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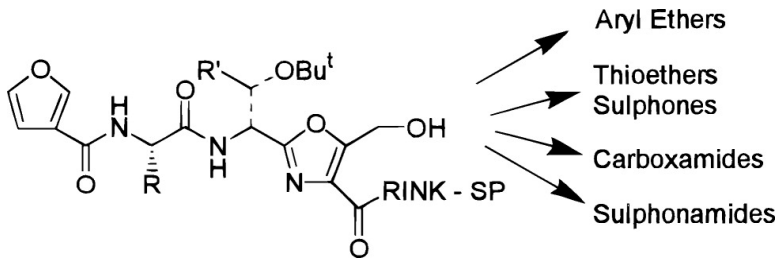

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5-(Hydroxymethyl)oxazoles: Versatile Scaffolds for Combinatorial Solid-Phase Synthesis of 5-Substituted Oxazoles

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A scheme combining the preparation of building blocks in solution followed by solid-phase combinatorial chemistry has been developed to side-chain diversify 5-(hydroxymethyl)oxazole scaffold (**1**) into aryl ethers, thioethers, sulfones, sulfonamides, and carboxamides. Protected heterocyclic scaffolds **2** were linked to the solid phase and N-terminal derivatized using active ester chemistry, providing chemset **4**{*1*−*4*,*1*−*4*}. The free side-chain hydroxyl of **4** was smoothly converted to aryl ethers **6** under Mitsunobu conditions, with a broad range of substituted phenols. Alternatively, quantitative conversion of hydroxyl to bromide followed by displacement with alkyl and aryl thiols gave thioethers **8**. Thioethers were optionally oxidized to sulfones **9**. Bromide displacement by azide, followed by reduction to amine and acylation with a range of carboxylic acids and sulfonyl chlorides gave carboxamides **11** and sulfonamides **13**, respectively. Crude purity at typically >90% was observed for each of the five modifications detailed. A series of 20 compounds, exemplifying each modification, was reprepared, purified, and fully characterized.

Introduction

The conceptually simple idea of modifying a molecule which is anchored to a polymeric support was first presented by R. B. Merrifield in 1962.[1] He outlined basic theoretical and experimental principles that were originally directed toward the specialized field of solid-phase peptide synthesis, but later evolved to include oligonucleotide and more recently oligosaccharide syntheses. During the last 10 years, the fundamental concepts that emerged from "oligo"-type solid-phase research have been increasingly applied and adapted toward a much more diverse range of chemistries. This interest has fuelled the rapidly expanding field of general solid-phase organic chemistry (SPOC), an area which has emerged to become a major part of modern medicinal chemistry research.[2,3] Currently, there is enormous interest in generating synthetic protocols that exploit the versatility of chemistry that can be performed in solution, combined with the sheer power of parallel solid phase synthesis. The potential for such a scheme is clearly seen: A sequence of chemical reactions that have been successfully transferred to the solid phase can routinely generate 1000 analogues as single compounds. Arrays of this size are not only redirecting the initial stages of drug discovery toward molecules with good biological potency and selectivity, but are also offering researchers an expanding appreciation of preliminary pharmacokinetic properties. Thus, the screening of compound arrays should identify early lead molecules that exhibit a broad range of attractive properties which can be subsequently exploited to generate more robust drug leads and more successful clinical candidates.

The trend toward large analogue arrays has necessitated parallel developments in compound and data management. The logistics of integrating synthesis, purification, registration, and screening results for many thousands of compounds have essentially been tackled. Now, the major hold-up to fully exploiting the potential offered by SPOC techniques lies in the relatively low number of reactions readily performed in solution that have been adequately transferred to the solid phase. The progress made to date has been collated in a number of concise review articles,[4−7] together with the most recent contributions at numerous Internet sites.[8]

As part of an in-house medicinal chemistry program, a diverse range of molecules based upon the substituted oxazole unit (**1**) was sought. In particular, we aimed to develop a synthetic scheme that provided flexible derivatization of (**1**), primarily though N-terminal extension and the introduction of multiple functionality at oxazole ring position 5. Although the solid-phase synthesis of numerous heterocyclic cores has been described previously,[9] our preferred strategy involved the preparation in solution of an appropriately functionalized and protected core, followed by solid-phase attachment, assembly, and derivitization. Here, we describe a combined solution−solid-phase scheme in which a solution-generated heterocyclic scaffold is "side-chain diversified" on the solid phase into five distinct compound series.

Results and Discussion

Successful SPOC is built around the smooth conversion of a solid-phase bound intermediate, through a number of high-yielding chemical conversions, to an easily released final product. Of the numerous factors that needed to be considered toward the development of a flexible combinatorial synthesis based around oxazole unit (**1**), the global protecting group strategy and choice of linkage chemistry

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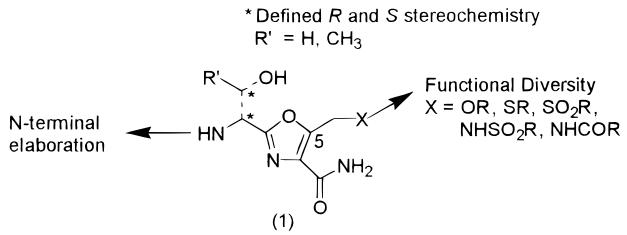


Figure 1. Oxazole core for combinatorial elaboration.

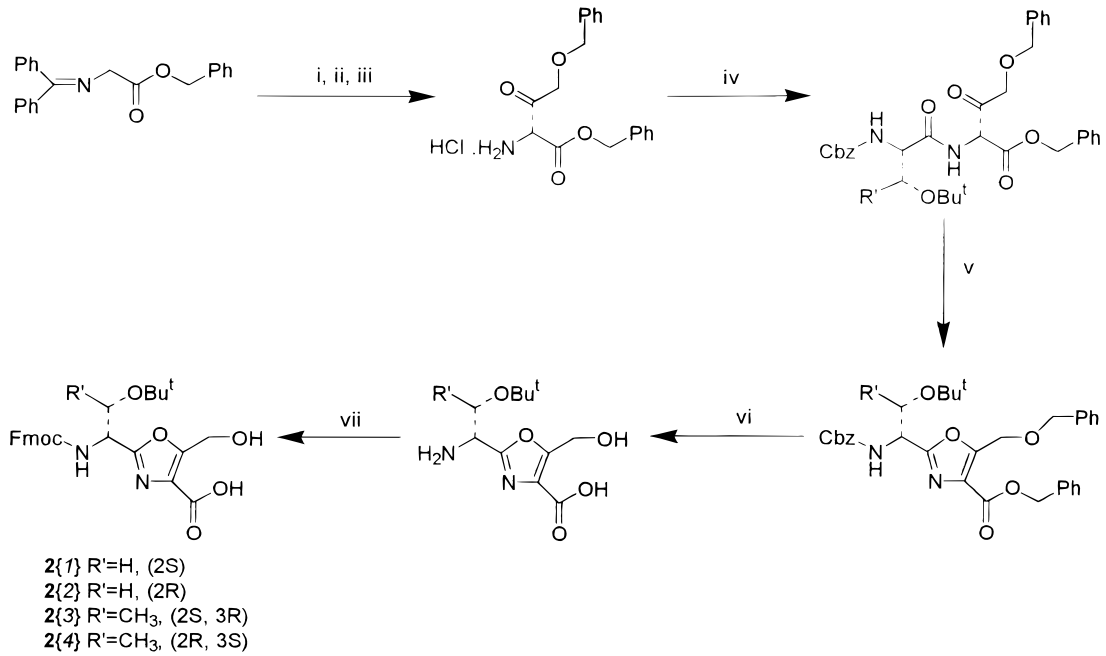
were crucial. Our preferred design strategy was based upon high-fidelity N-α-fluorenylmethoxy carbonyl (Fmoc) chemistry[10] for N-terminal elaboration, protection compatible with an acid labile linkage. A key element of oxazole (**1**) (Figure 1) was the primary carboxamide at ring position 4, which enabled the use of acid labile Rink amide linker[11] as a convenient site for attachment to the solid phase. These chemical considerations were used to design a series of heterocyclic scaffolds, reagent chemset **2**{*1*−*4*} derived from **2**{*1*} L-serine, **2**{*2*} D-serine, **2**{*3*} L-threonine, and **2**{*4*} D-threonine which were prepared in solution (Scheme 1). Chemset **2**{*1*−*4*} provided the core templates for the subsequent solid phase assembly of oxazoles (1).

The solution preparation of reagent chemset **2**{*1*−*4*} commenced from N-(diphenyl methylene)glycine benzyl ester.[12] The anion generated by treatment with lithium hexamethyldisilazane was acylated by benzyloxyacetyl chloride. The resultant product was hydrolyzed in situ to the more stable hydrochloride salt, isolated in essentially quantitative yield, and used without further purification. The salt was divided into four batches, each separately coupled to the appropriate N-benzyloxycarbonyl-L-amino acid, using mixed anhydride activation via isobutylchloroformate. The precyclized building blocks were purified by flash chromatography and isolated as foams in 32% (L-serine), 32% (D-serine), 21% (L-threonine), and 30% (D-threonine) yields. Cyclodehydration under Mitsunobu conditions with triphenylphosphine/iodine/diisopropylethylamine (DIEA) followed by flash chromatography yielded the benzyl-protected oxazole intermediates as foams in 85% (L-serine), 87% (D-serine), 56% (L-threonine), and 73% (D-threonine) yields.[13] In each case, the benzyl urethane, ether, and ester protecting groups were removed in a clean single hydrogenation step. Finally, intermediates were Nα-Fmoc protected providing reagent chemset **2**{*1*−*4*} isolated, following flash chromatography, as fully characterized compounds in **2**{*1*} (43%), **2**{*2*} (48%), **2**{*3*} (20%), and **2**{*4*} (50%) yields.

The solid-phase research was divided into two phases, the first of which was the efficient assembly of the N-terminal derivatized solid-phase bound chemset **4**{*1*−*4,1*−*4*}. Reagent chemset **2**{*1*−*4*} was loaded onto Rink amide derivatized multipin gears or crowns (1.2 μmole/gear or 5 μmole/crown),[14] through BOP/1-hydroxy benzotriazole hydrate (HOBt)/*N*-methylmorpholine (NMM) carboxyl activation in dimethylformamide (DMF). Three equivalent reagent excess for 16 h gave high-yield loading (as judged by quantitative Fmoc reading) with excellent purity at >98% (as judged by HPLC analysis of a trifluoroacetic acid (TFA)/Et_3SiH cleaved product). Following removal of Nα-Fmoc protection, gears/crowns were coupled with a series of Fmoc−amino acid pentafluorophenyl esters, reagent chemset **3**{*1*−*4*} which consisted of **3**{*1*} L-homo-*tert*-butylglycine, **3**{*2*} L-leucine, **3**{*3*} L-homoleucine, and **3**{*4*} L-norleucine. The first stage of solid-phase research was completed by subsequent removal of Nα-Fmoc protection and capping with 3-carboxyfuran pentafluorophenyl ester, providing chemset **4**{*1*−*4,1*−*4*} (Scheme 2).

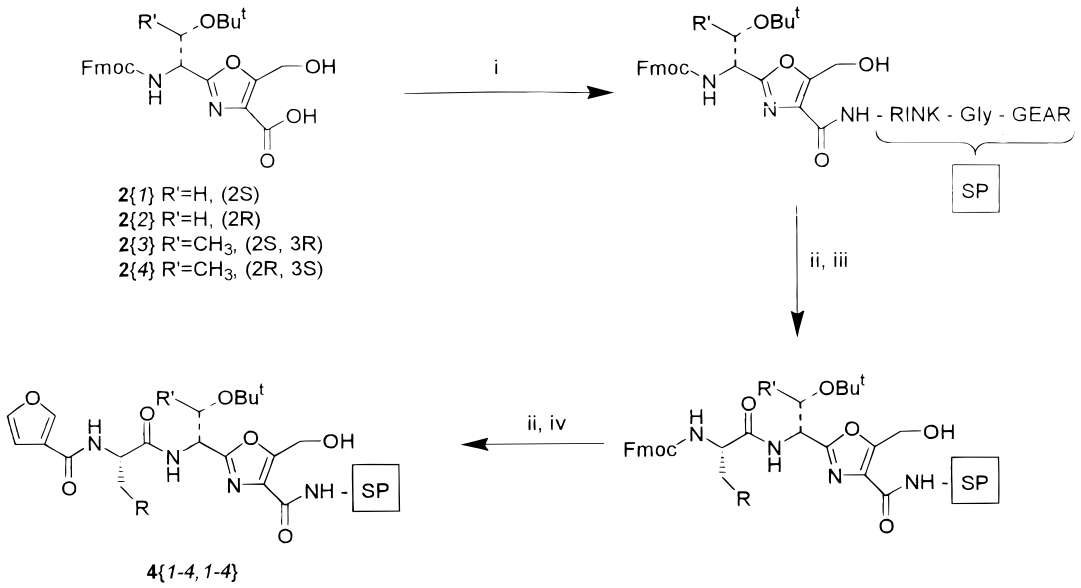
The simple high-fidelity methods illustrated in Scheme 2 stemmed from a detailed investigation. Because solid-phase chemistry traditionally involves forcing conditions in order to drive reactions to completion, a prudent starting point in

Scheme 1. Solution Preparation of Key Reagent Chemset **2**{*1*−*4*}[a]



[a] Reagents: (i) LiHMDS, THF, −78 °C, 2 h. (ii) Benzyloxyacetyl chloride. (iii) HCl/H_2O. (iv) Cbz-amino acid, isobutylchloroformate, THF, −20 °C, NMM. (v) Ph_3P, I_2, Et_3N, THF, −78 °C, 2−16 h. (vi) H_2/Pd/C. (vii) Fmoc-Cl (1.05 equiv), Na_2CO_3 (2.1 equiv), dioxan/H_2O.

Scheme 2. Solid-Phase Assembly of Core Reagent Chemset **4**{*1−4,1−4*}[a]



2{*1*} R'=H, (2S)
2{*2*} R'=H, (2R)
2{*3*} R'=CH_3, (2S, 3R)
2{*4*} R'=CH_3, (2R, 3S)

4{*1-4, 1-4*}

[a] Reagents: (i) 3 equiv reagent chemset **2**{*1−4*}/3 equiv BOP/3 equiv HOBt/6 equiv NMM in DMF o/n, *H*-RINK−Gly−GEAR. (ii) 20% Piperidine/DMF, 30 min. (iii) 5 equiv Fmoc-AA-Opfp, reagent chemset **3**{*1−4*},/5 equiv HOBt, DMF, o/n. (iv) 5 equiv 3-carboxyfuranpentafluorophenyl ester/5 equiv HOBt, DMF, o/n.

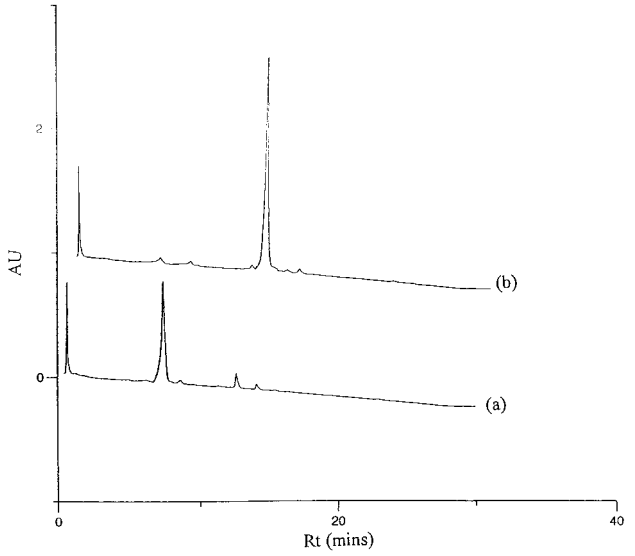


Figure 2. Analytical HPLC of crude product from Mitsunobu reaction. Conditions: Vydac C_4 (system 1) 10−90% B in A, 2−27 min, 1.5 mL/min, 215 nm UV, where solvent A = 0.1% aq TFA and solvent B = acetonitrile/10% A. (a) Chemset member **4**{*4,2*}, R_t = 7.94 min. (b) Aryl ether member **6**{*4,2,19*}, R_t = 13.97 min.

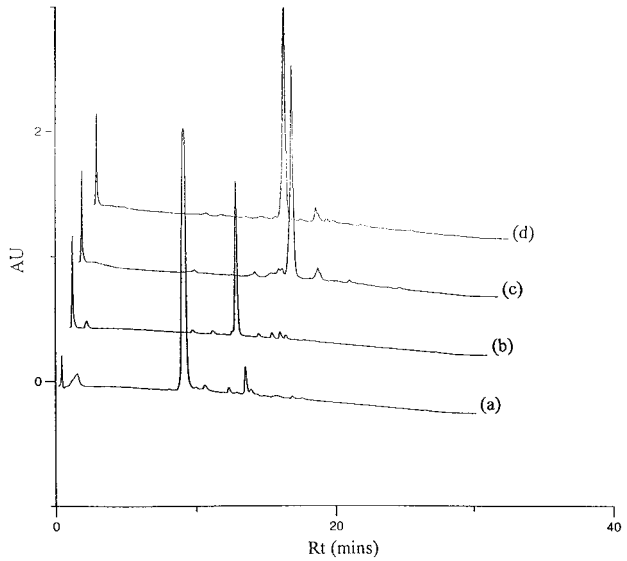
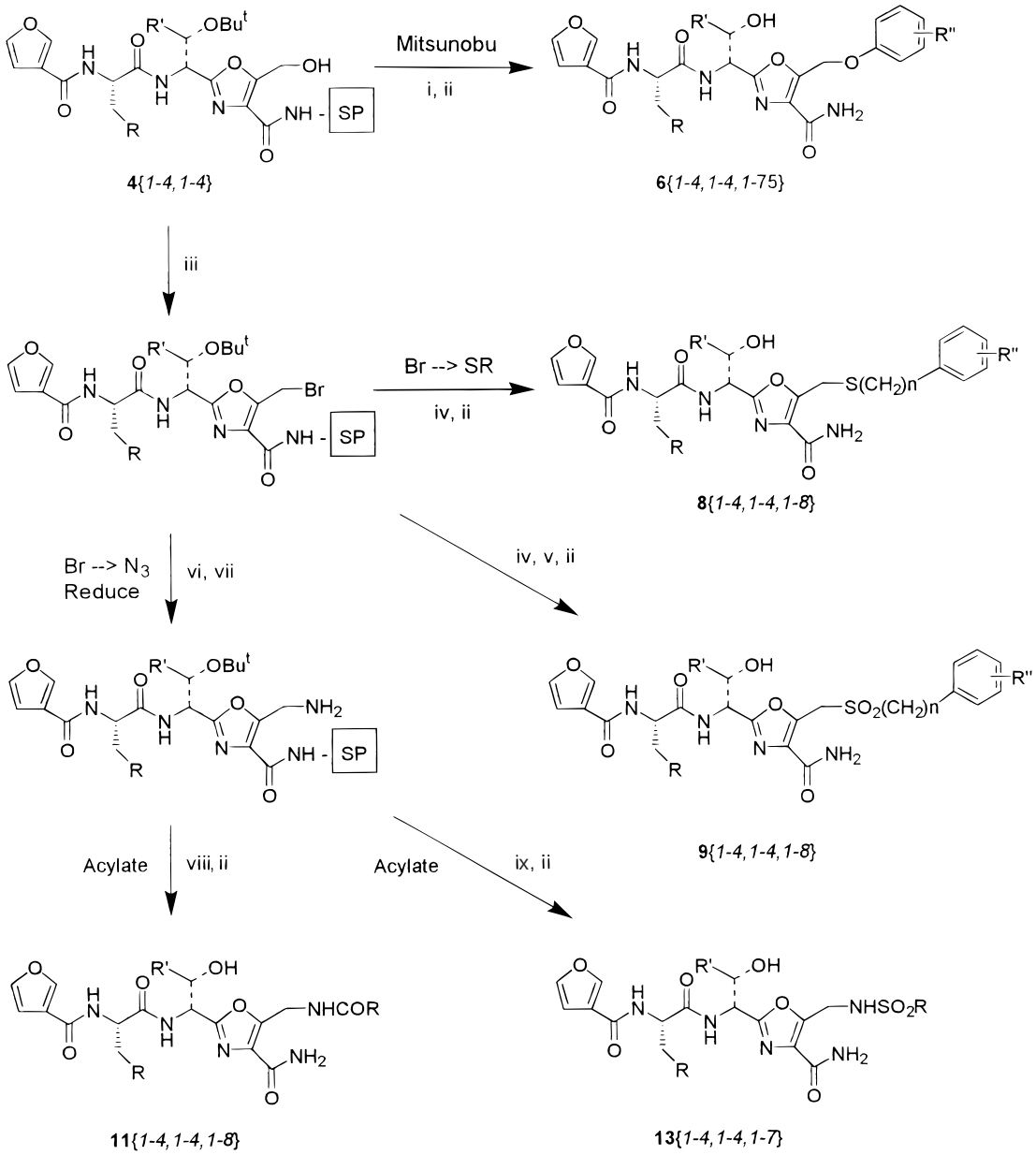


Figure 3. Analytical HPLC of crude intermediates to sulfide and sulfone analogues. Conditions: Vydac C_4 (system 1) 10−90% B in A, 2−27 min, 1.5 mL/min, 215 nm UV, where solvent A = 0.1% aq TFA and solvent B = acetonitrile/10% A. (a) Chemset member **4**{*1,1*}, R_t = 8.56 min. (b) Bromide analogue of **4**{*1,1*}, R_t = 11.84 min. (c) Alkyl sulfide member **8**{*1,1,4*}, R_t = 15.04 min. (d) Alkyl sulfone member **9**{*1,1,4*}, R_t = 13.68 min.

any scheme is the design of a building block containing maximal protection of potentially reactive functionalities. Thus, a large proportion of our initial investigation centered on protected analogues of reagent chemset **2**, in particular, analogues containing O-allyl ether protection of the hydroxyl group. These were prepared by a simple variation of Scheme 1, through the addition of allyloxyacetyl chloride to the glycine anion equivalent. The hydroxyl-protected analogues of **2** were used to generate O-allyl-protected analogues of **4**. Suprisingly, the seemingly simple removal of O-allyl protection to generate chemset **4** was never satisfactorily achieved, despite a wealth of existing literature supporting the clean and easy removal of allyl protection on solid phase.[15,16] These findings prompted our design and synthesis of reagent chemset **2** containing the free hydroxyl group. However, the use of **2** on solid phase provided an alternative problem. Use of the free acids of reagent chemset **3** and capping group (conditions under which the earlier O-allyl-protected analogues of **2** gave excellent crude O-allyl-protected analogues of chemset **4**) gave significant branching at the free hydroxyl during the acylation cycles, in some instances >50%. The branching problem was, however, virtually eliminated through the use of pentafluorophenyl active ester chemistry for the acylation cycles. Under these milder conditions, the crude quality of chemset **4**{*1−4,1−4*} was excellent at typically >90% (as judged by HPLC, e.g., Figure 2a and Figure 3a,

Scheme 3. Combinatorial Diversification of Chemset **4**{*1−4,1−4*}[a]



[a] Reagents: (i) DEAD, Ph_3P, triethylamine, phenol reagent chemset **5**{*1−75*}, 37 °C, o/n. (ii) 95% TFA/5% Et_3SiH, 90 min. (iii) CBr_4, PPh_3, DCM, RT, 1 h. (iv) NMP/thiol reagent chemset **7**{*1−8*},/DIEA (93:5:2, v/v/v), RT, o/n. (v) 3-chloroperoxybenzoic acid, DCM, RT, 1−3 days. (vi) NMP/H_2O (9:1), NaN_3 (50 equiv), DIEA (10 equiv), RT, o/n. (vii) 2 M DTT/1 M DIEA in DMF, 50 °C, 2 × 1 h. (viii) 10 equiv Carboxylic acid reagent chemset **10**{*1−8*},/10 equiv HBTU/10 equiv HOBt/20 equiv NMM in DMF o/n. (ix) 50 equiv Sulfonyl chloride reagent chemset **12**{*1−7*},/50 equiv DMAP, DMF, RT, o/n.

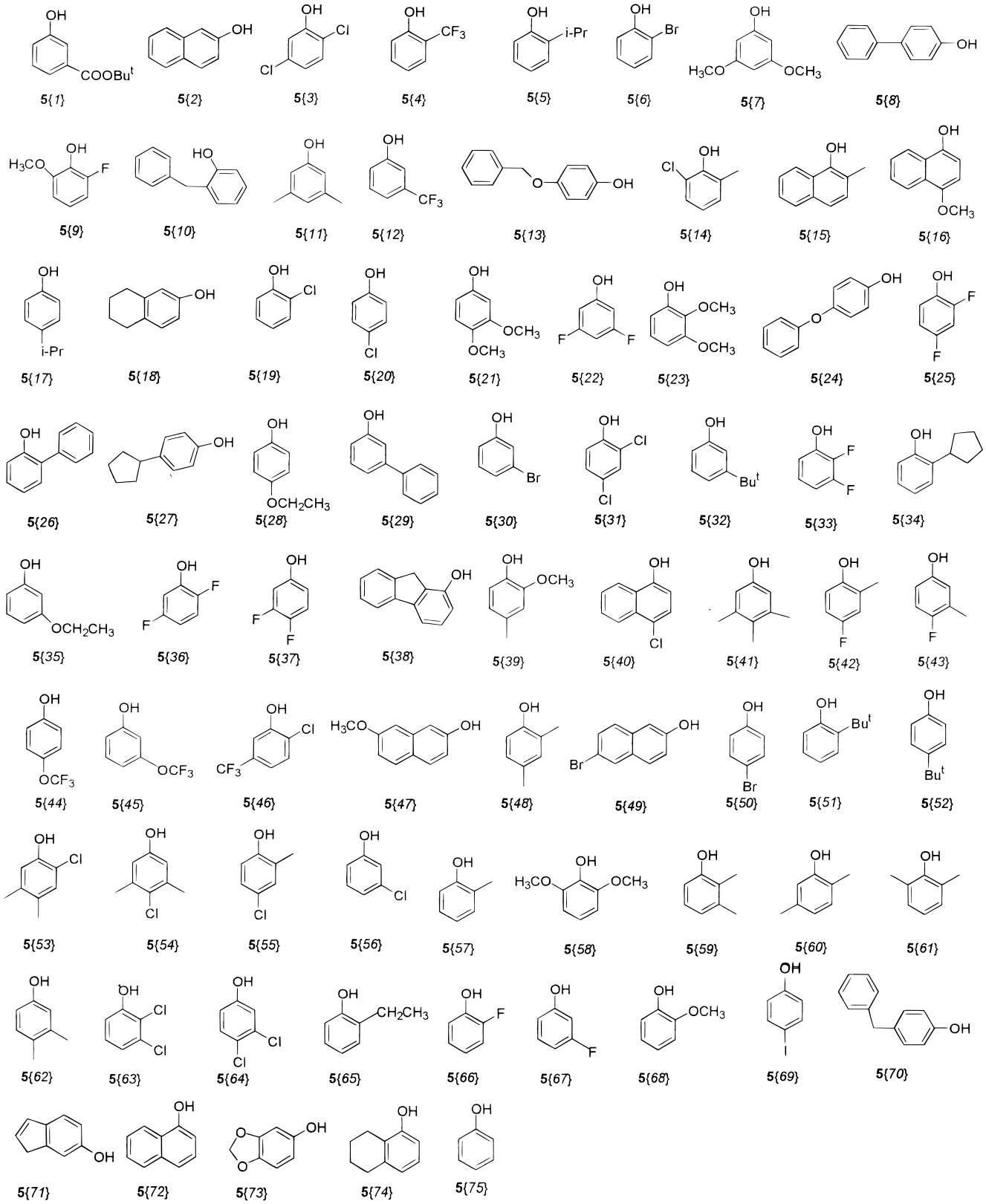
the later eluting minor impurity corresponded to trifluoroacetylated hydroxyl at M + 96, generated upon cleavage).

The second phase of the solid-phase research involved the optimization of a series of reactions that converted the free hydroxyl group of the oxazole core chemset **4**{*1−4,1−4*} into a multitude of functionalities. To date, five conversions have been optimized, which are summarized in Scheme 3 and discussed in detail individually.

Synthesis of Alkyl Aryl Ethers: 4 → 6. The Mitsunobu reaction, an intermolecular dehydration between an alcohol and an acidic component upon treatment with diethyl azodicarboxylate (DEAD) and triphenylphosphine (Ph_3P), is one of the most extensively used transformations in synthetic chemistry.[17] A number of studies have described the successful use of Mitsunobu chemistry on the solid phase, utilizing a phenol and primary alcohol to prepare alkyl aryl ethers.[18−20] Most existing reaction schemes describe the phenol as the solid-phase bound species, although Rano and Chapman have described high purity products commencing from both solid-phase bound phenol and primary alcohol.[21] The multicomponent nature of the Mitsunobu reaction provides a wide range of potential experimental variation such as reagent concentrations, order of addition, solvent, temperature, and reaction time. In addition, because different types of solid-phase support with various loadings have been used, it is not surprising that virtually all of the solid-phase experimental protocols described to date advocate different optimal reaction conditions.

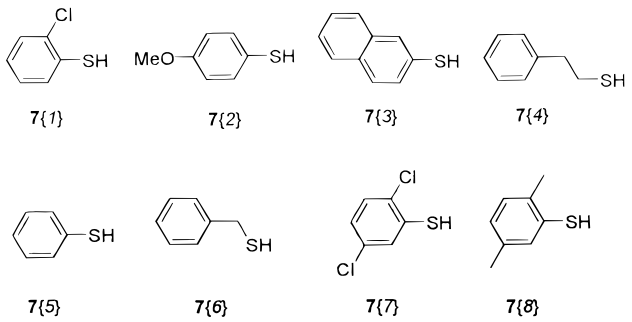
The present study sought to optimize the formation of ethers from multipin bound primary alcohol chemset **4**{*1−*

Chart 1



4,1−4} and solution phase phenol chemset **5**{*1−75*}. Many of our early experimental investigations gave poor quality crude products that were consistently contaminated by a side-product corresponding to addition of the DEAD reagent to the solid-phase primary alcohol (at +158 Da). However, this undesired reaction was eliminated following a thorough investigation concerning the order of addition and concentration of reagents. The optimal protocol for the test reaction, between **4**{*4,2*} and **5**{*19*}, involved the dropwise addition of DEAD (0.15 M in tetrahydrofuran (THF)) to Ph_3P (0.15 M in THF) followed by triethylamine (to give 0.225 M) and **5**{*19*} (0.15 M in THF). This reagent solution was then added

Chart 2



to solid-phase bound **4**{*4,2*} and heated at 37 °C for 16 h. Under these conditions, the crude quality of member **6**{*4,2,19*} was excellent at >90% purity by analytical HPLC (Figure 2b). Reagent chemset **5**{*1*−*75*} (Chart 1) contained phenols with a wide variety of electronic and stereochemical properties. Thus we were encouraged to find that the use of the optimal test conditions between an analogue of **4**{*3,4*}[22] and the full phenol chemset **5**{*1*−*75*} gave excellent crude products **6** in the majority of cases (each crude product was analyzed by analytical HPLC and electrospray mass spectra (ESMS) and gave essentially a single main peak at >90%). The main exceptions in general contained a bulky alkyl group ortho to the hydroxyl; **6**{*3,4,5*} (<20%), **6**{*3,4,34*} (<25%), **6**{*3,4,41*} (<20%), **6**{*3,4,48*} (<20%), **6**{*3,4,51*} (<10%), and **6**{*3,4,65*} (<30%). A number of other products were of a medium quality with the desired material present at approximately 50%, **6**{*3,4,13*}, **6**{*3,4,28*}, **6**{*3,4,71*}, and **6**{*3,4,74*}.

Synthesis of Thioethers: 4 → 8. The conversion of alcohol to thioether under Mitsunobu conditions has been previously described in solution[23] but not on solid phase. Despite a wide-ranging investigation of reaction parameters, we never satisfactorily achieved Mitsunobu reaction between chemset **4** and reagent chemset **7** (Chart 2). Poor quality crude products that were consistently contaminated by the addition of the DEAD reagent to the solid-phase primary alcohol were observed, under all variations of reaction conditions investigated. Thus, an alternative strategy was employed for the synthesis of thioethers.

Recently, Mayer et al.[24] described the conversion of serinyl side chain hydroxyl to bromide, followed by intramolecular displacement of bromide with cysteinyl thiol, while investigating the solid-phase preparation of lanthionines. A modification of the general experimental procedures described proved very successful in the current studies. Controlled addition of a solution of CBr_4 (0.05 M in dichloromethane (DCM)) to Ph_3P (0.1 M in DCM) provided a reaction mixture that quantitatively converted chemset **4** to the corresponding bromides in 1 h (Scheme 3). In each case, the quality of crude bromide was excellent as judged by HPLC (Figure 3b) and ESMS analysis.[25] The bromide analogues of chemset **4** provided versatile intermediates for the preparation of thioethers. Overnight treatment with a solution of *N*-methylpyrrolidone/thiol reagent chemset **7**{*1*−*8*}/DIEA (93:5:2, v/v/v) smoothly converted bromides to a range of alkyl and aryl thioethers **8**{*1,1,1*−*8*}, with excellent crude quality (e.g., Figure 3c).

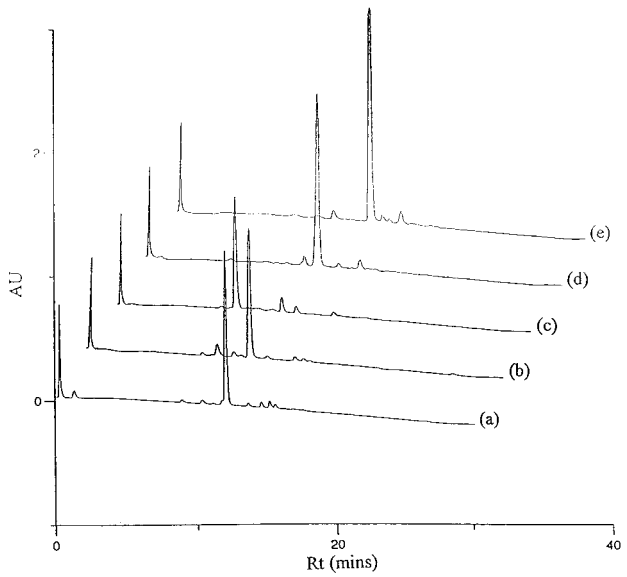


Figure 4. Analytical HPLC of crude intermediates to carboxamide and sulfonamide analogues. Conditions: Vydac C_4 (system 1) 10−90% B in A, 2−27 min, 1.5 mL/min, 215 nm UV, where solvent A = 0.1% aq TFA and solvent B = acetonitrile/10% A. (a) Bromide analogue of **4**{*1,1*}, R_t = 11.84 min. (b) Azide analogue of **4**{*1,1*}, R_t = 11.48 min. (c) Amine analogue of **4**{*1,1*}, R_t = 8.41 min. (d) Carboxamide member **11**{*1,1,1*}, R_t = 12.25 min. (e) Sulfonamide member **13**{*1,1,1*}, R_t = 13.93 min.

Synthesis of Sulfones: 8 → 9. Many reagents are described in the literature for the oxidation of a sulfide to sulfone. In the present studies, we found that oxidation of multipin bound sulfides **8**{*1,1,1*−*8*} proceeded in high yield and purity, by simple treatment with a solution of 5 equiv of *m*-chloroperbenzoic acid (mCPBA) in DCM for 16 h (e.g., Figure 3d). The only exceptions were the oxidation of solid-phase bound 2-chlorophenylsulfides and 2,5-dichlorophenylsulfides **8**{*1,1,1*} and **8**{*1,1,7*} which required extended reaction times for 48 and 72 h, respectively, for full oxidation.

Synthesis of Carboxamides: 4 → 11. The bromide analogues of chemset **4** described previously, provided versatile intermediates for the preparation of carboxamides. The bromides were readily converted to the corresponding azide analogues by treatment with a solution of sodium azide (50 equiv)/DIEA (10 equiv) in *N*-methyl pyrrolidine (NMP)/H_2O (9:1, v/v) at room temperature (RT) for 16 h (e.g., Figure 4b, azide analogue of **4**{*1,1*}). The azides were subsequently reduced to the corresponding amines by repeat treatment with a solution of 2 M dithiothreitol (DTT)/1 M DIEA in DMF at 50 °C for 45 min (e.g., Figure 4c).[26] The amine analogues of chemset **4** were acylated by a range of alkyl and aryl carboxylic acids and anhydrides, reagent chemset **10** (Chart 3), to yield high-quality crude carboxamides in all of the examples examined (e.g., Figure 4d, **11**{*1,1,1*}).

Synthesis of Sulfonamides: 4 → 13. We previously found that the general preparation of sulfonamides by N-acylation of multipin bound amines requires forcing reaction conditions.[27] Typically 50 equiv of sulfonyl chloride with 50 equiv of *N,N*-dimethylaminopyridine in DMF for 16 h are required to effect quantitative acylation. Using these general condi-

Chart 3

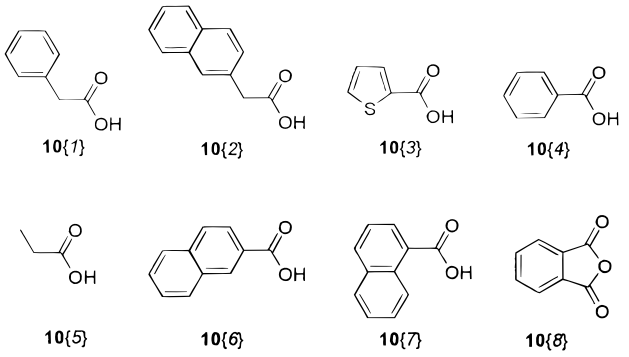
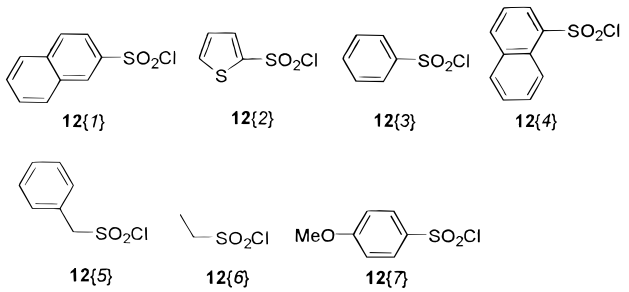


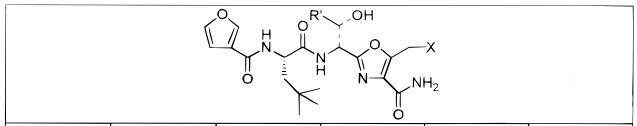
Chart 4



tions, the amine analogues of chemset **4** described previously were acylated by a range of alkyl and aryl sulfonyl chlorides: reagent chemset **12** (Chart 4). The general quality of crude aryl sulfonamides **13** was excellent at >90% (e.g., Figure 4e, **13**{*1,1,1*}). However, the alkyl sulfonamides were of a poorer quality crude as judged by HPLC at **13**{*1,1,5*} (51.1%) and **13**{*1,1,6*} (39.2%).

Characterization of Compounds 1−20. The relationship between structure and activity (SAR) for a compound series in a given biological assay represents a cornerstone of drug development. Therefore, when screening a large array of molecules, confidence in both the *qualitative* and *quantitative* aspects of the combinatorial synthesis are required. In many instances, here being a typical example, arrays of molecules are initially prepared on a sub-milligram scale. This small synthetic scale often provides ample material for many biological assays at an economical cost, but has the disadvantage that parallel purification and accurate quantification are problematic.[28] Thus, an important aspect of the current investigation was a confirmation that the screening results obtained for crude molecules enabled the most active molecules to be identified with confidence. Because each crude molecule was obtained from the closely related analogues, chemset **4**, through a common linker, any variation in crude/purified activity data could be attributed to a facet of the modification chemistry. Thus, a series of 20 compounds, exemplifying each of the five modifications described, were reprepared on a 10−20 mg crude scale, purified, and fully characterized (Table 1). Biological assay (detailed results to be presented elsewhere) showed that nonside chain functionalized chemset **4** {*1−4,1*} (IC_{50} 100−150 μM), when converted to compounds 1−20, gave protease inhibitors with IC_{50} 1.6−70.3 μM. These values represent a maximum of 2-fold variation in potency between the crude and purified materials, highlighting the quality of crude

Table 1. Synthetic Scale-Up and Purification of Compounds **1−20**



X P1	-O-R	-S-R	$-SO_2R$	-NHCOR	$-NHSO_2R$
 4{*1,1*}	**6**{*1,1,4*} 19.85, 567.1 10.3 (3.5)	**8**{*1,1,4*} 19.78, 543.1 17.7 (1.5)	**9**{*1,1,4*} 18.47, 575.1 7.4 (7.3)	**11**{*1,1,4*} 16.80, 526.1 9.6 (3.4)	**13**{*1,1,4*} 17.92, 612.2 21.9 (1.9)
 4{*2,1*}	**6**{*2,1,3*} 19.95, 567.2 18.2 (6.0)	**8**{*2,1,3*} 20.06, 565.2 16.9 (6.7)	**9**{*2,1,3*}*	**11**{*2,1,3*} 16.29, 532.2 18.0 (3.0)	**13**{*2,1,3*} 17.06, 562.1 12.1 (1.4)
 4{*3,1*}	**6**{*3,1,1*}*	**8**{*3,1,1*} 19.62, 563.2 6.5 (3.2)	**9**{*3,1,1*} 17.75, 595.2 5.6 (2.1)	**11**{*3,1,1*} 17.16, 554.2 19.1 (1.8)	**13**{*3,1,1*} 18.90, 626.2 10.1 (6.9)
 4{*4,1*}	**6**{*4,1,2*} 20.53, 563.1 19.2 (6.8)	**8**{*4,1,2*} 18.81, 559.1 22.7 (6.5)	**9**{*4,1,2*} 17.69, 591.1 19.9 (4.6)	**11**{*4,1,2*} 19.09, 604.1 16.0 (1.4)	**13**{*4,1,2*} 17.09, 582.1 18.2 (2.5)

Analytical data for compounds **1**−**20**: member, HPLC (system 2) R_t (min), observed ESMS $[M + H]^+$, yield (mg) crude (purified). Recovery yields are variable primarily due to low solubility in aqueous acetonitrile. * Materials were lost during automated analysis and purification.

products and high fidelity of the modification chemistry described. Placed into perspective, when screening large crude libraries such a variation enables compound groups differing by approximately 1 log unit activity (∼50 nM from ∼500 nM from ∼5 μM from ∼50 μM, etc.) to clearly be distinguished with confidence.

Conclusions

Synthetic strategies for the diversification of a 5-(hydroxymethyl)oxazole scaffold into aryl ethers, thioethers, sulfones, sulfonamides, and carboxamides on the solid phase were developed. A comparison of 20 fully characterized resynthesized compounds, with their crude counterparts, highlighted the excellent qualitative and quantitative nature of the crude materials produced. The modifications described use readily synthesized core scaffolds and commonly available reagents such as alcohols, thiols, carboxylic acids, and sulfonyl chlorides. Given the enormous availability of these common reagents, the combinatorial chemistry described here could conceivably be used for the preparation of millions of oxazole analogues and probably adapted for use with many other heterocyclic scaffolds.

Experimental Section

Unless otherwise specified, all solvents and reagents were obtained from commercial suppliers and used without further purification. DMF and acetonitrile were super purity grade solvents from ROMIL Ltd., Waterbeach, Cambridge, U.K. Polystyrene and polypropylene 96-well plates were obtained from Beckman Instruments, Fullerton, CA. Two milliliter screw-cap vials were obtained from CamLab Ltd., Nuffield Road, Cambridge, U.K. Gears and crowns were obtained from Chiron UK Ltd., Salamander Quay West, Harefield, U.K. General peptide synthesis reagents were obtained from Calbiochem-Novabiochem, U.K. Analytical HPLCs were obtained using an automated Gilson 215/233XL. A gradient of 10−90% B in A, 2−27 min, 1.5 mL/min, where solvent

A was 0.1% aq TFA and solvent B was acetonitrile/10% A, with UV detection at 215 nm, was used unless otherwise stated. HPLC samples were run on a Vydac C_4 250 × 4.6 mm (system 1) or Phenomenex Jupiter C_4 (5 μ) 250 × 4.6 mm (system 2) analytical columns. Samples were purified on an automated Gilson 215/233XL, using Vydac C_4 250 × 10 mm semiprep column. HPLC-ESMS analysis was conducted through Hewlett-Packard HP1050 auto-injection onto a Phenomenex Columbus C_8 5 μ, 50 × 2.0 mm column, employing a gradient of 10−100% B in A over 10 min, 250 μL/min, where solvent A was 0.1% aq TFA and solvent B was acetonitrile/10% A, with UV detection at 215 nm. Sample flow from the column was diverted to a SEDEX 55 residue analyzer and a Fisons/VG platform mass spectrometer (*m*/*z*) (electrospray positive, ESP^+). The University of Cambridge Spectrometry Service recorded high-resolution mass spectroscopy (HRMS) mass spectra (*m*/*z*) (ESP^+) using a Q-TOF Micromass spectrometer. The University of Cambridge NMR Department recorded nuclear magnetic resonance (NMR) spectra at the field strength in the solvents indicated, using standard pulse sequences on a DRX-500 machine. Chemical shifts are expressed in parts per million (δ) and are referenced to residual signals of the solvent. Coupling constants (*J*) are expressed in Hz. Thin-layer chromatography (TLC) was performed on precoated plates (Merck aluminum sheets silica 60 F254, art. no. 5554). Visualization of compounds was achieved by illumination under ultraviolet light (254 nm) or using an appropriate dyeing reagent. Flash column chromatography was performed on silica gel 60 (Merck 9385).

1. General Synthesis of Building Blocks. (a) 2-Amino-4-benzyloxy-3-oxobutyric Acid Benzyl Ester Hydrochloride. *N*-(Diphenylmethylene)glycine benzyl ester (20.00 g) was prepared from glycine benzyl ester (20.00 g, 0.059 mol) dissolved in dichloromethane (600 mL) to which benzophenone imine (11.82 g, 10.94 mL, 0.065 mol) was added and stirred at RT for 18 h. The suspension was washed with water (3 × 500 mL), dried (Na_2SO_4), and concentrated in vacuo, and the residue (19.70 g) was used without further purification. To a solution of *N*-(diphenylmethylene)glycine benzyl ester (19.70 g, 0.059 mol) in THF (200 mL) at −78 °C, was added Li−hexamethyldisilane (HMDS) (10.02 g, 59.9 mL of 1 M solution in THF, 0.059 mol) and stirred at −78 °C for 1 h. The solution was transferred via cannula to a solution of phenylmethoxyacetyl chloride (11.05 g, 0.059 mol) in THF (200 mL) at −78 °C. Once the addition was complete, the reaction mixture was allowed to warm to RT for 2 h. The reaction mixture was then quenched with 2 M HCl (500 mL) and allowed to stir at RT for 1 h. The THF was removed in vacuo and the resultant aqueous phase extracted with EtOAc (2 × 20 mL). The organic phase was re-extracted with 2 M HCl (2 × 20 mL) then discarded, the combined aqueous phases were concentrated in vacuo, and the hydrochloride salt was used directly without further purification. Analytical HPLC (system 2) R_t = 16.0 min (95%), ESMS 314 $[M + H]^+$.

(b) 4-Benzyloxy-2*S*-(2-benzyloxycarbonylamino-3-*tert*-butoxy-propionylamino)-3-oxo-butyric Acid Benzyl Ester. Cbz-L-Ser(tBu)-OH (4.22 g, 0.014 mol) in THF (500 mL) at −20 °C, was treated with NMM (1.45 g, 1.57 mL, 0.014 mol), followed by the dropwise addition of isobutylchloroformate (1.95 g, 1.86 mL, 0.014 mol). The reaction mixture was stirred at −20 °C for 1 h, then the cooling bath was removed, and 2-amino-4-benzyloxy-3-oxobutyric acid benzyl ester hydrochloride salt (5.00 g, 0.014 mol) in DMF (50 mL) was added. NMM (1.56 g, 1.69 mL, 0.015 mol) was then added dropwise via syringe pump to the reaction mixture for 1 h. Once the addition was complete, the reaction was stirred at RT for an additional hour and then the solvents were removed in vacuo. The residue was dissolved in EtOAc (150 mL) and washed with saturated $NaHCO_3$ solution (50 mL), 0.5 M citric acid (50 mL), and brine (50 mL), and then dried (Na_2SO_4) and concentrated in vacuo. Purification by flash column chromatography [heptane/EtOAc 75:25 to 50:25, gradient] gave a foam (2.70 g, 32%), TLC R_f 0.13 (heptane/EtOAc 70:30), ESMS 591 $[M + H]^+$.

Analogous methodology afforded 4-benzyloxy-2*R*-(2-benzyloxycarbonylamino-3-*tert*-butoxy-propionylamino)-3-oxo-butyric acid benzyl ester (32%), TLC R_f 0.10 (heptane/EtOAc 75:25), ESMS 591 $[M + H]^+$; 4-benzyloxy-2*S*-(2-benzyloxycarbonylamino-3*R*-*tert*-butoxy-butyrylamino)-3-oxo-butyric acid benzyl ester (21%), TLC R_f 0.14 (heptane/EtOAc 75:25), ESMS 605 $[M + H]^+$; 4-benzyloxy-2*R*-(2-benzyloxycarbonylamino-*3S*-*tert*-butoxy-butyrylamino)-3-oxo-butyric acid benzyl ester (30%), TLC R_f 0.14 (heptane/EtOAc 70:30), ESMS 605 $[M + H]^+$.

(c) 2-(1*S*-Benzyloxycarbonylamino-2-*tert*-butoxyethyl)-5-benzyloxymethyloxazole-4-carboxylic Acid Benzyl Ester. To a solution of triphenylphosphine (2.88 g, 0.011 mol), iodine (2.32 g, 0.009 mol), and triethylamine (1.76 g, 2.42 mL, 0.017 mol) in THF (50 mL) at −78 °C was added 4-benzyloxy-2*S*-(2-benzyloxycarbonylamino-3-*tert*-butoxy-propionylamino)-3-oxobutyric acid benzyl ester (2.70 g, 0.0046 mol) in THF (30 mL) dropwise. The reaction was complete after 2 h at −60 °C, by HPLC. Water (10 mL) was added, and the reaction was allowed to warm to RT and concentrated in vacuo. The residue was dissolved in DCM (100 mL) and washed with saturated $NaHCO_3$ solution (30 mL), 0.5 M citric acid (30 mL), and brine (30 mL), and then dried (Na_2SO_4) and concentrated in vacuo. Purification by flash column chromatography [heptane/EtOAc 70:30] gave a foam (2.22 g, 85%), TLC R_f 0.21 (heptane/EtOAc 75:25), ESMS 573 $[M + H]^+$.

Analogous methodology afforded foams 2-(1*R*-benzyloxycarbonylamino-2-*tert*-butoxyethyl)-5-benzyloxymethyl-oxazole-4-carboxylic acid benzyl ester (87%), TLC R_f 0.21 (heptane/EtOAc 70:30), ESMS 573 $[M + H]^+$; 2-(1*S*-benzyloxycarbonylamino-2*R*-*tert*-butoxypropyl)-5-benzyloxymethyl-oxazole-4-carboxylic acid benzyl ester (56%), TLC R_f 0.21 (heptane/EtOAc 75:25), ESMS 587 $[M + H]^+$; 2-(1*R*-benzyloxycarbonylamino-2S-tert-butoxypropyl)-5-benzyloxymethyl-oxazole-4-carboxylic acid benzyl ester (73%), TLC R_f 0.19 (heptane/EtOAc 75:25), ESMS 587 $[M + H]^+$.

(d) Chemset 2{*1*}, 2-[2-*tert*-Butoxy-1*S*-(9H-fluoren-9-ylmethoxycarbonylamino)ethyl]-5-hydroxymethyl-oxazole-4-carboxylic Acid. Benzyl-protected oxazole (0.520 g, 0.91 mmol) was dissolved in ethanol (50 mL) and 10% palladium on carbon (0.200 g) was added; the system was then

evacuated and hydrogen was introduced. After vigorous stirring at RT overnight, deprotection was complete by HPLC and ESMS analysis. The reaction mixture was filtered and the catalyst washed with ethanol (500 mL). The combined washings were concentrated in vacuo and the residue was used without purification. The fully deprotected residue (0.230 g, 0.89 mmol) was dissolved in dioxane (7 mL), Na_2CO_3 (0.208 g, 1.96 mmol, 10 mL in H_2O) was added, and the reaction mixture was cooled to 0 °C with stirring. 9-Fluorenylmethyl chloroformate (0.254 g, 0.98 mmol) was added dropwise over 45 min and stirring continued until the reaction was complete by HPLC (2−4 h). Diethyl ether (100 mL) was added and the mixture was acidified to pH 3 with 0.1 M HCl. The diethyl ether was removed and the aqueous layer was extracted with ether (2 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried, ($MgSO_4$), and concentrated in vacuo. Purification by flash column chromatography [chloroform/methanol 100:0 to 95:5, gradient] gave a white foam (0.42 g, 43%). Analytical HPLC (system 1) R_t = 15.14 min (>98%), TLC R_f 0.10 (chloroform/methanol 90:10), HRMS $C_{26}H_{28}O_7N_2Na$ requires *M*, 503.1794, found: MNa^+, 503.1789 (δ − 1.1 ppm), δ_H (500 MHz; DMSO-d_6 at 373 K) 1.12 (9H, s, NHCHCH$_2$OC(C*H*$_3$)$_3$), 3.66 (1H, br m, NHCHC*H*$_{2A}$OC(CH$_3$)$_3$), 3.73 (1H, br m, NHCHC*H*$_{2B}$OC(CH$_3$)$_3$), 4.24 (1H, br m, C*H*CH$_2$OC(O)NH), 4.33 (2H, br m, CHC*H*$_2$OC(O)NH), 4.67 (2H, br s, C*H*$_2$OH), 4.81 (1H, br m, NHC*H*CH$_2$OC(CH$_3$)$_3$), 7.33 (2H, br m, 2 × H-3 Fmoc), 7.40 (2H, br m, 2 × H-4 Fmoc), 7.67 (2H, br m, 2 × H-2 Fmoc), 7.81 (1H, d, *J* 7, N*H*CHCH$_2$OC(CH$_3$)$_3$), and 7.85 (2H, br m, 2 × H-5 Fmoc).

Analogous methodology afforded chemset **2**{*2*}, 2-[2-*tert*-butoxy-1*R*-(9H-fluoren-9-ylmethoxycarbonylamino)ethyl]-5-hydroxymethyl-oxazole-4-carboxylic acid (48%), analytical HPLC (system 1) R_t = 15.16 min (>97%), TLC R_f 0.10 (chloroform/methanol 90:10), HRMS $C_{26}H_{28}O_7N_2Na$ requires *M*, 503.1794, found: MNa^+, 503.1815 (δ + 4.4 ppm), δ_H (500 MHz; DMSO-d_6 at 373 K) 1.12 (9H, s, NHCHCH$_2$OC(CH$_3$)$_3$), 3.66 (1H, dd, *J* 9.5 and 6.5, NHCHC*H*$_{2A}$OC(CH$_3$)$_3$), 3.73 (1H, dd, *J* 9.5 and 6, NHCHC*H*$_{2B}$OC(CH$_3$)$_3$), 4.24 (1H, t, *J* 7, C*H*CH$_2$OC(O)NH), 4.31 (1H, dd, *J* 10.5 and 7, CHC*H*$_{2A}$OC(O)NH), 4.35 (1H, dd, *J* 10.5 and 7, CHC*H*$_{2B}$OC(O)NH), 4.67 (2H, s, C*H*$_2$OH), 4.81 (1H, ddd, *J* 7, 6.5 and 6, NHC*H*CH$_2$OC(CH$_3$)$_3$), 7.33 (2H, br m, 2 × H-3 Fmoc), 7.40 (2H, br m, 2 × H-4 Fmoc), 7.67 (2H, dd, *J* 7.5 and 3, 2 × H-2 Fmoc), 7.81 (1H, d, *J* 7, N*H*CHCH$_2$OC(CH$_3$)$_3$), and 7.85 (2H, br m, 2 × H-5 Fmoc).

Chemset **2**{*3*}, 2-[2*R*-*tert*-butoxy-1*S*-(9H-fluoren-9-ylmethoxycarbonylamino)propyl]-5-hydroxymethyl-oxazole-4-carboxylic acid (20%), analytical HPLC (system 1) R_t = 15.79 min (>99%), TLC R_f 0.15 (chloroform/methanol 95:5), HRMS $C_{27}H_{30}O_7N_2Na$ requires *M*, 517.1951, found: MNa^+, 517.1974 (δ + 4.6 ppm), δ_H (500 MHz; DMSO-d_6 at 373 K) 1.07 (12H, m, NHCHCH$_2$OC(C*H*$_3$)$_3$ and NHCHCH(C*H*$_3$)OC(CH$_3$)$_3$), 4.04 (1H, br m, NHCHC*H*(CH$_3$)OC(CH$_3$)$_3$), 4.23 (1H, br m, C*H*CH$_2$OC(O)NH), 4.35 (2H, br m, CHC*H*$_2$OC(O)NH), 4.67 (2H, s, C*H*$_2$OH), 4.73 (1H, br m, NHC*H*CH(CH$_3$)$_2$OC(CH$_3$)$_3$), 7.31 (2H, br m, 2 × H-3 Fmoc), 7.40 (2H, br m, 2 × H-4 Fmoc), 7.67 (2H, dd, *J* 7.5 and 3, 2 × H-2 Fmoc), 7.81 (1H, d, *J* 7.5, N*H*CHCH$_2$OC(CH$_3$)$_3$), and 7.85 (2H, br m, 2 × H-5 Fmoc).

Chemset **2**{*4*}, 2-[2*S*-*tert*-butoxy-1*R*-(9H-fluoren-9-ylmethoxycarbonylamino)propyl]-5-hydroxymethyl-oxazole-4-carboxylic acid (50%), analytical HPLC (system 1) R_t = 16.01 min (>99%), TLC R_f 0.18 (chloroform/methanol 95:5), HRMS $C_{27}H_{30}O_7N_2Na$ requires *M*, 517.1951, found: MNa^+, 517.1957 (δ + 1.2 ppm), δ_H (500 MHz; DMSO-d_6 at 373 K) 1.06 (9H, s, NHCHCH$_2$OC(C*H*$_3$)$_3$), 1.10 (3H, d, *J* 5, NHCHCH(C*H*$_3$)OC(CH$_3$)$_3$), 4.06 (1H, br m, NHCHC*H*(CH$_3$)OC(CH$_3$)$_3$), 4.23 (1H, t, *J* 7, C*H*CH$_2$OC(O)NH), 4.32 (1H, dd, *J* 10.5 and 7, CHC*H*$_{2A}$OC(O)NH), 4.37 (1H, dd, *J* 10.5 and 7, CHC*H*$_{2B}$OC(O)NH), 4.67 (2H, s, C*H*$_2$OH), 4.73 (1H, br m, NHC*H*CH(CH$_3$)$_2$OC(CH$_3$)$_3$), 7.31 (2H, br m, 2 × H-3 Fmoc), 7.40 (2H, br m, 2 × H-4 Fmoc), 7.67 (2H, dd, *J* 7.5 and 3, 2 × H-2 Fmoc), 7.81 (1H, d, *J* 7.5, N*H*CHCH$_2$OC(CH$_3$)$_3$), and 7.85 (2H, br m, 2 × H-5 Fmoc).

2. Synthesis of Pentafluorophenyl Esters. (a) Chemset 3{*1*}, Fmoc-L-*β*-*tert*-butylalanine Pentafluorophenyl Ester. Fmoc-L-*β*-*tert*-butylalanine (5.0 g, 13.6 mmol) and pentafluorophenol (2.76 g, 15.0 mmol, 1.1 equiv) were dissolved in dry THF (100 mL), ice-cooled, and stirred. Dicyclohexylcarbodiimide (2.95 g, 14.3 mmol, 1.05 equiv) in dry THF (25 mL) was added dropwise over 10 min and the solution was left stirring overnight. The precipitated urea was filtered, washed with THF (3 × 20 mL), and the combined THF was concentrated in vacuo to give a pale yellow oily solid. The solid was purified by flash chromatography (loading and eluting with chloroform) to yield a white solid (6.4 g, 88.2%), HPLC (system 1) R_t = 23.55 min (97%).

(b) Chemset 3{*3*}, Fmoc-L-*homo*leucine Pentafluorophenyl Ester. Prepared from Fmoc-L-*homo*leucine on the scale and method described above to give a white solid (6.9 g, 95.1%), HPLC (system 1) R_t = 23.78 min (98%).

(c) Chemset 3{*2*}, Fmoc-L-leucine pentafluorophenyl ester and chemset 3{*4*}, Fmoc-L-*nor*leucine pentafluorophenyl ester were commercially available.

(d) 3-Carboxyfuran Pentafluorophenyl Ester. Prepared from furan-3-carboxylic acid on the scale employing the method described above to give a clear gel that solidified upon storage (3.25 g, 85.5%), HPLC (system 1) R_t = 17.29 min (98%).

3. General Solid-Phase Techniques. All solid-phase syntheses were performed using the Chiron Technologies multipin kit. This consisted of a standard 8 × 12 pin holder containing 96 pin stems to which gears or crowns are reversibly attached, providing a reactive polymer surface upon which the growing molecule is anchored during solid-phase synthesis. Each gear/crown (the equivalent of the peptide-resin in standard solid-phase synthesis) can be considered to be an independent reactor because synthesis is performed in the 1 mL wells of a standard 96-well plate. Each well, and thus each gear/crown, may be charged with a unique set of reagents providing spatially addressed unique sequences. Common steps such as washing or removal of Nα protecting groups can be performed concomitantly.

(a) Preparation of Multipin Assembly. The appropriately derivitized gears/crowns are assembled (simply clipped) onto

stems and slotted into the 8 × 12 stem holder in the desired pattern for synthesis.

(b) Removal of Nα-Fmoc Protection. A 250 mL solvent-resistant bath was charged with 200 mL of a 20% piperidine/DMF solution. The multipin assembly was added and deprotection left for 30 min. The assembly was then removed and excess solvent was removed by brief shaking. The assembly was washed consecutively with (200 mL each) DMF (3 × 3 min) and CH_3CN (3 × 3 min), and then briefly dried in vacuo.

(c) Quantitative UV Measurement of Fmoc Chomophore Release. A 1 cm path length UV cell was charged with 1.2 mL of a 20% piperidine/DMF solution and used to zero the absorbance of the UV spectrometer at a wavelength of 290 nm. A UV standard was then prepared consisting of 3.2 mg Fmoc−Asp(OBut)−Pepsyn KA (0.08 mmol/g) in 2.0 mL of a 20% piperidine/DMF solution. This standard gave $Abs_{290} = 0.55-0.65$ (at RT). An aliquot of the multipin deprotection solution was then diluted as appropriate to give a theoretical $Abs_{290} = 0.6$. This value, compared with the experimental value, provided a calculation of the loading of Fmoc per gear/crown.

(d) Coupling Reactions. The appropriate pentafluorophenyl esters (5 equiv calculated from the loading of each gear/crown to be coupled) and HOBt (5 equiv) were dissolved in the appropriate volume of DMF (200 μL for each gear and 500 μL for each crown) and left for 5 min. The coupling solution(s) were then pipetted into the individual wells of the 96-well plate, in the required pattern for a particular round of coupling. The mounted gear/crown assembly was then added and the reaction was left overnight. If the removal of Nα-Fmoc protection was the next step, the assembly was washed with DMF (2 × 3 min). Alternatively, if synthesis had concluded and the next stage was cleavage, the assembly was washed consecutively with (200 mL each) DMF (3 × 3 min) and CH_3CN (3 × 3 min) and then briefly dried in vacuo.

(e) Acidolytic Mediated Cleavage of Multipin Assembly. Appropriate wells of a polystyrene 96-well plate (1 mL/well) were charged with a trifluoroacetic acid/Et_3SiH (95:5, v/v, 250 μL per gear or 500 μL per crown) cleavage solution, in a pattern corresponding to that of the multipin assembly to be cleaved. The assembly was added, then the entire construct was covered in tin foil and left for 2 h. The assembly was removed, then added to a second polystyrene 96-well plate (1 mL/well) containing trifluoroacetic acid/Et_3SiH (as above) for 5 min. The primary cleavage plate (2 h cleavage) and the secondary plate (5 min wash) were then placed in a GeneVac drier for 90 min. The contents of the secondary polystyrene plate were transferred to their corresponding wells on the primary plate using an acetonitrile/water/acetic acid (50:45:5, v/v/v) solution (1 × 300 μL) and the spent secondary plate was discarded. An aliquot was removed for analytical analysis and the plate was covered with tin foil, firmly held in place with an elastic band. A pin prick was made in the foil directly above each well and the plate was placed at −80 °C for 60 min. The plate was then lyophilized overnight.

(f) Analysis of Cleaved Libraries. An aliquot of the prelyophilized solution (20 μL per gear or 5 μL per crown, from above) was added to a mixture of HPLC solvents A and B (1:1, 50 μL) and 40 μL was analyzed by analytical HPLC (system 1 or 2). Appropriate fractions were taken for ESMS. Alternatively, the lyophilized plate was dissolved in dimethyl sulfoxide (DMSO) (120 μL per gear, providing an approximately 10 mM DMSO stock solution) and 10 μL was added to a mixture of HPLC solvents A and B (1:1, 50 μL), then the mixture was analyzed by ESMS.

(g) Cleavage and Analysis of Individual Test Sequences. A test gear was placed into a 15 mL Falcon tube and treated with TFA/Et_3SiH (95:5, v/v, 500 μL) for 90 min. The gear was removed, washed with neat TFA (500 μL), and the TFA solution was sparged to dryness in a stream of nitrogen. The residue was dissolved in a mixture of HPLC solvents A and B (1:1, 500 μL) and analyzed by HPLC (30 μL injection). Fractions were then analyzed by ESMS.

4. Preparation of Chemset 4{*1*−*4*,*1*−*4*}. (a) Derivatization of Gears/Crowns with Rink Linker. Chiron gears (GEXXOGAP, 500 × 1.2 μmole) were Nα-Fmoc deprotected, washed, and dried in vacuo. *p*-[(*R*,*S*)-α-[1-(9H-Fluoren-9-yl)methoxyformamido]-2,4-dimethoxybenzyl]-phenoxyacetic acid (5 equiv, 1.62 g), 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU, 4.95 equiv, 1.13 g), HOBt (5 equiv, 460 mg) and NMM (9.95 equiv, 660 μL) were preactivated in DMF (100 mL) for 5 min. Gears were added and the reaction was left for 6 h. The spent solution was filtered, coupled gears were washed with DMF (4 × 200 mL × 3 min), then Nα-Fmoc deprotected, washed and dried in vacuo. In a similar manner, Chiron crowns (SPMDINOF, 200 × 5.0 μmole) were derivatized.

(b) Loading of Chemset 2{*1*−*4*}. Reagent **2**{*1*}, 2-[1*S*-(9*H*-Fluoren-9-ylmethoxycarbonylamino)-2-tertbutoxyethyl]-5-hydroxymethyl oxazole-4-carboxylic acid (3 equiv, 245 mg), benzotriazole-1-yloxy-tris-(dimethylamino)phosphonium hexafluorophosphate (BOP, 3 equiv, 227 mg), HOBt (3 equiv, 79 mg), and NMM (6 equiv, 113 μL) were preactivated in DMF (5 mL) for 5 min. Gears (45 × 1.2 μmole) and crowns (25 × 5 μmole) were added plus additional DMF (15 mL) to just cover the reagents; the mixture was then left overnight. The spent solution was filtered, and coupled gears/crowns were washed with DMF (4 × 200 mL × 3 min) then Nα-Fmoc deprotected, washed, and dried in vacuo. Quantitative Fmoc measurement gave loadings of 1.2 and 4.85 μmole, respectively. In an identical manner, reagent **2**{*2*}, 2-[1*R*-(9*H*-fluoren-9-ylmethoxycarbonylamino)-2-tertbutoxyethyl]-5-hydroxymethyl oxazole-4-carboxylic acid, reagent **2**{*3*}, 2-[1*S*-(9*H*-fluoren-9-ylmethoxycarbonylamino)-2*R*-tertbutoxypropyl]-5-hydroxymethyl oxazole-4-carboxylic acid and reagent **2**{*4*}, 2-[1*R*-(9*H*-fluoren-9-ylmethoxycarbonylamino)-2*S*-tertbutoxypropyl]-5-hydroxymethyl oxazole-4-carboxylic acid were quantitatively loaded, respectively.

(c) N-Terminal Elaboration to Chemset 4{*1*−*4*,*1*−*4*}. Following the general coupling methods described, gears/crowns were mounted onto multipin holder and acylated with the appropriate Fmoc-amino acid pentafluorophenyl ester of *tert*-butyl-L-alanine (1), L-leucine (2), L-homoleucine (3), L-norleucine (4) (5 equiv), and HOBt (5 equiv) in DMF overnight. The spent solution was removed, the assembly

was briefly shaken, and coupled gears were washed with DMF (2 × 3 min) then Nα-Fmoc deprotected, washed, and dried in vacuo. The procedure was then repeated but all gears were coupled with 3-carboxyfuranpentafluorophenyl ester (5 equiv), HOBt (5 equiv) in DMF overnight. The spent solution was removed, the assembly was briefly shaken, and coupled gears were washed with DMF (2 × 3 min) and then treated with 20% piperidine/DMF for 30 min (to effect removal of any minor acylation of the free oxazole hydroxyl). Finally, the gears were washed with DMF (3 × 3 min) and CH_3CN (3 × 3 min), and then dried in vacuo.

Acidolytic cleavage and analysis of a single gear of each sequence gave member, HPLC (system 1) R_t (min) (%), ESMS $[M + H]^+$: **4**{*1,1*}, 8.56 (89%) (Figure 2a), 423.3; **4**{*1,2*}, 7.18 (91%), 409.2; **4**{*1,3*}, 8.89 (90%), 423.2; **4**{*1,4*}, 7.34 (91%), 409.2; **4**{*2,1*}, 8.57 (90%), 423.2; **4**{*2,2*}, 7.19 (88%), 409.2; **4**{*2,3*}, 9.01 (92%), 423.2; **4**{*2,4*}, 7.38 (90%), 409.2; **4**{*3,1*}, 9.06 (92%), 437.2; **4**{*3,2*}, 7.70 (89%), 423.2; **4**{*3,3*}, 9.36 (91%), 437.2; **4**{*3,4*}, 7.90 (92%), 423.2; **4**{*4,1*}, 9.26 (92%), 437.2; **4**{*4,2*}, 7.94 (89%) (Figure 2a), 423.2; **4**{*4,3*}, 9.80 (89%), 437.2; **4**{*4,4*}, 8.24 (90%), 423.2.

5. Mitsunobu Derivatization of Chemset 4 → 6. (a) Test Coupling of 4{*4,2*} and 5{*19*} → 6{*4,2,19*}. DEAD (0.15 M in THF, 0.5 mL) was added dropwise over 3 min to Ph_3P (0.15 M in THF, 0.5 mL), followed by triethylamine (32 μL giving 0.225 M). Reagent **5**{*19*}, 2-chlorophenol (0.15 M in THF, 0.5 mL) was added and the reaction mixture was dispensed to solid-phase bound **4**{*4,2*} (1.2 μmole gear), sealed in a 2 mL screw cap vial, and heated at 37 °C overnight. The gear was washed with DMF (3 × 5 min) and DCM (2 × 5 min), and dried in vacuo. Acidolytic cleavage and analysis of the gear gave **6**{*4,2,19*}, Figure 2b (HPLC system 1) R_t 13.97 min (92%), ESMS $[M + H]^+$ 533.1/535.1.

(b) Coupling of 4{*3,4*} Analogue and 5{*1−75*} → 6{*3,4,1−75*}. Following the methods described above, an analogue of **4**{*3,4*}[22] (75 × 1.2 μmole) was coupled to each member of reagent chemset **5**{*1−75*}. The coupled gears were loaded onto a multipin holder at the correct spatial address, washed, and then dried in vacuo. Acidolytic cleavage and analysis gave member, HPLC (system 2) R_t (%), ESMS $[M + H]^+$: **6**{*3,4,1*}, 18.49 (>75%), 585.2; **6**{*3,4,2*}, 21.31 (>85%), 587.2; **6**{*3,4,3*}, 21.58 (>85%), 605.2/607.2/609.2; **6**{*3,4,4*}, 20.94 (>85%), 605.1; **6**{*3,4,5*}, 21.78 (<20%), 579.1; **6**{*3,4,6*}, 20.28 (>85%), 615.1/617.1; **6**{*3,4,7*}, 19.57 (>75%), 597.1; **6**{*3,4,8*}, 21.79 (>85%), 613.2; **6**{*3,4,9*}, 19.06 (>85%), 585.2; **6**{*3,4,10*}, 22.38 (>75%), 627.2; **6**{*3,4,11*}, 20.80 (>85%), 565.2; **6**{*3,4,12*}, 21.24 (>85%), 605.2; **6**{*3,4,13*}, 21.83 (50%), 643.2; **6**{*3,4,14*}, 20.79 (>85%), 585.2/587.1; **6**{*3,4,15*}, 21.14 (>85%), 601.2; **6**{*3,4,16*}, 21.15 (>85%), 617.2; **6**{*3,4,17*}, 21.83 (>85%), 579.1; **6**{*3,4,18*}, 21.82 (>75%), 591.2; **6**{*3,4,19*}, 20.35 (>85%), 571.2/573.2; **6**{*3,4,20*}, 20.51 (>85%), 571.2/573.2; **6**{*3,4,21*}, 18.22 (>85%), 597.2; **6**{*3,4,22*}, 20.36 (>85%), 573.2; **6**{*3,4,23*}, 18.62 (>85%), 597.2; **6**{*3,4,24*}, 21.87 (>85%), 629.1; **6**{*3,4,25*}, 19.87 (>75%), 573.2; **6**{*3,4,26*}, 21.68 (>85%), 613.2; **6**{*3,4,27*}, 22.98 (>75%), 605.2; **6**{*3,4,28*}, 19.90 (50%), 581.2; **6**{*3,4,29*}, 21.92 (>75%), 613.1; **6**{*3,4,30*}, 20.63 (>85%), 615.1/617.1; **6**{*3,4,31*}, 21.28 (>85%), 605.2/607.2/609.2; **6**{*3,4,32*}, 22.41 (>75%), 593.2; **6**{*3,4,33*}, 20.00 (>75%), 573.2; **6**{*3,4,34*}, 21.98 (<25%), 605.2; **6**{*3,4,35*}, 21.02 (>85%), 581.1; **6**{*3,4,36*}, 19.96 (>75%), 573.2; **6**{*3,4,37*}, 20.35 (>85%), 573.2; **6**{*3,4,38*}, 21.83 (>85%), 625.1; **6**{*3,4,39*}, 19.72 (>75%), 581.2; **6**{*3,4,40*}, 22.24 (>85%), 621.2/623.2; **6**{*3,4,41*}, 21.74 (<20%), 579.2; **6**{*3,4,42*}, 20.46 (>85%), 569.2; **6**{*3,4,43*}, 20.39 (>75%), 569.2; **6**{*3,4,44*}, 21.61 (>85%), 621.1; **6**{*3,4,45*}, 21.60 (>85%), 621.1; **6**{*3,4,46*}, 21.81 (>85%), 639.1/641.2; **6**{*3,4,47*}, 20.81 (>85%), 617.2; **6**{*3,4,48*}, 21.45 (<20%), 565.2; **6**{*3,4,49*}, 22.63 (>75%), 665.2/667.1; **6**{*3,4,40*}, 21.38 (>75%), 615.2/617.2; **6**{*3,4,51*}, 21.98 (<10%), 593.2; **6**{*3,4,52*}, 22.89 (>75%), 593.2; **6**{*3,4,53*}, 21.91 (>85%), 599.2/601.2; **6**{*3,4,54*}, 22.53 (>85%), 599.2/601.2; **6**{*3,4,55*}, 21.75 (>85%), 585.1/587.1; **6**{*3,4,56*}, 20.98 (>85%), 571.1/573.2; **6**{*3,4,57*}, 20.69 (>75%), 551.2; **6**{*3,4,58*}, 19.55 (>85%), 597.2; **6**{*3,4,59*}, 21.35 (>75%), 565.2; **6**{*3,4,60*}, 21.49 (>75%), 565.2; **6**{*3,4,61*}, 21.05 (>75%), 565.2; **6**{*3,4,62*}, 21.24 (>75%), 565.2; **6**{*3,4,63*}, 21.45 (>85%), 605.2/607.2/609.2; **6**{*3,4,64*}, 21.58 (>85%), 605.2/607.2/609.2; **6**{*3,4,65*}, 21.66 (<30%), 565.1; **6**{*3,4,66*}, 19.97 (>85%), 555.2; **6**{*3,4,67*}, 20.71 (>85%), 555.2; **6**{*3,4,68*}, 20.28 (>85%), 567.2; **6**{*3,4,69*}, 21.53 (>85%), 663.1; **6**{*3,4,70*}, 22.75 (>85%), 627.2; **6**{*3,4,71*}, 21.62 (50%), 577.2; **6**{*3,4,72*}, 21.41 (>85%), 587.1; **6**{*3,4,73*}, 19.53 (>85%), 583.2; **6**{*3,4,74*}, 22.34 (50%), 591.2; **6**{*3,4,75*}, 19.97 (>85%), 537.2.

6. Conversion of Chemset 4 Hydroxyl → Bromide. CBr_4 (0.05 M in DCM, 1 mL) was added dropwise over 3 min to Ph_3P (0.1 M, in DCM, 1 mL) and mixed thoroughly. Chemset **4** gears were placed into individual screw cap vials and 1.4 mL of reaction solution was added to each vial. After 1 h reaction at RT, each gear was washed with DMF and replaced onto the multipin holder at the correct spatial address. The array of gears was washed with MeOH (200 mL, 5 min), DMF (200 mL, 2 × 5 min), and DCM (200 mL, 2 × 5 min), and dried in vacuo. Acidolytic cleavage and analysis gave the following bromide analogues. Member, HPLC (system 1) R_t (%), ESMS $[M + H]^+$: **4**{*1,1*}, 11.84 (88.3%) (Figure 3b, 4a), 485.0/487.1; **4**{*1,2*}, 10.48 (86.7%), 471.1/473.2; **4**{*1,3*}, 12.13 (90.1%), 485.1/487.1; **4**{*1,4*}, 10.78 (91.3%), 471.1/473.1; **4**{*2,1*}, 11.86 (89.2%), 485.1/487.1; **4**{*2,3*}, 12.11 (91.3%), 485.1/487.1; **4**{*3,1*}, 12.31 (90.6%), 499.0/501.1; **4**{*4,1*}, 12.54 (91.2%), 499.0/501.1.

7. Conversion of Chemset 4 Bromides → Alkyl and Aryl Sulfides 8. A solution of *N*-methylpyrrolidine/thiol reagent chemset **7**/DIEA (93:5:2 v/v/v or v/w/v) was prepared. Bromide analogues of chemset **4** gears were placed into individual screw cap vials and 1 mL of reaction solution was added to each vial; vials were then capped and left at RT for 20 h. Gears were washed with DMF and replaced onto the multipin holder at the correct spatial address. The array of gears was washed with MeOH (200 mL, 5 min), DMF (200 mL, 2 × 5 min), and DCM (200 mL, 2 × 5 min), and dried in vacuo. Acidolytic cleavage and analysis gave the following sulfides **8**. Member, HPLC (system 2) R_t (%), ESMS $[M + H]^+$: **8**{*1,1,1*}, 19.27 (89.3%), 549.1/551.1;

8{*1,1,2*}, 19.02 (86.9%), 544.1; **8**{*1,1,3*}, 20.09 (91.3%), 565.1; **8**{*1,1,4*}, 19.78 (91.4%) (Figure 3c (HPLC system 1, R_t = 15.04 min)), 543.1; **8**{*1,1,5*}, 18.53 (93.1%), 515.1; **8**{*1,1,6*}, 18.88 (89.7%), 529.1; **8**{*1,1,7*}, 20.05 (87.7%), 583.2/585.2/587.2; **8**{*1,1,8*}, 19.96 (92.2%), 543.1.

8. Conversion of Alkyl and Aryl Sulfides 8 → Alkyl and Aryl Sulfones 9. Sulfide chemset **8** gears were placed into individual screw cap vials and 1 mL of mCPBA (5 equiv in DCM) was added to each vial; vials were then capped and left at RT for 20 h. Gears were washed with DMF and replaced onto the multipin holder at the correct spatial address. The array of gears was washed with MeOH (200 mL, 5 min), DMF (200 mL, 2 × 5 min), and DCM (200 mL, 2 × 5 min), and dried in vacuo. Acidolytic cleavage and analysis gave the following sulfones **9**. Member, HPLC (system 2) R_t (%), ESMS $[M + H]^+$: **9**{*1,1,1*}, 17.96 (86.2%), 581.1/583.1; **9**{*1,1,2*}, 17.76 (87.1%), 576.1; **9**{*1,1,3*}, 18.81 (90.0%), 597.1; **9**{*1,1,4*}, 18.37 (94.1%) (Figure 3d (HPLC system 1, R_t = 13.68 min)), 575.1; **9**{*1,1,5*}, 17.18 (91.1%), 547.1; **9**{*1,1,6*}, 17.53 (84.7%), 5651.1; **9**{*1,1,7*}, 18.77 (85.4%), 615.2/617.2/619.3; **9**{*1,1,8*}, 18.57 (91.1%), 575.1.

9. Conversion of Chemset 4 Bromides → Chemset 4 Azides. Sodium azide (50 equiv per gear) was dissolved in *N*-methylpyrrolidine/water (9:1, v/v) with shaking. Bromide analogues of chemset **4** gears were placed onto the multipin holder and 500 μL of reagent was dispensed to the appropriate wells of a polypropylene 96-well plate. The array was added and left at RT for 16 h, then washed with DMF/water (200 mL, 9:1, v/v, 2 × 5 min), CH_3CN (200 mL, 2 × 5 min), and DCM (200 mL, 2 × 5 min), and dried in vacuo. Acidolytic cleavage (effected with 95% TFA/5% H_2O) and analysis gave the following azide analogues. Member, HPLC (system 1) R_t (%), ESMS $[M + H]^+$: **4**{*1,1*}, 11.48 (87.3%) (Figure 4b), 448.2; **4**{*2,1*}, 11.49 (90.2%), 448.2; **4**{*3,1*}, 12.22 (88.2%), 462.2; **4**{*4,1*}, 12.38 (91.3%), 462.2.

10. Conversion of Chemset 4 Azides → Chemset 4 Amines. A solution of dithiothreitol (2 M) and DIEA (1 M) in DMF was prepared. Azide analogues of chemset **4** gears were placed into individual screw cap vials and 0.7 mL of reaction solution was added to each vial; vials were then capped and heated at 50 °C for 1 h. An additional 0.7 mL aliquot of reagent was added and again capped and heated at 50 °C for 1 h. Gears were washed with DMF and replaced onto the multipin holder at the correct spatial address. The array of gears was washed with DMF (200 mL, 2 × 5 min), CH_3CN (200 mL, 2 × 5 min), and DCM (200 mL, 2 × 5 min), and dried in vacuo. Acidolytic cleavage and analysis gave the following amine analogues. Member, HPLC (system 1) R_t (%), ESMS $[M + H]^+$: **4**{*1,1*}, 8.41 (90.2%) (Figure 4c), 422.2; **4**{*2,1*}, 8.44 (87.3%), 422.2; **4**{*3,1*}, 9.00 (91.0%), 436.2; **4**{*4,1*}, 9.16 (91.4%), 436.1.

11. Conversion of Chemset 4 Amines → Carboxamides 11. A solution of carboxylic acid reagent chemset **10** (5 equiv), HBTU (4.95 equiv), HOBt (5 equiv), and NMM (9.95 equiv) were preactivated in DMF (250 μL) for 5 min. Amine analogues of chemset **4** gears were placed onto the multipin holder, reagents were dispensed to the appropriate wells, and the reaction was left at RT for 16 h. The array of gears was washed with DMF (200 mL, 3 × 5 min) and CH_3CN (200 mL, 3 × 5 min), and dried in vacuo. Acidolytic cleavage and analysis gave the following carboxamides **11**. Member, HPLC (system 1) R_t (%), ESMS $[M + H]^+$: **11**{*1,1,1*}, 12.25 (93.3%) (Figure 4d), 540.2; **11**{*1,1,2*}, 14.32 (89.8%), 590.1; **11**{*1,1,3*}, 11.99 (90.2%), 532.1; **11**{*1,1,4*}, 12.01 (92.9%) 526.2; **11**{*1,1,5*}, 9.71 (87.6%), 478.1; **11**{*1,1,6*}, 13.95 (94.2%), 576.2; **11**{*1,1,7*}, 13.99 (91.6%), 576.1; **11**{*1,1,8*}, 12.63 (86.1%), 570.1.

12. Conversion of Chemset 4 Amines → Sulfonamides 13. A solution of sulfonyl chloride reagent chemset **12** (50 equiv) and (dimethylamino)pyridine (50 equiv) were premixed in DMF (250 μL). Amine analogues of chemset **4** gears were placed onto the multipin holder, reagents were dispensed to the appropriate wells, and the reaction was left at RT for 16 h. The array of gears was washed with DMF (200 mL, 3 × 5 min) and CH_3CN (200 mL, 3 × 5 min), and dried in vacuo. Acidolytic cleavage and analysis gave the following sulfonamides **13**. Member, HPLC (system 1) R_t (%), ESMS $[M + H]^+$: **13**{*1,1,1*}, 13.93 (91.9%) (Figure 4e), 612.0; **13**{*1,1,2*}, 12.01 (88.3%), 568.2; **13**{*1,1,3*}, 12.22 (92.6%), 562.1; **13**{*1,1,4*}, 14.36 (88.6%) 612.2; **13**{*1,1,5*}, 13.73 (51.1%), 576.2; **13**{*1,1,6*}, 9.62 (39.2%), 514.1; **13**{*1,1,7*}, 12.81 (92.1%), 592.2.

13. Synthesis of Compounds 1−20. Following the procedures detailed in section 4 (a)−(c), each of the four members of chemset **4**{*1−4,1*} were reprepared commencing from 25 × 5.0 μmole crowns SPMDINOF. Then, following the procedures detailed in sections 5−12, 5 × 5.0 μmole of each member was converted into functionalized oxazole compounds **1**−**20**. For modifications detailed in sections 5−10, the 5.0 μmole crown simply replaced the 1.2 μmole gear retaining the same reaction volumes, times, and concentrations. For acylations detailed in sections 11 and 12, with carboxamides **10** and sulfonyl chlorides **12**, the reaction volumes increased to 500 μL per crown.

Chemset **4**{*1,1*} was converted to **6**{*1,1,4*}, **8**{*1,1,4*}, **9**{*1,1,4*}, **11**{*1,1,4*}, **13**{*1,1,4*}; Chemset **4**{*2,1*} was converted to **6**{*2,1,3*}, **8**{*2,1,3*}, **9**{*2,1,3*}, **11**{*2,1,3*}, **13**{*2,1,3*}; Chemset **4**{*3,1*} was converted to **6**{*3,1,1*}, **8**{*3,1,1*}, **9**{*3,1,1*}, **11**{*3,1,1*}, **13**{*3,1,1*}; and Chemset **4**{*4,1*} was converted to **6**{*4,1,2*}, **8**{*4,1,2*}, **9**{*4,1,2*}, **11**{*4,1,2*}, **13**{*4,1,2*}. Full analytical data were summarized in Table 1.

Compound 1; 6{***1,1,4***}**. 2-(1*S*-{2*S*-[(Furan-3-carbonyl)-amino]-4,4-dimethyl-pentanoylamino}-2-hydroxyethyl)-5-(2-trifluoromethyl-phenoxymethyl)-oxazole-4-carboxamide.** Crude compound **1** (10.3 mg) was dissolved with sonication in 0.1% aq TFA/acetonitrile (1:1, v/v, 2 mL) and purified by semipreparative HPLC, eluting with a 30−90% gradient of solvent B in solvent A over 35 min. The desired fractions were lyophilized to give a white solid (3.5 mg, 26%). Analytical HPLC (system 2) R_t 19.85 min (>99%), HRMS $C_{26}H_{29}O_7N_4NaF_3$ requires *M*, 589.1886, found MNa^+, 589.1910 (δ +4.0 ppm). δ_H (500 MHz; $CDCl_3$) 0.92 (9H, s, $NHCHCH_2C(CH_3)_3$), 1.60 (1H, dd, *J* 14 and 8, $NHCHCH_{2A}C(CH_3)_3$), 1.92 (1H, dd, *J* 14 and 4, $NHCHCH_{2B}C(CH_3)_3$), 3.87 (1H, dd, *J* 12 and 3.5, $NHCHCH_{2A}OH$), 3.95 (1H, dd, *J* 12 and 4, $NHCHCH_{2B}OH$), 4.60 (1H, ddd, *J* 8.5, 8, and 4,

NHC*H*$CH_2C(CH_3)_3$), 5.15 (1H, ddd, *J* 8, 4, and 3.5, NHC*H*CH_2OH), 5.50 (1H, d, *J* 13.5, CH_{2A}O-phenyl), 5.55 (1H, d, *J* 13.5, CH_{2B}O-phenyl), 6.69 (1H, s, H-4 furan), 7.02 (1H, t, *J* 7.5, H-4 phenyl), 7.27 (2H, m, H-6 phenyl and N*H*$CHCH_2C(CH_3)_3$), 7.40 (1H, s, H-5 furan), 7.44 (1H, t, *J* 7.5, H-5 phenyl), 7.52 (1H, d, *J* 7.5, H-3 phenyl), 7.79 (1H, d, *J* 8, N*H*$CHCH_2OH$), and 7.98 (1H, s, H-2 furan).

Compound 2; 8{*1,1,4*}. 2-(1*S*-{2*S*-[(Furan-3-carbonyl)-amino]-4,4-dimethylpentanoylamino}-2-hydroxyethyl)-5-(phenethylsulfanylmethyl)-oxazole-4-carboxamide. Crude compound **2** (17.7 mg) was dissolved in 0.1% aq TFA/acetonitrile (1:1, v/v, 2 mL) and purified by semipreparative HPLC, eluting with a 30−90% gradient of solvent B in solvent A over 35 min. The desired fractions were lyophilized to give a white solid (1.5 mg, 12%). Analytical HPLC (system 2) R_t 19.78 min (>99%), HRMS $C_{27}H_{34}O_6N_4NaS$ requires *M*, 565.2097, found MNa^+, 565.2098 (δ +0.2 ppm). δ_H (500 MHz; $CDCl_3$) 0.99 (9H, s, NHCHCH_2C(CH_3)$_3$), 1.60 (1H, dd, *J* 14.5 and 7.5, NHCHC$H_{2A}C(CH_3)_3$), 2.02 (1H, dd, *J* 14.5 and 5, NHCHC$H_{2B}C(CH_3)_3$), 2.78 (2H, m, SCH_2-CH_2Ph), 2.90 (2H, m, SCH_2CH_2Ph), 3.90 (1H, dd, *J* 11.5 and 4, NHCHCH_{2A}OH), 4.02 (1H, dd, *J* 11.5 and 4, NHCHCH_{2B}OH), 4.10 (1H, d, *J* 15, C$H_{2A}S(CH_2)_2$ phenyl), 4.20 (1H, d, *J* 15, C$H_{2B}S(CH_2)_2$phenyl), 4.61 (1H, ddd, *J* 7.5, 7.5, and 5, NHC*H*$CH_2C(CH_3)_3$), 5.19 (1H, d, *J* 8 and 4, NHC*H*CH_2OH), 5.55 (1H, br s, $CONH_{2A}$), 6.16 (1H, d, *J* 7.5, N*H*$CHCH_2C(CH_3)_2$), 6.59 (1H, br s, H-4 furan), 6.77 (1H, br s, $CONH_{2B}$), 7.13 (1H, d, *J* 8, N*H*$CHCH_2OH$), 7.18 (3H, m, H-2, H-4, and H-6 phenyl), 7.28 (2H, m, H-3 and H-5 phenyl), 7.44 (1H, s, H-5 furan), and 7.94 (1H, s, H-2 furan).

Compound 3; 9{*1,1,4*}. 2-(1*S*-{2*S*-[(Furan-3-carbonyl)-amino]-4,4-dimethylpentanoylamino}-2-hydroxyethyl)-5-(phenethylsulfonylmethyl)-oxazole-4-carboxamide. Crude compound **3** (7.4 mg) was dissolved in 0.1% aq TFA/acetonitrile (1:1, v/v, 2 mL) and purified by semipreparative HPLC, eluting with a 30−90% gradient of solvent B in solvent A over 35 min. The desired fractions were lyophilized to give a white solid (7.3 mg, 53%). Analytical HPLC (system 2) R_t 18.47 min (>99%), HRMS $C_{27}H_{34}O_8N_4NaS$ requires *M*, 597.1995, found MNa^+, 597.2014 (δ +3.3 ppm). δ_H (500 MHz; $CDCl_3$) 0.99 (9H, s, NHCHCH_2C(CH_3)$_3$), 1.60 (1H, dd, *J* 14.5 and 8, NHCHC$H_{2A}C(CH_3)_3$), 2.00 (1H, dd, *J* 14.5 and 5, NHCHC$H_{2B}C(CH_3)_3$), 3.16 (2H, m, SO_2-CH_2CH_2Ph), 3.32 (2H, m, $SO_2CH_2CH_2$Ph), 4.03 (1H, dd, *J* 11.5 and 4, NHCHCH_{2A}OH), 4.08 (1H, dd, *J* 11.5 and 4.5, NHCHCH_{2B}OH), 4.61 (1H, d, *J* 15, C$H_{2A}S(CH_2)_2$-phenyl), 4.67 (1H, ddd, *J* 8, 8 and 5, NHC*H*$CH_2C(CH_3)_3$), 4.93 (1H, d, *J* 15, C$H_{2B}S(CH_2)_2$-phenyl), 5.11 (1H, ddd, *J* 8.5, 4.5, and 4, NHC*H*CH_2OH), 5.64 (1H, br s, $CONH_{2A}$), 6.49 (1H, d, *J* 8, N*H*$CHCH_2C(CH_3)_2$), 6.65 (1H, br s, H-4 furan), 6.89 (1H, br s, $CONH_{2B}$), 7.23 (3H, m, H-2, H-4, and H-6 phenyl), 7.29 (2H, m, H-3 and H-5 of Ph), 7.44 (1H, br s, H-5 furan), 7.47 (1H, d, *J* 8.5, N*H*$CHCH_2OH$), and 7.94 (1H, s, H-2 furan).

Compound 4; 11{*1,1,4*}. 5-(Benzoylaminomethyl)-2-(1*S*-{2*S*-[(furan-3-carbonyl)amino]-4,4-dimethylpentanoylamino}-2-hydroxyethyl)-oxazole-4-carboxamide. Crude compound **4** (9.6 mg) was dissolved in 0.1% aq TFA/acetonitrile (1:1, v/v, 2 mL) and purified by semipreparative HPLC, eluting with a 30−90% gradient of solvent B in solvent A over 35 min. The desired fractions were lyophilized to give a white solid (3.4 mg, 27%). Analytical HPLC (system 2) R_t 16.80 min (>99%), HRMS $C_{26}H_{31}O_7N_5Na$ requires *M*, 548.2121, found MNa^+, 548.2127 (δ +1.0 ppm). δ_H (500 MHz; $CDCl_3$) 0.98 (9H, s, NHCHCH_2C(CH_3)$_3$, 1.59 (1H, dd, *J* 14.5 and 8, NHCHC$H_{2A}C(CH_3)_3$), 1.95 (1H, dd, *J* 14.5 and 4, NHCHC$H_{2B}C(CH_3)_3$), 3.99 (1H, dd, *J* 8 and 4, NHCHCH_{2A}OH), 4.01 (1H, dd, *J* 8 and 4, NHCHCH_{2B}-OH), 4.67 (1H, br dd, *J* 8 and 4, NHC*H*$CH_2C(CH_3)_3$), 4.84 (2H, m, CH_2NHCOPh), 5.13 (1H, br m, NHC*H*CH_2OH), 5.92 (1H, br s, $CONH_{2A}$), 6.65 (1H, s, H-4 furan), 6.73 (1H, br s, N*H*$CHCH_2C(CH_3)_3$), 7.17 (1H, br s, $CONH_{2B}$), 7.41 (1H, s, H-5 furan), 7.43 (2H, m, H-3 and H-5 phenyl), 7.49 (1H, t, *J* 7, H-4 phenyl), 7.57 (1H, br s, N*H*$CHCH_2OH$), 7.84 (2H, d, *J* 7.5, H-2 and H-6 phenyl), 7.98 (1H, s, H-2 furan), and 8.58 (1H, br s, CH_2N*H*COPh).

Compound 5; 13{*1,1,4*}. 2-(1*S*-{2*S*-[(Furan-3-carbonyl)amino]-4,4-dimethylpentanoylamino}-2-hydroxyethyl)-5-[(naphthalene-1-sulfonylamino)methyl]-oxazole-4-carboxamide. Crude compound **5** (21.9 mg) was dissolved in 0.1% aq TFA/acetonitrile (1:1, v/v, 2 mL) and purified by semipreparative HPLC, eluting with a 30−90% gradient of solvent B in solvent A over 35 min. The desired fractions were lyophilized to give a white solid (1.9 mg, 13%). Analytical HPLC (system 2) R_t 17.92 min (>99%), HRMS $C_{29}H_{33}O_8N_5NaS$ requires *M*, 634.1948, found MNa^+, 634.1941 (δ −1.1 ppm). δ_H (500 MHz; $CDCl_3$) 0.99 (9H, s, NHCHCH_2C(CH_3)$_3$), 1.63 (1H, dd, *J* 14.5 and 8, NHCHC$H_{2A}C(CH_3)_3$), 2.02 (1H, dd, *J* 14.5 and 5, NHCHC$H_{2B}C(CH_3)_3$), 3.82 (2H, d, *J* 3.5, NHCHCH_2OH), 4.35 (2H, d, *J* 6.5, CH_2NHSO_2-naphthalene), 4.60 (1H, ddd, *J* 8, 7, and 5, NHC*H*$CH_2C(CH_3)_3$), 4.89 (1H, dt, *J* 7 and 3.5, NHC*H*CH_2-OH), 5.70 (1H, br s, $CONH_{2A}$), 6.35 (1H, d, *J* 7, N*H*$CHCH_2C(CH_3)_2$), 6.48 (1H, br s, $CONH_{2B}$), 6.63 (1H, br d, *J* 1, H-4 furan), 7.01 (1H, t, *J* 6.5, CH_2N*H*SO_2-naphthalene), 7.14 (1H, d, *J* 7, N*H*$CHCH_2OH$), 7.44 (1H, s, H-5 furan), 7.52 (1H, t, *J* 8, H-3 naphthalene), 7.57 (1H, t, *J* 8, H-6 naphthalene), 7.62 (1H, t, *J* 8, H-7 naphthalene), 7.86 (1H, d, *J* 8, H-5 naphthalene), 7.94 (1H, s, H-2 furan), 8.02 (1H, d, *J* 8, H-2 or H-4 naphthalene), 8.23 (1H, d, *J* 8, H-2 or H-4 naphthalene), and 8.56 (1H, d, *J* 8, H-8 naphthalene).

Compound 6; 6{*2,1,3*}. 5-(2,5-Dichlorophenoxymethyl)-2-(1*R*-{2*S*-[(furan-3-carbonyl)amino]-4,4-dimethylpentanoylamino}-2-hydroxyethyl)-oxazole-4-carboxamide. Crude compound **6** (18.2 mg) was dissolved in 0.1% aq TFA/acetonitrile (1:1, v/v, 2 mL) and purified by semipreparative HPLC, eluting with a 30−90% gradient of solvent B in solvent A over 35 min. The desired fractions were lyophilized to give a white solid (6.0 mg, 44%). Analytical HPLC (system 2) R_t 19.95 min (>99%), HRMS $C_{25}H_{28}O_7N_4NaCl_2$ requires *M*, 589.1233, found MNa^+, 589.1229 (δ −0.7 ppm). δ_H (500 MHz; $CDCl_3$) 1.00 (9H, s, NHCHCH_2C(CH_3)$_3$), 1.60 (1H, dd, *J* 14.5 and 8.5, NHCHC$H_{2A}C(CH_3)_3$), 2.04 (1H, dd, *J* 14.5 and 4.5, NHCHC$H_{2B}C(CH_3)_3$), 4.01 (1H, dd, *J* 11.5 and 4, NHCHCH_{2A}OH), 4.14 (1H, dd, *J* 11.5 and 3.5, NHCHCH_{2B}OH), 4.75 (1H, ddd, *J* 8.5, 8, and 4.5, NHC*H*-$CH_2C(CH_3)_3$), 5.23 (1H, ddd, *J* 6, 4, and 3.5, NHC*H*CH_2-

OH), 5.34 (1H, d, *J* 13, CH_{2A}O-phenyl), 5.45 (1H, d, *J* 13, CH_{2B}O-phenyl), 6.00 (1H, br s, CONH$_{2A}$), 6.35 (1H, d, *J* 8, N*H*CHCH$_2$C(CH$_3$)$_2$), 6.60 (1H, br d, *J* 1, H-4 furan), 6.89 (1H, br s, CONH$_{2B}$), 6.91 (1H, dd, *J* 8.5 and 2, H-4 phenyl), 7.17 (1H, d, *J* 2, H-6 phenyl), 7.25 (1H, d, *J* 8.5, H-3 phenyl), 7.40 (1H, br d, *J* 1, H-5 furan), 7.54 (1H, br d, *J* 6, N*H*CHCH$_2$OH), and 7.94 (1H, s, H-2 furan).

Compound 7; 8{*2,1,3*}. 2-(1*R*-{2*S*-[(Furan-3-carbonyl)-amino]-4,4-dimethylpentanoylamino}-2-hydroxyethyl)-5-(naphthalene-2-ylsulfanylmethyl)-oxazole-4-carboxamide. Crude compound **7** (16.9 mg) was dissolved in 0.1% aq TFA/acetonitrile (1:1, v/v, 2 mL) and purified by semipreparative HPLC, eluting with a 30−90% gradient of solvent B in solvent A over 35 min. The desired fractions were lyophilized to give a white solid (6.7 mg, 49%). Analytical HPLC (system 2) R_t 20.06 min (>99%), HRMS $C_{29}H_{32}O_6N_4NaS$ requires *M*, 587.1940, found MNa$^+$, 587.1929 (δ −2.0 ppm). δ_H (500 MHz; CDCl$_3$) 0.99 (9H, s, NHCHCH$_2$C(C*H*$_3$)$_3$), 1.58 (1H, dd, *J* 14.5 and 8, NHCH-C*H*$_{2A}$C(CH$_3$)$_3$), 2.02 (1H, dd, *J* 14.5 and 5, NHCHC*H*$_{2B}$C-(CH$_3$)$_3$), 3.78 (1H, dd, *J* 11 and 3.5, NHCHC*H*$_{2A}$OH), 3.91 (1H, dd, *J* 11 and 4, NHCHC*H*$_{2B}$OH), 4.45 (1H, d, *J* 15, C*H*$_{2A}$S naphthalene), 4.55 (1H, d, *J* 15, C*H*$_{2B}$S naphthalene), 4.70 (1H, ddd, *J* 8.5, 8, and 5, NHC*H*CH$_2$C(CH$_3$)$_3$), 5.10 (1H, ddd, *J* 9, 4, and 3.5, NHC*H*CH$_2$OH), 5.75 (1H, br s, CONH$_{2A}$), 6.13 (1H, d, *J* 8.5, N*H*CHCH$_2$C(CH$_3$)$_3$), 6.54 (1H, br s, H-4 furan), 6.64 (1H, br s, CONH$_{2B}$), 7.35 (1H, br d, *J* 9, N*H*CHCH$_2$OH), 7.40 (1H, d, *J* 1, H-5 furan), 7.42−7.49 (3H, m, H-3, H-6, and H-7 naphthalene), 7.70−7.77 (4H, H-1, H-4, H-5, and H-8 naphthalene), and 7.89 (1H, br s, H-2 furan).

Compound 9; 11{*2,1,3*}. 2-(1*R*-{2*S*-[Furan-3-carbonyl)-amino]-4,4-dimethylpentanoylamino}-2-hydroxyethyl)-5-{[(thiophene-2-carbonyl)amino]methyl}-oxazole-4-carboxamide. Crude compound **9** (18.0 mg) was dissolved in 0.1% aq TFA/acetonitrile (1:1, v/v, 2 mL) and purified by semipreparative HPLC, eluting with a 30−90% gradient of solvent B in solvent A over 35 min. The desired fractions were lyophilized to give a white solid (3.0 mg, 24%). Analytical HPLC (system 2) R_t 16.29 min (>99%), HRMS $C_{24}H_{29}O_7N_5NaS$ requires *M*, 554.1685, found MNa$^+$, 554.1664, (δ −3.9 ppm). δ_H (500 MHz; CDCl$_3$) 0.99 (9H, s, NHCHCH$_2$C(C*H*$_3$)$_3$), 1.63 (1H, dd, *J* 14.5 and 8.5, NHCH-C*H*$_{2A}$C(CH$_3$)$_3$), 2.00 (1H, dd, *J* 14.5 and 4.5, NHCHC*H*$_{2B}$C-(CH$_3$)$_3$), 3.95 (1H, dd, *J* 11.5 and 3.5, NHCHC*H*$_{2A}$OH), 4.12 (1H, dd, *J* 11.5 and 3.5, NHCHC*H*$_{2B}$OH), 4.69 (1H, dd, *J* 16.5 and 5, C*H*$_{2A}$NHCO-thiophene), 4.77 (1H, dd, *J* 16.5 and 6, C*H*$_{2B}$NHCO-thiophene), 4.81 (1H, m, NHC*H*CH$_2$C-(CH$_3$)$_3$), 5.16 (1H, dt, *J* 6.5 and 3.5, NHC*H*CH$_2$OH), 5.95 (1H, br s, CONH$_{2A}$), 6.68 (1H, s, H-4 furan), 6.74 (1H, br d, *J* 8, N*H*CHCH$_2$C(CH$_3$)$_3$), 7.04 (1H, t, *J* 4.5, H-4 thiophene), 7.15 (1H, br s, CONH$_{2B}$), 7.40 (1H, s, H-5 furan), 7.49 (1H, d, *J* 4.5, H-3 thiophene), 7.59 (1H, d, *J* 4.5, H-5 thiophene), 7.69 (1H, br d, *J* 6.5, N*H*CHCH$_2$OH), 8.00 (1H, s, H-2 furan), and 8.44 (1H, br s, CH$_2$N*H*CO-thiophene).

Compound 10; 13{*2,1,3*}. 5-(Benzenesulfonylamino-methyl)-2-(1*R*-{2*S*-[(furan-3-carbonyl)amino]-4,4-dimethyl-pentanoylamino}-2-hydroxyethyl)-oxazole-4-carboxamide. Crude compound **10** (12.1 mg) was dissolved in 0.1% aq TFA/acetonitrile (1:1, v/v, 2 mL) and purified by semipreparative HPLC, eluting with a 30−90% gradient of solvent B in solvent A over 35 min. The desired fractions were lyophilized to give a white solid (1.4 mg, 14%). Analytical HPLC (system 2) R_t 17.06 min (>99%), HRMS $C_{25}H_{31}O_8N_5NaS$ requires *M*, 584.1791, found MNa$^+$, 584.1770 (δ −2.5 ppm). δ_H (500 MHz; CDCl$_3$) 0.99 (9H, s, NHCHCH$_2$C(C*H*$_3$)$_3$), 1.66 (1H, dd, *J* 14.5 and 8.5, NHCH-C*H*$_{2A}$C(CH$_3$)$_3$), 1.99 (1H, dd, *J* 14.5 and 4.5, NHCHC*H*$_{2B}$C-(CH$_3$)$_3$), 3.95 (1H, dd, *J* 11.5 and 3.5, NHCHC*H*$_{2A}$OH), 4.08 (1H, dd, *J* 11.5 and 3, NHCHC*H*$_{2B}$OH), 4.34 (2H, m, C*H*$_2$-NHSO$_2$-naphthalene), 4.74 (1H, ddd, *J* 8.5, 7.5, and 4.5, NHC*H*CH$_2$C(CH$_3$)$_3$), 5.13 (1H, ddd, *J* 6.5, 3.5, and 3, NHC*H*CH$_2$OH), 6.11 (1H, br s, CONH$_{2A}$), 6.49 (1H, d, *J* 7.5, N*H*CHCH$_2$C(CH$_3$)$_2$), 6.64 (1H, s, H-4 furan), 6.82 (1H, br s, CONH$_{2B}$), 6.94 (1H, br m, CH$_2$N*H*SO$_2$-phenyl), 7.43 (1H, br s, H-5 furan), 7.45 (2H, m, H-3 and H-5 phenyl), 7.49 (1H, m, H-4 phenyl), 7.62 (1H, d, *J* 6.5, N*H*CHCH$_2$-OH), 7.78 (2H, d, *J* 7.5, H-2 and H-6 phenyl), 8.00 (1H, s, H-2 furan).

Compound 12; 8{*3,1,1*}. 5-(2-Chlorophenylsulfanyl-methyl)-2-(1*S*-{2*S*-[(furan-3-carbonyl)amino]-4,4-dimethyl-pentanoylamino}-2*R*-hydroxypropyl)-oxazole-4-carboxamide. Crude compound **12** (6.5 mg) was dissolved in 0.1% aq TFA/acetonitrile (1:1, v/v, 2 mL) and purified by semipreparative HPLC, eluting with a 30−90% gradient of solvent B in solvent A over 35 min. The desired fractions were lyophilized to give a white solid (3.2 mg, 24%). Analytical HPLC (system 2) R_t 19.62 min (>99%), HRMS $C_{26}H_{31}O_6N_4NaClS$ requires *M*, 585.1551, found MNa$^+$, 585.1553 (δ +0.4 ppm). δ_H (500 MHz; CDCl$_3$) 0.99 (9H, s, NHCHCH$_2$C(C*H*$_3$)$_3$), 1.17 (3H, d, *J* 6.5, NHCHCH(OH)-C*H*$_3$), 1.58 (1H, dd, *J* 14 and 7.5, NHCHC*H*$_{2A}$C(CH$_3$)$_3$), 2.04 (1H, dd, *J* 14 and 5.5, NHCHC*H*$_{2B}$C(CH$_3$)$_3$), 4.30 (1H, dq, *J* 6.5 and 3, NHCHC*H*(OH)CH$_3$), 4.54 (2H, s, C*H*$_2$S-phenyl), 4.64 (1H, ddd, *J* 8, 7.5, and 5.5, NHC*H*CH$_2$C(CH$_3$)$_3$), 5.05 (1H, dd, *J* 9 and 3, NHC*H*CH(OH)CH$_3$), 5.56 (1H, br s, CONH$_{2A}$), 6.13 (1H, d, *J* 8, N*H*CHCH$_2$C(CH$_3$)$_2$), 6.60 (1H, br d, *J* 1, H-4 furan), 6.70 (1H, br s, CONH$_{2B}$), 6.96 (1H, d, *J* 9, N*H*CHCH(OH)CH$_3$), 7.18 (2H, m, H-4 and H-5 phenyl), 7.36 (1H, dd, *J* 7.5 and 1.5, H-6 phenyl), 7.44 (1H, br d, *J* 1, H-5 furan), 7.50 (1H, dd, *J* 7.5 and 1.5, H-3 phenyl), and 7.95 (1H, s, H-2 furan).

Compound 13; 9{*3,1,1*}. 5-(2-Chlorobenzenesulfonyl-methyl)-2-(1*S*-{2*S*-[(furan-3-carbonyl)amino]-4,4-dimeth-ylpentanoylamino}-2*R*-hydroxypropyl)-oxazole-4-carbox-amide. Crude compound **13** (5.6 mg) was dissolved in 0.1% aq TFA/acetonitrile (1:1, v/v, 2 mL) and purified by semipreparative HPLC, eluting with a 30−90% gradient of solvent B in solvent A over 35 min. The desired fractions were lyophilized to give a white solid (2.1 mg, 15%). Analytical HPLC (system 2) R_t 17.75 min (>99%), HRMS $C_{26}H_{31}O_8N_4NaClS$ requires *M*, 617.1449, found MNa$^+$, 617.1477, (δ +4.5 ppm). δ_H (500 MHz; CDCl$_3$) 0.99 (9H, s, NHCHCH$_2$C(C*H*$_3$)$_3$), 1.21 (3H, d, *J* 6.5, NHCHCH(OH)-C*H*$_3$), 1.63 (1H, dd, *J* 14.5 and 8, NHCHC*H*$_{2A}$C(CH$_3$)$_3$), 2.08 (1H, dd, *J* 14.5 and 5, NHCHC*H*$_{2B}$C(CH$_3$)$_3$), 4.35 (1H, dq, *J* 6.5 and 3, NHCHC*H*(OH)CH$_3$), 4.68 (1H, ddd, *J* 8.5, 8, and 5, NHC*H*CH$_2$C(CH$_3$)$_3$), 5.00 (1H, dd, *J* 8.5 and 3,

NHC*H*CH(OH)CH_3), 5.11 (1H, d, *J* 14.5, C$H_{2A}$$SO_2$Ph), 5.20 (1H, d, *J* 14.5, C$H_{2B}$$SO_2$Ph), 5.44 (1H, br s, $CONH_{2A}$), 6.25 (1H, br d, *J* 8.5, NHC*H*$CH_2C(CH_3)_3$), 6.65 (2H, br s, $CONH_{2B}$ and H-4 furan), 7.12 (1H, br d, *J* 8.5, N*H*CHCH(OH)CH_3), 7.40 (1H, m, H-5 phenyl), 7.46 (1H, br s, H-5 furan), 7.58 (2H, d, *J* 4, H-3 and H-4 phenyl), 7.89 (1H, d, *J* 8, H-6 phenyl), and 7.96 (1H, s, H-2 furan).

Compound 14; 11{*3,1,1*}. 2-(1*S*-{2*S*-[(Furan-3-carbonyl)amino]-4,4-dimethylpentanoylamino}-2*R*-hydroxypropyl)-5-(phenylacetylaminomethyl)-oxazole-4-carboxamide. Crude compound **14** (19.1 mg) was dissolved in 0.1% aq TFA/acetonitrile (1:1, v/v, 2 mL) and purified by semipreparative HPLC, eluting with a 30−90% gradient of solvent B in solvent A over 35 min. The desired fractions were lyophilized to give a white solid (1.8 mg, 14%). Analytical HPLC (system 2) R_t 17.16 min (>99%), HRMS $C_{28}H_{36}O_7N_5$ requires *M*, 554.2614, found MNa^+, 554.2614 (δ 0.0 ppm). δ_H (500 MHz; $CDCl_3$) 0.98 (9H, s, NHCHCH_2C-(CH_3)$_3$), 1.19 (3H, d, *J* 6.5, NHCHCH(OH)CH_3), 1.62 (1H, dd, *J* 14.5 and 7.5, NHCHC$H_{2A}$$C(CH_3)_3$), 2.02 (1H, dd, *J* 14.5 and 4.5, NHCHC$H_{2B}$$C(CH_3)_3$), 3.57 (2H, s, CH_2-NHCOCH_2Ph), 4.35 (1H, br m, NHCHC*H*(OH)CH_3), 4.62 (2H, m, CH_2NHCOCH_2Ph), 4.67 (1H, m, NHC*H*$CH_2C(CH_3)_3$), 4.99 (1H, dd, *J* 6 and 2.5, NHC*H*CH(OH)CH_3), 5.73 (1H, br s, $CONH_{2A}$), 6.49 (1H, br s, N*H*$CHCH_2C(CH_3)_3$), 6.64 (1H, br s, H-4 furan), 7.01 (1H, br s, $CONH_{2B}$), 7.25−7.29 (7H, m, N*H*CHCH(OH)CH_3, CH_2N*H*COCH_2Ph and Ph), 7.45 (1H, br s, H-5 furan), and 7.98 (1H, s, H-2 furan).

Compound 15; 13{*3,1,1*}. 2-(1*S*-{2*S*-[(Furan-3-carbonyl)amino]-4,4-dimethylpentanoylamino}-2*R*-hydroxypropyl)-5-[(naphthalene-2-sulfonylamino)methyl]-oxazole-4-carboxamide. Crude compound **15** (10.1 mg) was dissolved in 0.1% aq TFA/acetonitrile (1:1, v/v, 2 mL) and purified by semipreparative HPLC, eluting with a 30−90% gradient of solvent B in solvent A over 35 min. The desired fractions were lyophilized to give a white solid (6.9 mg, 46%). Analytical HPLC (system 2) R_t 18.90 min (>99%), HRMS $C_{30}H_{35}O_8N_5NaS$ requires *M*, 648.2104, found MNa^+, 648.2099 (δ −0.8 ppm). δ_H (500 MHz; $CDCl_3$) 0.99 (9H, s, NHCHCH_2C(CH_3)$_3$), 1.08 (3H, d, *J* 6, NHCHCH(OH)CH_3), 1.60 (1H, dd, *J* 14.5 and 8, NHCHC$H_{2A}$$C(CH_3)_3$), 2.04 (1H, dd, *J* 14.5 and 4, NHCHC$H_{2B}$$C(CH_3)_3$), 3.99 (1H, br m, NHCHC*H*(OH)CH_3), 4.45 (2H, d, *J* 6, C$H_2$$NHSO_2$-naphthalene), 4.61 (1H, br m, NHC*H*$CH_2C(CH_3)_3$), 4.74 (1H, br d, *J* 9, NHC*H*CH(OH)CH_3), 5.54 (1H, br s, $CONH_{2A}$), 6.11 (1H, m, NHC*H*$CH_2C(CH_3)_3$), 6.53 (1H, br s, $CONH_{2B}$), 6.61 (1H, br s, H-4 furan), 6.92 (2H, br m, CH_2N*H*SO_2-naphthalene and N*H*CHCH(OH)CH_3), 7.45 (1H, s, H-5 furan), 7.62 (2H, m, H-6 and H-7 of naphthalene), 7.73 (1H, d, *J* 8.5, H-3 of naphthalene), 7.88 (2H, d, *J* 8.5, H-4 and H-5 or H-8 of naphthalene), 7.96 (1H, d, *J* 8.5, H-5 or H-8 of naphthalene), 7.98 (1H, s, H-2 furan), and 8.36 (1H, s, H-1 naphthalene).

Compound 16; 6{*4,1,2*}. 2-(1*R*-{2*S*-[(Furan-3-carbonyl)amino]-4,4-dimethylpentanoylamino}-2*S*-hydroxypropyl)-5-(naphthalene-2-yloxymethyl)-oxazole-4-carboxamide. Crude compound **16** (19.2 mg) was dissolved in 0.1% aq TFA/acetonitrile (1:1, v/v, 2 mL) and purified by semipreparative HPLC, eluting with a 30−90% gradient of solvent B in solvent A over 35 min. The desired fractions were lyophilized to give a white solid (6.8 mg, 50%). Analytical HPLC (system 2) R_t 20.53 min (>99%), HRMS $C_{30}H_{34}O_7N_4Na$ requires *M*, 585.2325, found MNa^+, 585.2313 (δ −2.1 ppm). δ_H (500 MHz; $CDCl_3$) 1.00 (9H, s, NHCHCH_2C(CH_3)$_3$), 1.26 (3H, d, *J* 6.5, NHCHCH(OH)-CH_3), 1.54 (1H, dd, *J* 14.5 and 8, NHCHC$H_{2A}$$C(CH_3)_3$), 2.06 (1H, dd, *J* 14.5 and 5, NHCHC$H_{2B}$$C(CH_3)_3$), 4.41 (1H, dq, *J* 6.5 and 2.5, NHCHC*H*(OH)CH_3), 4.74 (1H, ddd, *J* 8.5, 8, and 5, NHC*H*$CH_2C(CH_3)_3$), 5.10 (1H, dd, *J* 9 and 2.5, NHC*H*CH(OH)CH_3), 5.43 (1H, d, *J* 13, CH_{2A}O-naphthalene), 5.53 (1H, d, *J* 13, CH_{2B}O-naphthalene), 6.00 (1H, d, *J* 8.5), 6.55 (1H, d, *J* 1, H-4 furan), 6.80 (1H, br m, N*H*CHCH_2C-$(CH_3)_3$), 7.12 (2H, dd, *J* 9 and 2.5, N*H*CHCH(OH)CH_3 and H-3 naphthalene), 7.20 (1H, d, *J* 1, H-5 furan), 7.31 (1H, d, *J* 2.5, H-1 naphthalene), 7.34 (1H, m, H-6 naphthalene), 7.50 (1H, dt, *J* 8 and 1, H-7 naphthalene), 7.71 (1H, d, *J* 8, H-8 naphthalene), 7.73 (1H, d, *J* 8, H-5 naphthalene), 7.75 (1H, d, *J* 9, H-4 naphthalene), and 7.90 (1H, s, H-2 furan).

Compound 17; 8{*4,1,2*}. 2-(1*R*-{2*S*-[(Furan-3-carbonyl)amino]-4,4-dimethylpentanoylamino}-2*S*-hydroxypropyl)-5-(4-methoxyphenylsulfanylmethyl)-oxazole-4-carboxamide. Crude compound **17** (22.7 mg) was dissolved in 0.1% aq TFA/acetonitrile (1:1, v/v, 2 mL) and purified by semipreparative HPLC, eluting with a 30−90% gradient of solvent B in solvent A over 35 min. The desired fractions were lyophilized to give a white solid (6.5 mg, 49%). Analytical HPLC (system 2) R_t 18.81 min, (>99%), HRMS $C_{27}H_{34}O_7N_4NaS$ requires *M*, 581.2046, found MNa^+, 581.2051 (δ +0.8 ppm). δ_H (500 MHz; $CDCl_3$) 1.00 (9H, s, NHCHCH_2C(CH_3)$_3$), 1.24 (3H, d, *J* 6.5, NHCHCH(OH)-CH_3), 1.57 (1H, dd, *J* 14.5 and 8, NHCHC$H_{2A}$$C(CH_3)_3$), 2.06 (1H, dd, *J* 14.5 and 4.5, NHCHC$H_{2B}$$C(CH_3)_3$), 3.79 (1H, s, OCH_3), 4.18 (1H, d, *J* 14.5, CH_{2A}S-phenyl), 4.30 (1H, dq, *J* 6.5 and 2.5, NHCHC*H*(OH)CH_3), 4.36 (1H, d, *J* 14.5, CH_{2B}S-phenyl), 4.75 (1H, ddd, *J* 8.5, 8, and 4.5, NHC*H*CH_2C-$(CH_3)_3$), 5.00 (1H, dd, *J* 9 and 2.5, NHC*H*CH(OH)CH_3), 5.59 (1H, br s, $CONH_{2A}$), 6.13 (1H, d, *J* 8.5, N*H*$CHCH_2C(CH_3)_2$), 6.59 (1H, br s, H-4 furan), 6.60 (1H, br s, $CONH_{2B}$), 6.77 (2H, d, *J* 8.5, H-3 and H-5 phenyl), 7.15 (1H, br d, *J* 9, N*H*CHCH(OH)CH_3), 7.27 (2H, d, *J* 8.5, H-2 and H-6 phenyl), 7.43 (1H, br s, H-5 furan), and 7.92 (1H, s, H-2 furan).

Compound 18; 9{*4,1,2*}. 2-(1*R*-{2*S*-[(Furan-3-carbonyl)amino]-4,4-dimethylpentanoylamino}-2*S*-hydroxypropyl)-5-(4-methoxybenzenesulfonylmethyl)-oxazole-4-carboxamide. Crude compound **18** (19.9 mg) was dissolved in 0.1% aq TFA/acetonitrile (1:1, v/v, 2 mL) and purified by semipreparative HPLC, eluting with a 30−90% gradient of solvent B in solvent A over 35 min. The desired fractions were lyophilized to give a white solid (4.6 mg, 32%). Analytical HPLC (system 2) R_t 17.69 min, (>99%), HRMS $C_{27}H_{34}O_9N_4NaS$ requires *M*, 613.1944, found MNa^+, 613.1967 (δ +3.7 ppm). δ_H (500 MHz; $CDCl_3$) 0.99 (9H, s, NHCHCH_2C(CH_3)$_3$, 1.31 (3H, d, *J* 6, NHCHCH(OH)CH_3), 1.62 (1H, dd, *J* 14.5 and 8.5, NHCHC$H_{2A}$$C(CH_3)_3$), 2.10 (1H, dd, *J* 14.5 and 3, NHCHC$H_{2B}$$C(CH_3)_3$), 3.84 (3H, s OCH_3), 4.35 (2H, m, NHCHC*H*(OH)CH_3 and C$H_{2A}$$SO_2$Ph), 4.84 (1H, ddd, *J* 8.5, 3.5, and 3, NHC*H*$CH_2C(CH_3)_3$), 4.96 (2H,

m, CH_{2B}SO$_2$Ph and NHC*H*CH(OH)CH$_3$), 5.49 (1H, br s, CONH$_{2A}$), 6.60 (1H, br s, CONH$_{2B}$), 6.74 (2H, br s, H-4 furan and N*H*CHCH$_2$C(CH$_3$)$_2$), 6.93 (2H, d, *J* 8.5, 2 × *o*-CH$_3$O*Ph*), 7.45 (1H, s, H-5 furan), 7.58 (1H, br s, N*H*CHCH(OH)CH$_3$), 7.63 (2H, d, *J* 8.5, 2 × *m*-CH$_3$O*Ph*), and 8.02 (1H, s, H-2 furan).

Compound 19; 11{*4,1,2*}. 2-(1*R*-{2*S*-[(Furan-3-carbonyl)amino]-4,4-dimethylpentanoylamino}-2*S*-hydroxypropyl)-5-[(2-naphthalene-2-yl-acetylamino)methyl]-oxazole-4-carboxamide. Crude compound **19** (16.0 mg) was dissolved in 0.1% aq TFA/acetonitrile (1:1, v/v, 2 mL) and purified by semipreparative HPLC, eluting with a 30−90% gradient of solvent B in solvent A over 35 min. The desired fractions were lyophilized to give a white solid (1.4 mg, 10%). Analytical HPLC (system 2) R_t 19.09 min (>99%), HRMS $C_{32}H_{37}O_7N_5Na$ requires *M*, 626.2591, found MNa$^+$, 626.2606 (δ +2.4 ppm). δ_H (500 MHz; CDCl$_3$) 0.99 (9H, s, NHCHCH$_2$C(C*H*$_3$)$_3$), 1.26 (3H, d, *J* 6, NHCHCH(OH)C*H*$_3$), 1.65 (1H, dd, *J* 14.5 and 8, NHCHC*H*$_{2A}$C(CH$_3$)$_3$), 2.00 (1H, dd, *J* 14.5 and 3, NHCHC*H*$_{2B}$C(CH$_3$)$_3$), 3.72 (2H, s, CH$_2$-NHCOC*H*$_2$-naphthalene), 4.35 (1H, m, NHCHC*H*(OH)CH$_3$), 4.50 (1H, dd, *J* 16 and 4.5, C*H*$_{2A}$NHCOCH$_2$-naphthalene), 4.59 (1H, dd, *J* 16 and 6, C*H*$_{2B}$NHCOCH$_2$-naphthalene), 4.83 (1H, br m, NHC*H*CH$_2$C(CH$_3$)$_3$), 4.99 (1H, br d, *J* 9, NHC*H*CH(OH)CH$_3$), 5.86 (1H, br s, CONH$_{2A}$), 6.64 (1H, s, H-4 furan), 6.75 (1H, br d, *J* 8, N*H*CHCH$_2$C(CH$_3$)$_2$), 7.04 (1H, br s, CONH$_{2B}$), 7.13 (1H, br s, CH$_2$N*H*COCH$_2$-naphthalene), 7.34 (1H, d, *J* 8.5, H-3 naphthalene), 7.38 (1H, s, H-5 furan), 7.48 (3H, m, N*H*CHCH(OH)CH$_3$, H-6 and H-7 naphthalene), 7.69 (1H, s, H-1 naphthalene), 7.80 (3H, m, H-4, H-5, and H-8 naphthalene), and 7.95 (1H, s, H-2 furan).

Compound 20; 13{*4,1,2*}. 2-(1*R*-{2*S*-[(Furan-3-carbonyl)amino]-4,4-dimethylpentanoylamino}-2*S*-hydroxypropyl)-5-[(thiophene-2-sulfonylamino)methyl]-oxazole-4-carboxamide. Crude compound **20** (18.2 mg) was dissolved in 0.1% aq TFA/acetonitrile (1:1, v/v, 2 mL) and purified by semipreparative HPLC, eluting with a 30−90% gradient of solvent B in solvent A over 35 min. The desired fractions were lyophilized to give a white solid (2.5 mg, 18%). Analytical HPLC (system 2) R_t 17.09 min (>99%), HRMS $C_{24}H_{31}O_8N_5NaS$ requires *M*, 604.1512, found MNa$^+$, 604.1509 (δ −0.5 ppm). δ_H (500 MHz; CDCl$_3$) 0.99 (9H, s, NHCHCH$_2$C(C*H*$_3$)$_3$), 1.30 (3H, d, *J* 6.5, NHCHCH(OH)-C*H*$_3$), 1.65 (1H, dd, *J* 14.5 and 8.5, NHCHC*H*$_{2A}$C(CH$_3$)$_3$), 1.99 (1H, dd, *J* 14.5 and 4.5, NHCHC*H*$_{2B}$C(CH$_3$)$_3$), 4.41 (3H, m, C*H*$_2$NHSO$_2$-thiophene and NHCHC*H*(OH)CH$_3$), 4.77 (1H, ddd, *J* 8.5, 7.5, and 4.5, NHC*H*CH$_2$C(CH$_3$)$_3$), 5.02 (1H, dd, *J* 9 and 2, NHC*H*CH(OH)CH$_3$), 6.04 (1H, br s, CONH$_{2A}$), 6.40 (1H, d, *J* 7.5, N*H*CHCH$_2$C(CH$_3$)$_3$), 6.64 (1H, br s, H-4 furan), 6.83 (1H, br s, CONH$_{2B}$), 6.97 (1H, t, *J* 5, H-4 thiophene), 7.06 (1H, br t, *J* 4, CH$_2$N*H*SO$_2$-thiophene), 7.41 (1H, d, *J* 9, N*H*CHCH(OH)CH$_3$), 7.43 (1H, s, H-5 furan), 7.49 (1H, dd, *J* 5 and 1, H-3 thiophene), 7.52 (1H, dd, *J* 5 and 1, H-5 thiophene), and 7.99 (1H, s, H-2 furan).

Supporting Information Available. Full proton and correlation spectra for compounds **1**−**20**. This material is available free of charge via the Internet at http://pubs.acs.org.

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