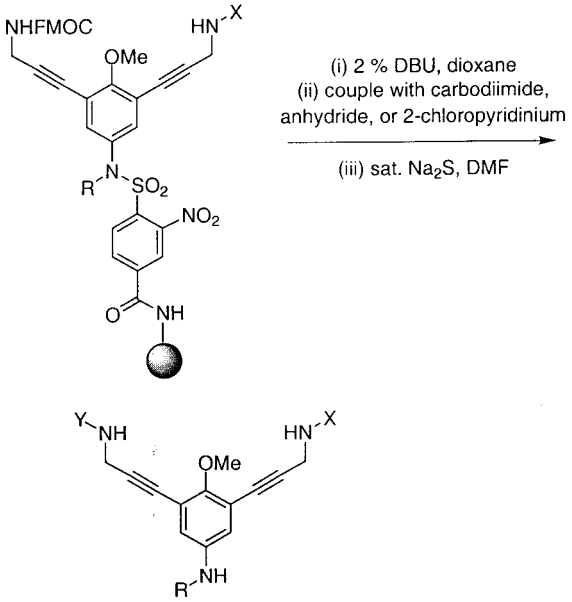


15

reaction 4

Heterodimers were made from systems **1a**, **2a**, and **3a** in transformations that involved removal of *N*-fluorenylmethyloxycarbonyl protecting groups. After considerable experimentation, it was found that the conventional deprotection conditions (20% piperidine in CH_2Cl_2) could be used, but the linker is slowly cleaved; this complication was most significant for **1a** and **3a**. Consequently, removal of the FMOC-groups was more reliably achieved using the basic but nonnucleophilic reagent, DBU. Reaction 5 shows the reaction sequence used, and Table 2 summarizes data for the compounds obtained.



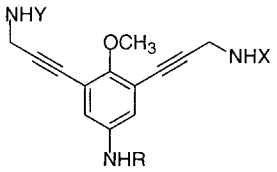


heterodimers (Table 2)

reaction 5

Nearly all the compounds listed in Tables 1 and 2 were formed with purities over 85%, and all gave an appropriate molecular ion in MALDI-MS. Selected compounds, illustrative of each structural type, were further characterized by NMR.

Table 2. Heterodimers



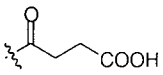
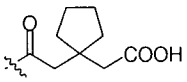
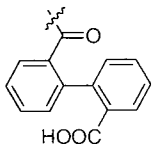
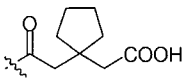
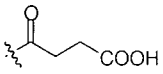
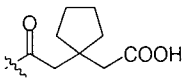
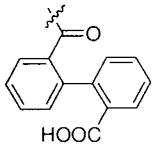
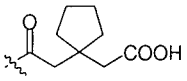
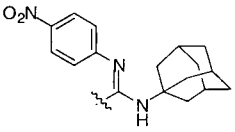
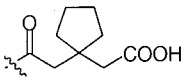
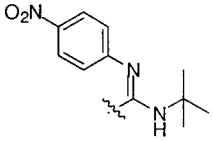
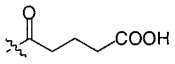
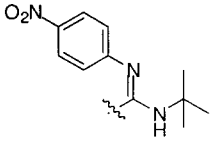
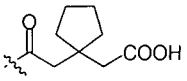
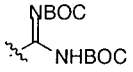
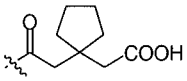
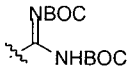
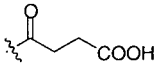
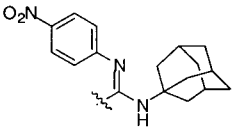
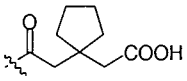
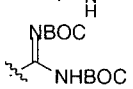
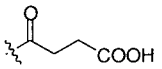
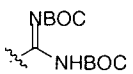
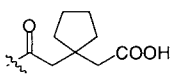
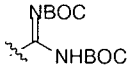
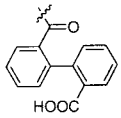
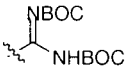
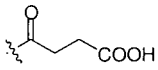
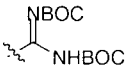
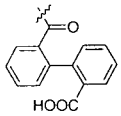
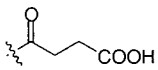
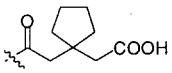
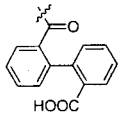
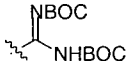
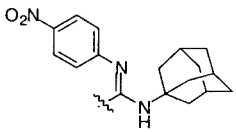
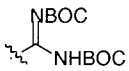
comp'd	R	X	Y	HPLC purity[a] (%)	yield (%)
46	Bn			90	82
47	Bn			72	45
48	$CH_2CO_2CH_3$			91	35
49	$CH_2CO_2CH_3$			91	31
50	CH_3			94	30
51	CH_3			94[b]	49
52	CH_3			88[b]	44
53	CH_3			91	49
54	CH_3			100	61
55	Bn			82	51
56	Bn			100	52
57	Bn			87	64
58	Bn			88	60

Table 2. (Continued)

comp'd	R	X	Y	HPLC purity[a] (%)	yield (%)
59	$CH_2CO_2CH_3$			87	58
60	$CH_2CO_2CH_3$			87	53
61	Bn			93	65
62	Bn			90	90
63	Bn			98	88
64	Bn			88	92
65	Bn			86	50

[a] Purity was based on the peak area of HPLC traces of crude products at 254 nm; molecular ions were detected for all compounds via MALDI-MS. The yields are based on the amount of recovery product, considering an estimated loading 0.28 mmol/g of resin. [b] Purity of product after being passed through a short silica plug.

Conclusions

This work has demonstrated that the linker-scaffolds **1**−**3** are useful for preparation of bivalent systems. Minor modifications of these linker-scaffold designs can easily be envisaged. These include using longer, reduced, aromatic arms on the scaffold, different core fragments in the scaffold, use of other *N*-alkylating groups, and other nucleophile-labile linking functionalities. Ultimately a diverse set of scaffolds, perhaps incorporating some of these modifications, will be required to address different problems in medicinal chemistry.

Preparation of the library described here was a pilot study for more ambitious undertakings. Indeed, conditions for the couplings, deprotection, and resin cleavage steps were refined as the synthesis of the library described above progressed. However, we are now confident that much larger collections of compounds could be made using systems **2a** and **2b**. These linker-scaffolds satisfy the design criteria that were outlined at the beginning of this project, and form the basis for further developments in this area.

Experimental Section

General. All chemicals were obtained from commercial suppliers and used without further purification. Di-*iso*-propylcarbodiimide (DIC), *N*-hydroxybenzotriazole (HOBt), di-*iso*-propylethylamine (DIEA), and trifluoroacetic acid (TFA) were purchased from Aldrich. Aminomethyl polystyrene resin was obtained from NovaBiochem. *N*,*N*-Bis-(*tert*-butyloxycarbonyl)-1-guanyl pyrazole was obtained from Advanced ChemTech. Reverse-phase high performance liquid chromatography (HPLC) was carried out on Vydac C-18 columns of the following dimensions: 25 × 0.46 cm for analysis, and 25 × 2.2 cm for preparative work. All HPLC experiments were performed using gradient conditions. Eluants used were as follows: solvent A (H_2O with 0.1% TFA), and solvent B (CH_3CN with 0.1% TFA). Flow rates used were 1.0 mL/min for analytical, and 6 mL/min for preparative work. The purity was monitored by UV absorbance at 254 nm.

All NMR spectra were recorded on Varian instruments at 300 MHz (^1H) and 75 MHz (^{13}C). NMR chemical shifts are expressed in ppm relative to internal solvent peaks, and coupling constants were measured in hertz.

The washing and drying protocol used in the solid-phase syntheses was as follows: DMF (2×), methanol, DMF, methanol, dichloromethane, methanol, and dichloromethane (3×). Henceforth this is referred to as "a washing cycle".

2-Iodo-4-nitro-6-*N*-(BOC)-(3′-amino-1′-propynyl)methoxybenzene 5. 2,6-Diiodo-4-nitromethoxybenzene **4**[61] (1.84 g, 4.54 mmol), tetrakis(triphenylphosphine)palladium (262 mg, 0.23 mmol), and copper(I) iodide (43 mg, 0.23 mmol) were combined in a 50 mL round-bottom flask which was then

evacuated and refilled with nitrogen three times. Freshly distilled toluene (20 mL) was added followed by triethylamine (3.16 mL, 22.7 mmol). *N*-*tert*-Butoxycarbonylprop-2-ynylamine[68] (1.20 g, 7.72 mmol) in 7 mL of toluene was added dropwise, and the solution was allowed to stir at 50 °C (oil bath) for 16 h. After concentration in vacuo, the material obtained was chromatographed with EtOAc−hexanes (5−20%) to provide the monosubstituted product **5** as an off-white crystalline material **(**824 mg, 42%) and the disubstituted product **6** as a viscous yellow liquid (1.13 g, 54%). **5:** mp 88−90 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.54 (d, J = 2.7 Hz, 1H), 8.20 (d, J = 2.7 Hz, 1H), 4.83 (bs, 1H), 4.17 (d, J = 5.4 Hz, 2H), 4.05 (s, 3H), 1.44 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.2, 143.4, 134.4, 129.5, 127.6, 125.6, 116.0, 93.6, 91.1, 80.3, 76.9, 61.4, 31.2, 28.3; HRMS (FAB) calcd for $[C_{15}H_{17}IN_2O_5Na]^+$ 455.0079, found 455.0079. **6:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (s, 2H), 4.98 (bs, 2H), 4.14 (d, J = 4.5 Hz, 4H), 4.11 (s, 3H), 1.42 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.1, 155.3, 142.1, 134.9, 128.9, 116.6, 92.7, 80.1, 76.9, 61.4, 31.1, 28.2; HRMS (FAB) calcd for $[C_{23}H_{29}N_3O_7Na]^+$ 482.1903, found 482.1903.

***N*,*N*′-Bis(BOC)-2,6-bis(3′-amino-1′-propynyl)-4-nitromethoxybenzene 6.** 2,6-Diiodo-4-nitromethoxybenzene **4**[61] (8.08 g, 19.9 mmol), tetrakis(triphenylphosphine)-palladium (690 mg, 0.597 mmol), copper(I) iodide (113 mg, 0.597 mmol), and triethylamine (13.9 mL, 99.8 mmol) were mixed in 100 mL of toluene, and *N*-*tert*-butoxycarbonylprop-2-ynylamine (7.75 g, 49.9 mmol) was added in one portion. The reaction mixture was stirred at 70 °C for 16 h. After concentration in vacuo, the material obtained was chromatographed with EtOAc−hexanes (10−30%) to yield **6 (**7.75 g, 84%).

***N*-(BOC)-*N*′-(Trifluoroacetyl)-2,6-(3′-amino-1′-propynyl)-4-nitromethoxybenzene 7.** This material was prepared following the procedure described for **6**, but using starting material **5** (1.98 g, 4.58 mmol), tetrakis(triphenylphosphine)-palladium (158 mg, 0.137 mmol), copper(I) iodide (26 mg, 0.137 mmol), triethylamine (3.19 mL, 22.9 mmol), toluene (20 mL), and *N*-trifluoroacetylprop-2-ynyamine[69] (865 mg, 5.73 mmol) to yield **7** as a yellow oil (1.55 g, 94%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 (s, 2H), 7.62 (bs, 1H), 4.42 (d, J = 5.4 Hz, 2H), 4.18 (d, J = 5.4 Hz, 2H), 4.13 (s, 3H), 1.47 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.7, 152.9, 152.4, 151.0, 137.6, 124.9, 124.4, 113.1, 112.1, 111.6, 88.0, 85.1, 75.7, 73.7, 57.0, 26.7, 25.9, 23.8; HRMS (FAB) calcd for $[C_{20}H_{20}F_3N_3O_6Na]^+$ 478.1201, found 478.1200.

***N*-(BOC)-*N*′-(Trifluoroacetyl)-3,5-(3′-amino-1′-propynyl)-4-methoxyaminobenzene 8.** A mixture of the substituted methoxynitrobenzene **7** (1.55 g, 3.40 mmol) and powdered iron (1.90 g, 34 mmol) in 25 mL of glacial acetic acid was mechanically stirred at 25 °C for 4 h. The reaction mixture was filtered through Celite and washed with approximately 50 mL of ethyl acetate. The resultant organic layer was washed with approximately 2 × 50 mL of H_2O and approximately 50 mL of saturated sodium bicarbonate. The extract was dried (Na_2SO_4), and the solvent was removed in vacuo. The crude material was chromatographed with EtOAc−hexane (20−30%) to afford product **8** as a yellow oil (1.08 g, 75%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.07 (bs, 1H), 6.65(m, 2H), 4.83 (bs, 1H), 4.35 (d, J = 5.4 Hz, 2H), 4.08 (d, J = 5.4 Hz, 2H), 3.83 (s, 3H), 2.81 (bs, 2H), 1.44 (s, 9H); ^{13}C NMR (75 MHz,$CDCl_3$) δ 152.8, 152.3, 151.0, 150.2, 137.6, 116.0, 115.5, 113.1, 112.9, 112.2, 85.2, 81.9, 75.7, 74.1, 57.1, 26.8, 26.0, 23.8; HRMS (FAB) calcd for $[C_{20}H_{22}F_3N_3O_4]^+$ 425.1562, found 425.1584.

4-Methoxycarbonyl-2-nitro-benzenesulfonyl Chloride 9.[60,62] Benzyl thiol (16.8 mL, 143 mmol) and methyl 4-chloro-3-nitrobenzoate (28 g, 129 mmol) were added to a cold solution of K_2CO_3 (53.8 g, 390 mmol) in 500 mL of MeOH. The reaction mixture was stirred for 2 h at 25 °C. A yellow precipitate formed and was separated by filtration. This solid was recrystallized from MeOH with gradual addition of water to decrease the solubility. This benzyl sulfide intermediate was then added to 600 mL of 40% acetic acid and stirred while chlorine gas was bubbled into the mixture for 4 h. A pale yellow solid was precipitated, isolated by filtration, and washed with petroleum ether. The product was recrystallized from dichloromethane/hexane to give colorless solid (28.3 g, 78%).

Methyl Ester 10. The sulfonyl chloride **9** (4.40 g, 15.7 mmol) was added as a solid, in one portion, to a solution of the substituted aniline **8** (5.14 g, 12.1 mmol) in 20 mL of pyridine. The reaction mixture was stirred at 80 °C for 1 h. The reaction mixture was then cooled to room temperature, and approximately 30 mL of $CH_2Cl_2$was added. The mixture was washed with 1 × 30 mL of 0.1 M HCl, then with 3 × 30 mL of H_2O, filtered, and dried (Na_2SO_4) to yield the desired product **10** (7.80 g, 97%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.08 (bt, 2H), 8.40 (d, J = 1.5 Hz, 1H), 8.29 (d of d, J = 8.1 Hz, 1.5 Hz, 1H), 8.06 (d, J = 8.1 Hz, 1H), 7.29 (m, 2H), 6.48 (bt, 1H), 4.39 (d, J = 5.4 Hz, 2H), 4.10 (d, J = 4.8 Hz, 2H), 3.95 (s, 3H), 3.88 (s, 3H), 1.40 (s, 9H); ^{13}C NMR (75 MHz,$CDCl_3$) δ 159.1, 155.9, 151.9, 151.7, 143.8, 131.5, 130.6, 128.4, 127.2, 126.7, 123.8, 122.9, 121.1, 113.4, 112.8, 109.9, 88.0, 85.0, 74.2, 73.0, 72.2, 56.3, 48.2, 26.0, 24.8, 23.2; HRMS (MALDI MS) calcd for $[C_{29}H_{27}F_3N_4O_{10}SNa]^+$ 691.1297, found 691.1278.

Carboxylic Acid 11. Compound **10** (7.80 g, 11.7 mmol) was dissolved in 1,4-dioxane (80 mL). Sodium hydroxide (1 M, 65 mL) was added in one portion, and the mixture was stirred for 1.5 h at 25 °C. The pH of the solution was first adjusted to 4 by addition of 2 M $KHSO_4$, then to pH 8 by addition of 10% sodium hydrogen carbonate (50 mL). Fmoc-succinimide (4.34 g, 12.9 mmol) was added, and the mixture was stirred at 25 °C for 2 h. This reaction mixture was then mixed with 400 mL of water, acidified to pH 3 with 2 M $KHSO_4$, and extracted with 3 × 100 mL of EtOAc. The extracts were combined and dried (Na_2SO_4), and the solvent was removed in vacuo. The crude material was chromatographed using chloroform/methanol/acetic acid (95:5:1) eluant to yield product **11** (7.29 g, 78%) as yellow oil: ^{1}H NMR (300 MHz, acetone-d_6) δ 8.40 (bs, 1H), 8.28 (d, J = 7.8 Hz, 1H), 8.01 (m, 1H), 7.82 (d, J = 7.5 Hz, 2H), 7.67 (d, J = 7.5 Hz, 2H), 7.37 (m, 3H), 7.30 (m, 4H), 7.05 (bt, 1H), 6.47 (bt, 1H), 4.35 (d, J = 7.0 Hz, 2H), 4.24 (m, 3H), 4.09 (d, J = 5.7 Hz, 2H), 3.87 (s, 3H), 1.39 (s, 9H); ^{13}C NMR (75 MHz, acetone-d_6) δ 172.7, 167.2, 161.8, 155.9, 151.8, 143.5, 139.2, 136.8, 131.2, 131.1, 129.2, 127.6, 125.9,

124.0, 123.2, 122.6, 122.1, 120.5, 115.5, 113.4, 113.3, 88.4, 75.9, 73.4, 62.7, 62.5, 56.9, 56.1, 42.5, 27.2, 26.8, 23.8; HRMS (MALDI MS) calcd for $[C_{40}H_{36}N_4O_{11}S\ Na]^+$ 803.1999, found 803.2030.

Aniline 12. The procedure used for preparation of compound **8** was applied, but using **7** (9.72 g, 21.2 mmol) and powdered iron (5.91 g, 106 mmol) in 80 mL of glacial acetic acid to yield product **12** (8.77 g, 96%) as a yellow oil. This crude product was used in the next step (conversion to the sulfonamide **13**) without any further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.60 (s, 2H), 5.18 (bs, 2H), 4.11 (d, J = 4.5 Hz, 4H), 3.81 (s, 3H), 1.42 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.9, 150.1, 137.6, 115.5, 112.8, 84.9, 75.4, 74.3, 56.9, 26.8, 23.8; HRMS (FAB) calcd for $[C_{23}H_{31}N_3O_5]^+$ 429.2264, found 429.2263.

Sulfonamide 13. The protocol used for preparation of compound **10** was followed, but using **12** (4.88 g, 11.4 mmol) in 20 mL of pyridine, and sulfonyl chloride **9** (4.14 g, 14.8 mmol) to yield **13** (6.65 g, 87%) as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.27 (bs, 1H), 8.41(d, J = 1.8 Hz, 1H), 8.29 (d of d, J = 9.0 Hz, 1.8 Hz, 1H), 8.05 (d, J = 8.4 Hz, 1H), 7.27 (s, 2H), 6.49 (bt, 2H), 4.10 (d, J = 6.0 Hz, 4H), 3.93 (s, 3H), 3.89 (s, 3H), 1.40 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.9, 155.9, 151.2, 144.0, 131.1, 130.6, 128.4, 127.2, 127.0, 123.3, 121.1, 113.6, 88.0, 74.2, 72.3, 56.3, 48.2, 26.1, 23.3; MALDI MS calcd for $[C_{31}H_{35}N_4O_{11}S]^-$ 671.2101, found 671.5810.

Carboxylic Acid 14. Lithium hydroxide monohydrate (530 mg, 12.6 mmol) was added to a solution of **13** (6.54 g, 9.72 mmol) in THF/methanol/H_2O 3:2:1 (20 mL). The resulting solution was stirred at 25 °C for 2 h and concentrated in vacuo, the crude material was diluted with 20 mL of water, then acidified with 1 N HCl. The resulting solution was extracted with 2 × 10 mL of EtOAc, dried over anhydrous Na_2SO_4, and concentrated in vacuo to yield product **14** (6.08 g, 95%) as a viscous yellow liquid. This crude material was sufficiently pure to be used in the next step without further purification: ^{1}H NMR (300 MHz, acetone-d_6) δ 8.45 (d, J = 1.5 Hz, 1H), 8.34 (d of d, J = 8.4 Hz, 1.5 Hz, 1H), 8.00 (d, J = 8.1 Hz, 1H), 7.317 (s, 2H), 6.53 (bt, 2H), 4.14 (bs, 4H), 3.94 (s, 3H), 1.45 (s, 18 H); ^{13}C NMR (75 MHz, acetone-d_6) δ 166.8, 160.4, 156.5, 148.4, 141.1, 133.5, 133.1, 131.7, 131.4, 127.8, 125.97, 118.34, 92.9, 78.4, 76.8, 60.9, 30.6, 27.9; HRMS (MALDI MS) calcd for $[C_{30}H_{34}N_4O_{11}SNa]^+$ 681.1842, found 681.1844

Procedure for Attaching the Linker-Scaffolds 11 and 14 to Aminomethyl Polystyrene Resin. Compound **11** or **14** was anchored to aminomethyl polystyrene resin (0.35 mmol/g) using standard peptide coupling procedures. Aminomethyl resin (1 equiv) was preswelled in dichloromethane for 30 min. The solvent was filtered, and then a CH_2Cl_2/DMF (v/v, 4:1) solution of **11** or **14** (1 equiv), HOBt (3 equiv), DIC (3 equiv), and a few crystals of DMAP were added. The mixture was agitated for 6 h, or until a negative ninhydrin test was observed. The resin was finally subjected to one washing cycle (see general procedures), then dried in vacuo.

Solid-Phase N-Alkylation of the Supported Sulfonamides 11 and 14. The resin-bound sulfonamides generated as described above were preswelled in DMF for 30 min. DIEA (5 equiv) and alkyl halide (10 equiv) were then introduced, and the reaction mixture was agitated for 4 h at 25 °C. The resin was then subjected to one washing cycle and dried in vacuo.

Preparation of Symmetrical Diacids 16−28. The resin-bound alkylated sulfonamide (0.75 g, loading ∼0.28 mmol/g) was swelled in dichloromethane for 30 min. The BOC protecting group on the scaffold was removed with 50% trifluoroacetic acid in dichloromethane for 30 min. After washing and drying, the resin was suspended in dry dichloromethane and treated with cyclic anhydride (5 equiv), a few crystals of DMAP, and DIEA (5 equiv). The reaction was monitored by the Kaiser ninhydrin test, and generally went to completion within an hour. The resin was then washed and dried, and cleaved as described below in the Cleavage of the Functionalized, Supported Linker-Scaffolds section. All the compounds gave satisfactory MALDI-MS data, and their purities are given in Table 1. Further spectral data were also obtained for three illustrative compounds, **16**−**18**. **16**: ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.06 (bs, 2H), 8.39 (t, J = 5.4 Hz, 2H), 6.48 (s, 2H), 5.65 (bd, 1H), 4.09 (d, J = 5.4 Hz, 4H), 3.71 (s, 3H), 2.59 (d, J = 4.2 Hz, 3H), 2.43 (m, 4H), 2.34 (m, 4H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 174.5, 171.5, 152.8, 146.5, 117.6, 116.5, 90.8, 78.7, 61.7, 30.5, 29.7, 29.4. Analytical HPLC: homogeneous single peak, retention time = 12.0 min (5−40% B in 30 min). MALDI MS: calcd (MH^+) 444.17, found 444.17. **17**: ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.06 (bs, 2H), 8.39 (t, J = 5.4 Hz, 2H), 6.49 (s, 2H), 4.09 (d, J = 5.4 Hz, 4H), 3.70 (s, 3H), 2.50 (s, 3H), 2.10−2.28 (m, 8H), 1.69−1.76 (m, 4H), 1.18−1.26 (m, 4H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 174.8, 172.1, 152.8, 146.4, 117.6, 116.6, 90.9, 78.6, 61.6, 34.9, 33.6, 30.5, 29.3, 21.3. Analytical HPLC: homogeneous single peak, retention time = 13.1 min (5−40% B in 30 min). MALDI MS: calcd (MH^+) 472.20, found 472.21. **18**: ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.0 (bs, 2H), 8.36 (t, J = 5.4 Hz, 2H), 6.49 (s, 2H), 5.66 (bs, 1H), 4.11 (d, J = 5.4 Hz, 4H), 3.72 (s, 3H), 2.62 (bs, 3H), 2.44 (m, 4H), 2.31 (m, 4H), 1.58 (bs, 12H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 174.1, 171.7, 152.7, 146.5, 117.6, 116.5, 90.9, 78.6, 61.7, 43.7, 43.4, 37.7, 30.5, 29.7, 24.4. Analytical HPLC: homogeneous single peak, retention time = 17.8 min (5−40% B in 30 min). MALDI MS: calcd (MH^+) 580.29, found 580.32.

Preparation of Symmetrical Diguanidines and Dipyridinium Compounds 29−45. (a) Formation of Carbodiimides 15. The following is an adaptation of a recent procedure.[67] Equal amounts of a primary amine and an isothiocyanate were mixed in dichloromethane (usually 0.75 mmol in 5 mL). Formation of the thioureas was generally rapid (TLC). After the reaction was completed, the solvent was removed, and the resulting solid was washed several times with 1:1 ether/petroleum ether and then dried in vacuo. The thioureas were typically obtained in a high state of purity and used directly in the next synthetic step.

Conversion of the thioureas to the carbodiimides was achieved via the following procedure. The thioureas were dissolved in 5 mL of dichloromethane and 5 equiv of triethylamine, and then 1 equiv of the methyl 2-chloropy-

ridium iodide (Mukaiyama's reagent) was added. The reaction mixture was briefly sonicated to obtain a homogeneous solution. Formation of the carbodiimides was usually complete within 1 min (by TLC). The solvent was then removed, and a small amount of dichloromethane and hexanes was added. The solution was then passed through a short pad of silica gel packed in a pipet and eluted with hexane. The products were sufficiently pure to use in the next stage without further purification.

(b) Syntheses of Bis-guanidines 29−35, 37−39, and 41. The resin-bound alkylated sulfonamides **1b**, **2b**, and **3b** were swelled in dichloromethane for 30 min, and then the BOC protecting groups were removed using 50% trifluoroacetic acid in dichloromethane for 30 min. After washing and drying, the resin was suspended in dry THF, and a THF solution of the freshly prepared carbodiimide (3−4 equiv) was then added in one portion. The mixture was agitated for a period of time that was adjusted depending on the reactivity of the carbodiimide. In most cases, the reaction was completed in 1 h (ninhydrin test). After the reaction is completed, the resin was washed, dried, and cleaved as described below in the Cleavage of the Functionalized, Supported Linker-Scaffolds section. All the compounds gave satisfactory MALDI-MS data, and their purities are given in Table 1. Further spectral data were also obtained for the illustrative compound, **38**: ^{1}H NMR (300 MHz, acetone-d_6) δ 8.09−8.13 (m, 4H), 7.32−7.36 (m, 5H, 6.91−6.94 (d of d, J = 6.9, 1.8 Hz, 4H), 6.81 (d, J = 8.7 Hz, 1H), 6.64 (s, 2H), 4.26 (m, 6H), 3.87 (s, 3H), 1.25−1.88 (m, 30 H); ^{13}C NMR (75 MHz, acetone-d_6) δ 157.7, 150.3, 144.2, 141.7, 138.9, 129.0, 127.5, 125.8, 125.3, 123.2, 122.3, 117.8, 117.5, 89.4, 80.1, 61.8, 52.1, 48.6, 33.0, 32.7, 27.4, 25.6, 23.7. Analytical HPLC: homogeneous single peak, retention time = 19.2 min (30−95% B in 30 min). MALDI MS: calcd (MH^+) 866.46, found 866.46.

(c) Syntheses of Bis(BOC)-guanidines 36, 40, and 42. The resin-bound alkylated sulfonamides **1b**, **2b**, and **3b** were swelled in dichloromethane for 30 min, and then the BOC protecting groups were removed using 50% trifluoroacetic acid in dichloromethane for 30 min. After washing and drying, the resin was suspended in dry THF and a THF solution of *N*,*N*′-bis-BOC-1-guanylpyrazole[70] (3 equiv), and ^{i}Pr$_2$NEt (3 equiv) was then added in one portion. The mixture was agitated and usually completed in 1 h (ninhydrin test). The resin was then washed, dried, and cleaved as described below in the Cleavage of the Functionalized, Supported Linker-Scaffolds section. All the compounds gave satisfactory MALDI-MS data, and their purities are given in Table 1. Further spectral data was also obtained for the illustrative compound, **36**: ^{1}H NMR (300 MHz, acetone-d_6) δ 11.64 (bs, 2H), 8.60 (bs, 2H), 6.652 (s, 2H), 5.03 (bm, 1H), 4.50 (m, 4H), 3.88 (s, 3H), 2.77 (d, J = 5.1 Hz, 3H), 1.56 (s, 18H), 1.478 (s, 18H); ^{13}C NMR (75 MHz, acetone-d_6) δ 163.8, 155.9, 146.2, 130.8, 117.8, 116.5, 113.4, 88.8, 83.3, 79.7, 78.8, 61.0, 35.5, 31.1, 27.8, 27.5. Analytical HPLC: homogeneous single peak, retention time = 23.0 min (30−95% B in 30 min). MALDI MS: calcd (MH^+) 728.39, found 528.27 corresponding to loss of all four ^{t}BuOCO- fragments from the molecular ion.

(d) Syntheses of Dipyridinium Compounds 43−45. The resin-bound alkylated sulfonamides **1b**, **2b**, and **3b** were swelled in dichloromethane for 30 min, and then the BOC protecting groups were removed using 50% trifluoroacetic acid in dichloromethane for 30 min. After washing and drying, the resin was suspended in DMF for 30 min, and the methyl 2-chloropyridium iodide (Mukaiyama's reagent) (3 equiv) and DIEA (3 equiv) were then added in one portion. The mixture was agitated and usually completed in 1 h (ninhydrin test). The resin was then washed, dried, and cleaved as described below in the Cleavage of the Functionalized, Supported Linker-Scaffolds section. All the compounds gave satisfactory MALDI MS data, and their purities are given in Table 1. Further spectral data was also obtained for the illustrative compound, **44**: ^{1}H NMR (300 MHz, acetone-d_6) δ 7.77 (d, J = 6.9 Hz, 2H), 7.54 (m, 2H), 7.31(m, 4H), 7.20 (m, 1H), 6.926 (d, J = 9 Hz, 2H), 6.61 (s, 2H), 6.343 (t, J = 6.9, 2H), 5.614 (bt, 1H), 4.36 (s, 4H), 4.28 (d, J = 5.1 Hz, 2H), 3.68 (m, 9H); ^{13}C NMR (75 MHz, acetone-d_6) δ 157.8, 154.1, 144.5, 141.2, 139.4, 129.1, 128.1, 117.8, 117.4, 112.7, 109.7, 107.5, 89.5, 79.1, 60.0, 46.2, 40.9, 34.8. Analytical HPLC: homogeneous single peak, retention time = 11.5 min (5−90% B in 30 min). MALDI MS: calcd $(M-H)^+$ 502.26, found 502.36.

Synthesis of Heterodimers 46−65. These were prepared simply by combining the procedures outlined above, but with deprotection of the BOC groups preceding removal of the FMOC groups. The resin-bound alkylated sulfonamide was swelled in dichloromethane for 30 min and then treated with 50% trifluoroacetic acid in dichloromethane for 30 min. After washing and drying, the deprotected resin was coupled to a monomeric unit as described above. Removal of the FMOC groups was effected with 2% DBU in 1,4-dioxane twice for 5 and 10 min each. A second monomeric unit was then coupled and finally washed and dried in vacuo, dried, and cleaved as described below in the Cleavage of the Functionalized, Supported Linker-Scaffolds section. All the compounds gave satisfactory MALDI-MS data, and their purities are given in Table 1. Further spectral data was also obtained for the illustrative compound **56**: ^{1}H NMR (300 MHz, $CDCl_3$) δ; 11.46 (bs, 1H), 8.56 (bt, 1H), 7.32 (bs, 5H), 6.59 (bs, 2H), 4.44 (bd, 2H), 4.23 (bs, 4H), 3.85 (s, 3H), 3.67(bs, 4H), 2.65(m, 2H), 2.52 (m, 2H), 1.51 (s, 18H). Analytical HPLC: homogeneous single peak, retention time = 19.0 min (5−90% B in 30 min). MALDI MS: calcd (MH^+) 661.31, found 462.20 corresponding to loss of two ^{t}BuOCO− fragments from the molecular ion.

Cleavage of the Functionalized, Supported Linker-Scaffolds. The cleavage was accomplished by agitating the resin with sodium sulfide (excess) in DMF at room temperature for 30 min. The resin was washed with DMF, a second portion of sodium sulfide solution was added, and the reaction mixture was agitated for 1 h and then allowed to stand for 18 h. The product was collected by suction, and the resin was washed many times with DMF. The combined filtrates were evaporated under reduced pressure.

Experiments to Investigate Rates of Cleavage. Cleavage rate studies were performed on ∼10 mg of resin (**1b**, **2b**, and **3b**) using acenaphthene as an internal standard. After

reagent was added, aliquots of reaction mixture (10 μL) were taken out at regular intervals, and the conversions were monitored by HPLC measuring at 254 nm (calibrated with authentic samples). Saturated sodium sulfide in DMF was prepared by sonicating solid Na_2S in DMF for 10 min.

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