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Solution-Phase Parallel Synthesis of a Benzoxazinone Library Using Complementary Molecular Reactivity and Molecular Recognition (CMR/R) Purification Technology

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Abstract: A solution-phase synthesis of a benzoxazinone library is described. The five-step synthesis is accomplished using combinations of complementary molecular reactivity and molecular recognition (CMR/R) purification concepts, including reactant-sequestering resins, reagent-sequestering resins, sequestration-enabling-reagents, reaction-quenching resins, as well as the judicious use of polymeric reagents. The multi-step synthesis affords the desired benzoxazinone products in excellent purities and yields. This study demonstrates that multi-step library syntheses can be performed in solution-phase, and that utilization of CMR/R purification strategies as the sole method of purification can lead to products of high purity. © 1998 Published by Elsevier Science Ltd. All rights reserved.

The development of solution-phase synthetic methodologies has recently emerged as a useful method for preparing arrays of small molecules in a chemical library format.[1,2] In the context of a broader interest in developing chemical libraries biased as protease inhibitors, we had need to build chemical libraries based on the benzoxazinone scaffold. This ring system has previously been utilized to generate nonpeptidic, alternate substrate inhibitors of serine proteases.[3] In an effort to automate the synthesis and prepare libraries of benzoxazinones in a parallel format, a solution-phase library synthesis was developed utilizing our recently disclosed CMR/R technology.[1c] Herein, we report a five-step solution-phase synthesis of benzoxazinones in which purification of all intermediates and final products is effected by the use of CMR/R sequestering resins, sequestration-enabling-reagents (SER),[4] and simple filtration. This library synthesis has been adapted for high-throughput production in a fully automated robotics laboratory.

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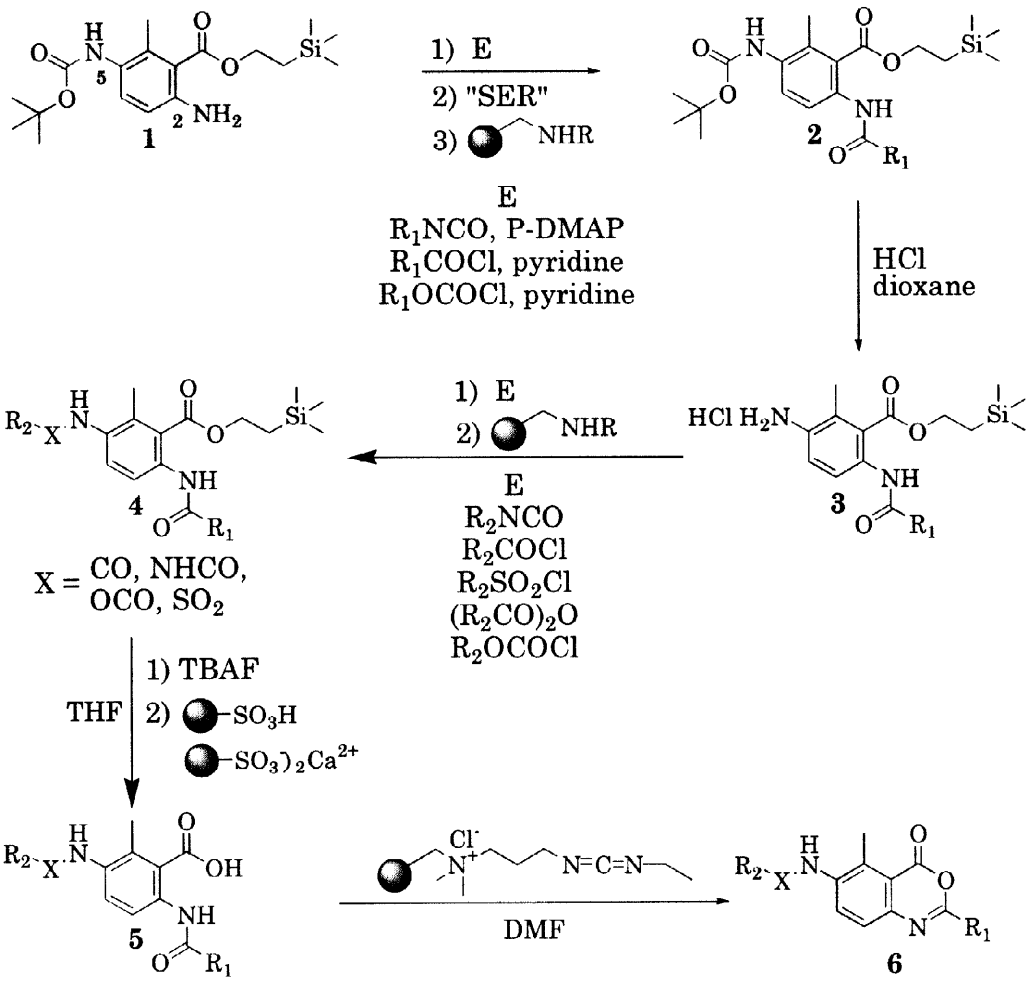
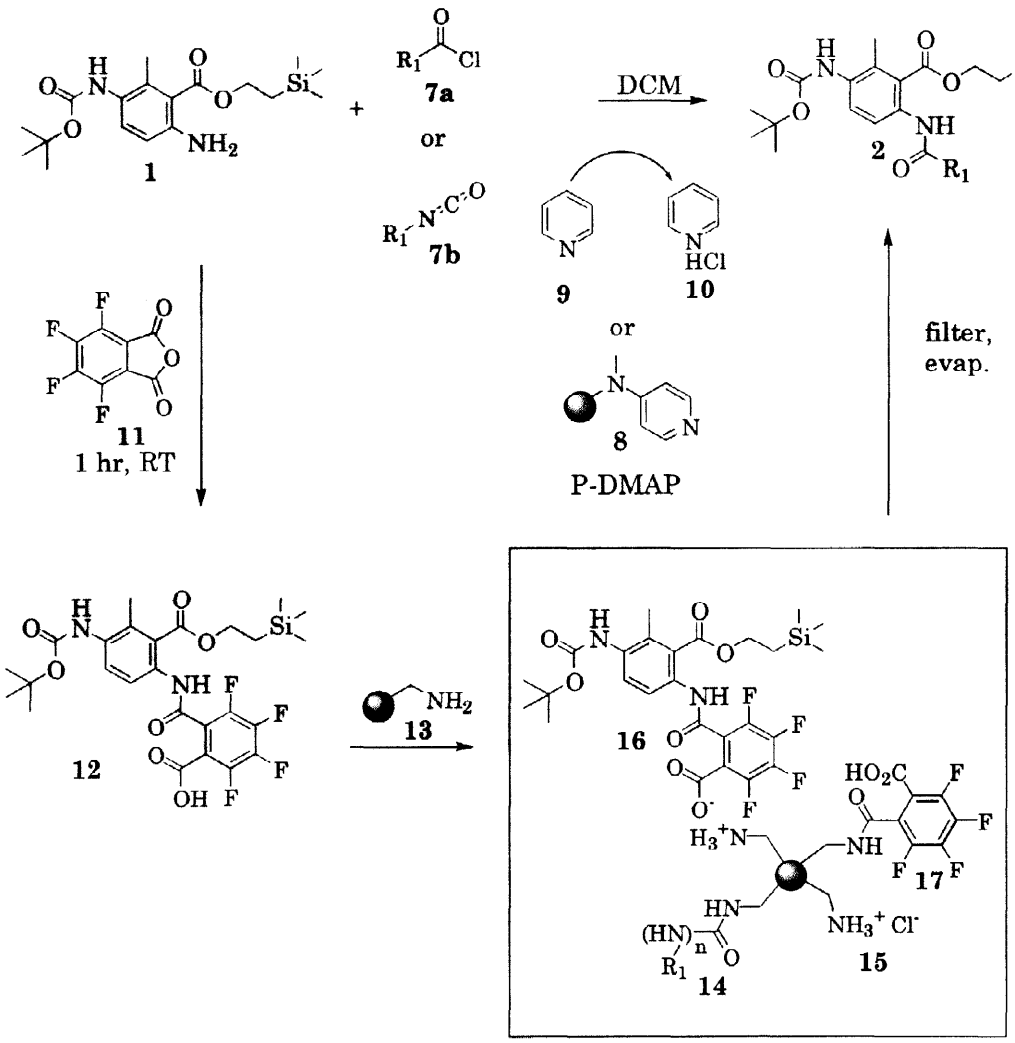
A summary description of the library synthesis is depicted in Scheme 1. Each of the steps in the synthesis underwent independent validation in order to identify and optimize conditions such that each transformation could be performed in a high-yielding, parallel format in our robotics laboratory reaction block apparatus.[5] Compound **1** was selected as the starting scaffold with the C-5 aniline nitrogen protected as the *t*-butyl carbamate and the acid function protected as the 2-(trimethylsilyl)ethyl ester. The protecting groups were chosen to allow for orthogonal deprotection and the release of volatile byproducts upon their removal. The synthesis (Scheme 1) was devised such that the last step of the synthesis was the formation of the benzoxazinone ring system. Since the final benzoxazinone products **6** are susceptible to attack by amine nucleophiles, the use of basic, nucleophilic amine CMR/R resins to scavenge acid-containing impurities (i.e. uncyclized acids **5**) is precluded. Therefore, a novel, less reactive sequestration strategy would be required for the final purification step of the synthesis.



Scheme 1. Synthesis of benzoxazinones using CMR/R technology.

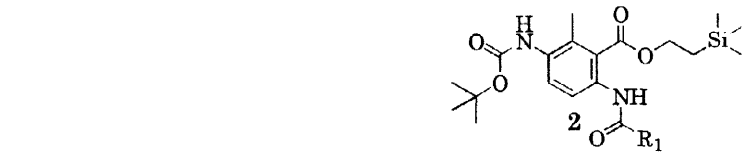
The first step of the synthesis (Scheme 2) involves reaction of the starting scaffold **1** with excess electrophiles **7**. Two protocols were utilized depending upon the nature of the electrophile. The first protocol involved the use of acid chlorides and chloroformates as the electrophiles **7a**. These reactions were run in dichloromethane at room temperature with a 20% excess of electrophile **7a** (to drive the reactions to completion) and pyridine **9** as the base to remove the HCl byproduct. After total consumption of the scaffold **1** was observed by TLC, the reactions contained the products **2**, excess electrophiles **7a**, and pyridine hydrochloride **10**. The reactant-sequestering nucleophilic CMR/R polyamine resin **13**[1c] was added to react with the excess electrophile **7a** in each reaction chamber, forming the insoluble polymeric adducts **14a** (n = 0). The basic CMR/R resin **13** also sequestered the HCl byproduct (HCl transfer from pyridine HCl **10**) as adduct **15**, leaving only volatile pyridine **9** and the desired acylated products **2** in solution-phase. Simple filtration and rinsing with dichloromethane yielded a filtrate whereupon evaporation of the solvents left highly purified product **2** from each parallel reaction. The second reaction protocol involved the use of isocyanates **7b** as the electrophiles. The scaffold **1** was reacted with two equivalents of the isocyanate **7b** in anhydrous dichloromethane at 55° C for 48 hours in the presence of polymer-bound DMAP **8**.[6] The reactions did not progress to completion despite the use of a large excess of isocyanate **7b**, heating, and/or longer reaction times (7 days), leaving approximately 10% of the unreacted starting scaffold **1** as an impurity in each reaction chamber in addition to the product **2**, excess isocyanate **7b**, and polymer-bound DMAP **8**. We have previously developed the use of tetrafluorophthalic anhydride (TFPA) as a sequestration-enabling-reagent to effect the *in situ* tagging of poorly-sequestrable amines (especially sterically hindered or electron-deficient anilines) and alcohols.[4] In the present case, utilization of TFPA proved to be useful for *in situ* conversion of the poorly-sequestrable aniline **1** to the readily-sequestrable carboxy-tagged derivative **12**. Thus, after 48 hours at 55° C, each reaction chamber solution was cooled to room temperature and tetrafluorophthalic anhydride, SER **11**, (excess relative to **1**) was added, quantitatively transforming starting aniline **1** into the *in situ* carboxy-tagged species **12**. The singular CMR/R resin **13** was then added to sequester excess isocyanate **7b**, the complementary carboxy-tagged aniline derivative **12**, and any excess SER **11**, as polymer-bound adducts **14b** (n = 1), **16**, and **17**, respectively. Filtration, rinsing with dichloromethane, and concentration afforded highly purified products **2** in each case. It is worth noting that solution-phase CMR/R purification techniques employing the use of sequestration-enabling-reagents such as TFPA allow for modestly-reactive intermediates (*incomplete reaction 'deletion errors'*) to be sequestered away from the library pool during the course of synthesis. By contrast, if solid-phase organic synthesis had been used as the chemical library synthesis paradigm, polymer-tethered deletion intermediates, such as unreacted intermediates **1**, would have been eventually released from the polymer support as contaminants in the final products.

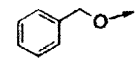
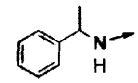
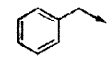
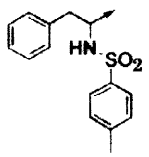
The reactions for step 1 were run in a 48 well reaction block[5] (6X8 spatially-addressed matrix) with five of the six rows (**A-E**) containing a unique electrophile **7** and the sixth row left empty. The electrophiles used (benzyl chloroformate, (R)-(+)-α-methylbenzylisocyanate, benzoyl chloride, isopropyl isocyanate, and N-*p*-tosyl-L-phenylalaninyl chloride) were selected to afford a diverse set of products **2** wherein R_1 is alkyl, alkoxy, or substituted amino. Sample was taken from each reaction vessel of the first column to obtain HPLC, ^{1}H NMR, and HRMS. Table 1 illustrates the analogs prepared for each row and the HPLC purity of each compound. The minimum purity realized for step 1 was 97% (row B).



Scheme 2. Synthetic step 1 of benzoxazinone synthesis.

Selective deprotection of the C-5 NH-Boc group was accomplished using 2N HCl in dioxane to afford the aniline hydrochloride salts **3** (Scheme 1).[7] In our initial validation studies with the urea compounds **2**, where R_1 = NHR, selective deprotection was accomplished with no evidence of concomitant deprotection of the 2-(trimethylsilyl)ethyl ester. However, during our production run, some deprotection of the ester occurred, affording the carboxylic acid equivalent of **3** as an impurity. For this run, the reactions were carried on with the acid present in the product mixture. However, in future runs the product mixtures were purified using CMR/R polyamine resin **13** to remove any carboxylic acid impurities, affording the salt-free 2-(trimethylsilyl)ethyl esters **3** in high purity. Other methods tried for selective deprotection of the Boc group included various conditions with acetic acid, mixtures of TFA/DCM, sulfonic acid resin (A-15), and nafion which led to non-selective deprotection or no reaction. *p*-Toluenesulfonic acid was successful in selective deprotection[8] of the Boc group to afford the salt-free aniline **3** but was not as clean as the 2N HCl and required removal of the *p*-toluenesulfonic acid with a CMR/R resin verses removal of excess HCl by evaporation.

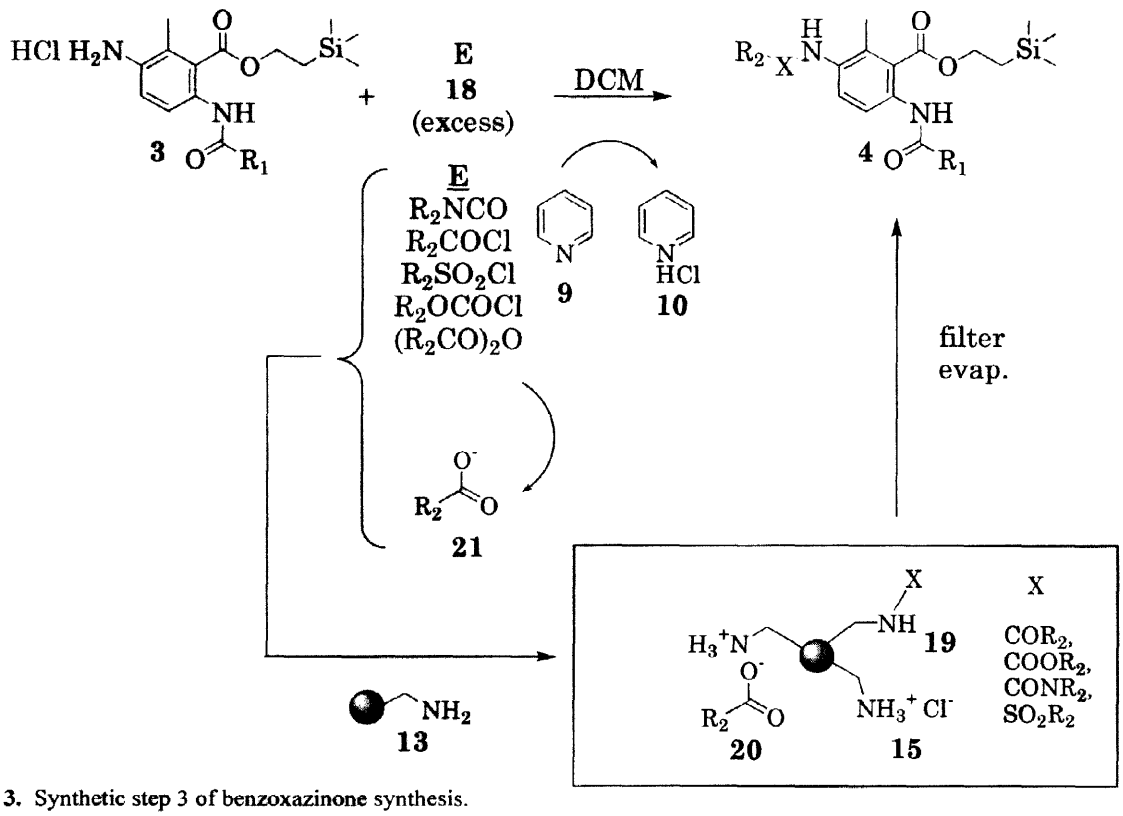


R_1									
	A	98[a]	-	-	-	-	-	-	-
	B	97	-	-	-	-	-	-	-
	C	99	-	-	-	-	-	-	-
	D	99	-	-	-	-	-	-	-
	E	99	a	b	c	d	e	f	g	h

[a]HPLC conditions: ODS Hypersil 5um 125 x 4 mm C18 column, 5-95% MeCN/1.0% TEA, 0.5% H_3PO_4, 30 min.

Table 1. HPLC purities (%) for compounds **2**.

The third step in the synthesis called for derivatization of the C-5 aniline nitrogen. Scheme 3 illustrates the reaction of the aniline hydrochlorides **3** with various electrophiles **18** including acid halides, isocyanates, a chloroformate, a sulfonyl halide, and an anhydride,[9] affording a diverse set of analogs. Intermediates **3** were dissolved into DCM and pyridine **9** (to trap HCl) and then reacted with a 20% excess of the electrophiles **18**. After 16 hours of agitation at room temperature, total consumption of the starting aniline **3** was observed by TLC for each of the reactions, avoiding the need for using SER-*in situ* tagging (TFPA **11**) during purification. Each reaction mixture contained the product **4**, excess electrophile **18**, carboxylic acid byproduct **21** (when electrophile **18** is anhydride), and pyridine hydrochloride **10**. The CMR/R polyamine resin **13** was added to sequester excess electrophile **18**, any acid byproduct **21**, and HCl as polymer-bound adducts **19**, **20** and **15**, respectively. Simple filtration and rinsing with dichloromethane yielded a filtrate whereupon evaporation of the solvents left highly purified product **4** from each parallel reaction.



Scheme 3. Synthetic step 3 of benzoxazinone synthesis.

In the 48 well reaction block, each column **a-f** (Table 2) contained a unique electrophile **18**. The electrophiles **18** used (carbobenzyloxy-L-valine anhydride, benzoyl chloride, hydrocinnamoyl chloride, benzene sulfonyl chloride, benzyl chloroformate, and benzyl isocyanate) were selected to represent a diverse set, affording products **4** containing an amide, carbamate, sulfonamide, or urea functionality. Column **g** contained the compounds with the C-5 Boc groups left intact from step 2 (omission of the HCl/dioxane-deprotection conditions). Sample was taken from each reaction vessel to obtain HPLC, ^{1}H NMR, and HRMS for each intermediate **4**. Table 2 illustrates the HPLC purities of compounds **4**. Compounds with R_1 = alkyl (**4Ca-g** and **4Ea-g**) or alkoxy (**4Aa-g**) had good to excellent purities ranging from 78-99%; compounds **4** wherein R_1 = NHR (**4Ba-g** and **4Da-g**) were generally of lower purity than the other analogs and usually contained a substantial amount of a second product. It was found that the acid impurity, carried on from the previous step, had undergone ring closure to afford the benzoxazinone, accounting for this new "impurity". Jarvest *et al* has reported a similar procedure for the preparation of benzoxazinones from anthranilic acids by activating the carboxylic acid for intramolecular nucleophilic attack to form the benzoxazinone.[3f] Since these

"impurities" were the eventual benzoxazinone targets, no effort was made to effect their removal from the product mixtures.

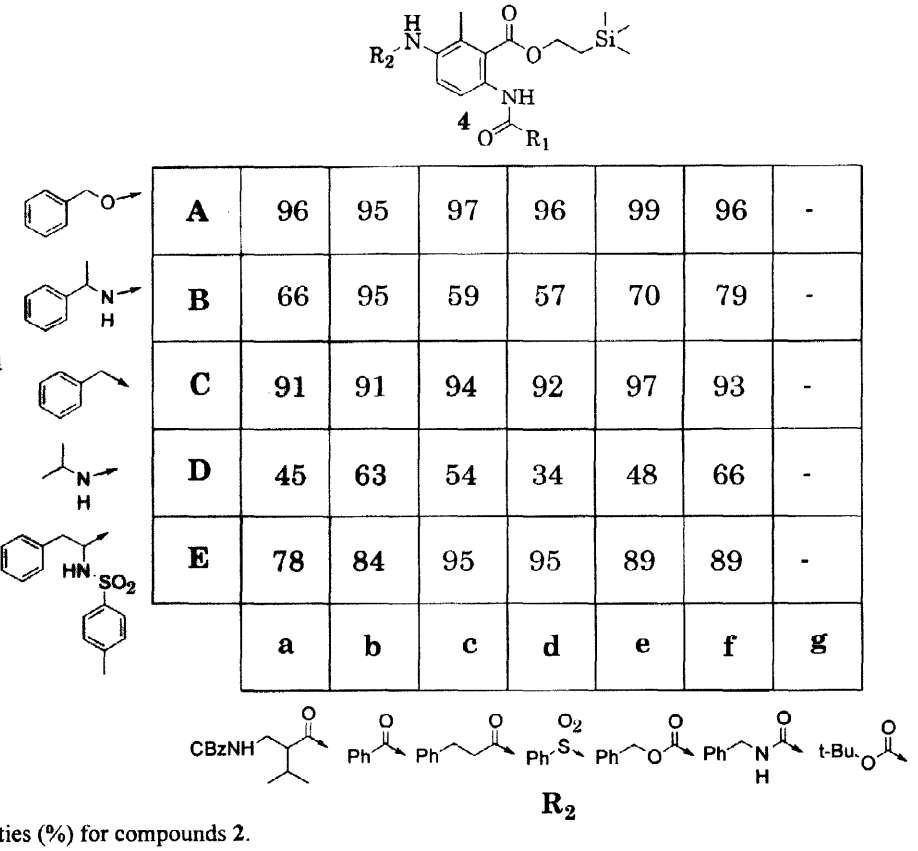
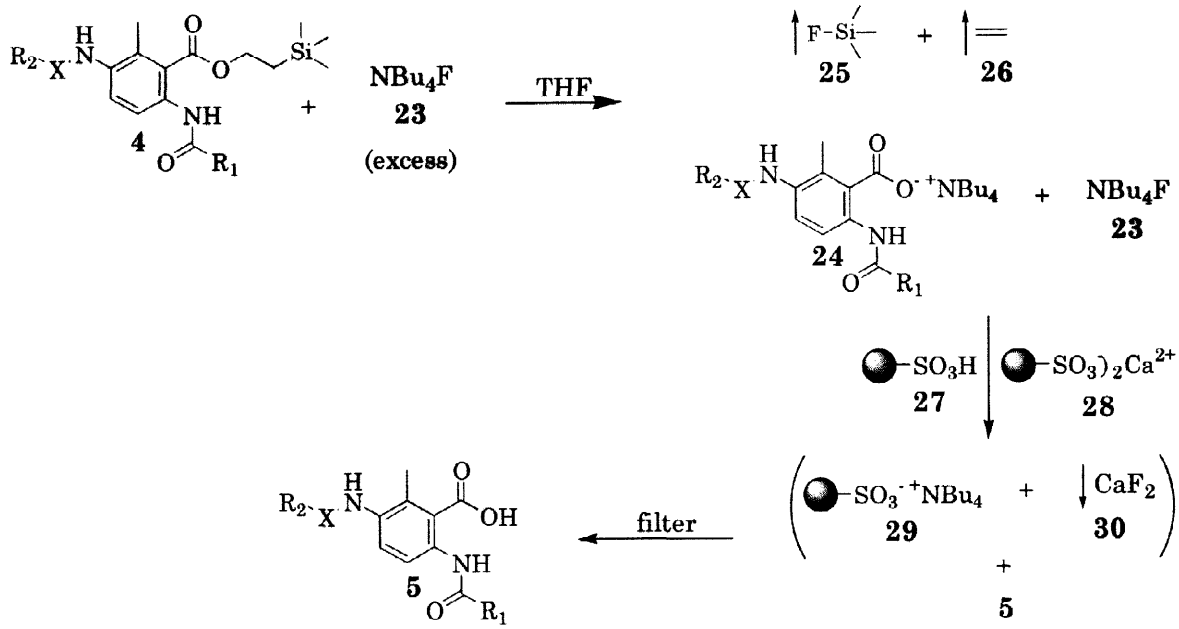


Table 2. HPLC purities (%) for compounds **2**.

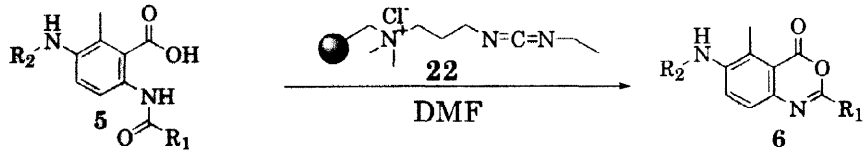
The fourth step of the synthesis involved deprotection of the 2-(trimethylsilyl)ethyl ester of compounds **4** as a prelude to final ring closure. Attempts at deprotection of the 2-(trimethylsilyl)ethyl ester group were unsuccessful using a polymer-bound fluoride source such as poly[4-vinylpyridinium poly(hydrogen fluoride)] or Amberlyst® A-26 (fluoride form). Attempts at deprotection using 4N HCl in dioxane were successful for the compounds **4** wherein R_1 = NHR (**4Ba-g** and **4Da-g**), but the reactions involving compounds **4** with R_1 = alkyl (**4Ca-g** and **4Ea-g**) or alkoxy (**4Aa-g**) did not proceed to completion. Other attempts at deprotection involving TFA did not afford a single condition compatible for all of the starting compounds **4**. The failure of the above attempts for the deprotection led to the more commonly-used solution phase reagent *tetra*-butylammonium fluoride, TBAF. However, using TBAF as the reagent classically requires a liquid-phase extraction protocol for reaction quench and workup. In preparing libraries of compounds in a parallel format, the need to pace all reactions through a liquid-phase extractive protocol was deemed to be a time-consuming process and difficult to automate. Employment of CMR/R resins for reaction work-up (*i.e.* complementary reaction-quenching functionality displayed on a resin surface) would obviate the need for liquid-phase extractive protocols; reaction quench/workup could simply be performed by the addition of reagent-sequestering and reaction-quenching CMR/R resins to each reaction mixture, followed by filtration to afford

the desired product. Scheme 5 illustrates the deprotection of the 2-(trimethylsilyl)ethyl ester group of compounds **4** using TBAF, followed by the simultaneous use of two CMR/R resins for the quenching and purification of the product mixtures. Each 2-(trimethylsilyl)ethyl ester **4** was dissolved into anhydrous THF (BHT free) and treated with excess TBAF **23** at room temperature for 16 hours to afford a product mixture containing the carboxylate *tetra*-butylammonium salt **24**, excess TBAF **23**, and the volatile byproducts fluorotrimethylsilane **25** and ethylene **26**. Upon completion of the reaction, a combination of the CMR/R resins **27** and **28** were added simultaneously. The CMR/R resin **27** quenched the *tetra*-butylammonium carboxylate salt **24**, affording polymer-bound *tetra*-butylammonium sulfonate **29** and the desired acid product **5**. The CMR/R resin **28** reacted with the excess TBAF **23**, forming the polymer-bound *tetra*-butylammonium sulfonate **29** and insoluble calcium fluoride **30**. Filtration (removal of **29** and **30**) and simple evaporation afforded the purified product **5** in each reaction chamber.



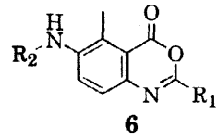
Scheme 5. Synthetic step 4 of benzoxazinone synthesis.

The fifth and last step of the synthesis involved ring closure (cyclodehydration) of intermediates **5** to afford the benzoxazinones **6**. It has been previously demonstrated that a carbodiimide can mediate ring closure to provide benzoxazinones, even when compounds **5** contains an urea (R_1 =NHR) which could alternatively close by attack of nitrogen to afford quinazolinediones.[3c, 3g] The use of polymeric-EDC permitted this transformation to be performed in a parallel format, as shown in Scheme 6. Moreover it was anticipated that polymeric EDC would also trap any uncyclized acid as sequestered imino-anhydride adducts. Thus polymeric EDC also served a dual role as a reactant-sequestering CMR/R resin. Each acid **5** was dissolved into DMF with an excess of polymer-bound EDC **22**, and the slurry was agitated at room temperature for 12 hours. Filtration and evaporation afforded the desired benzoxazinone **6** from each reaction chamber.



Scheme 6. Synthetic step 5 of benzoxazinone synthesis: Cyclodehydration mediated by polymeric EDC **22**.

The HPLC purities and overall yields for the desired benzoxazinones **6** are listed in Table 3. Compounds **6** with R_1 = alkyl (**6Ca-g** and **6Ea-g**) or alkoxy (**6Aa-g**) exhibited good to excellent purities ranging from 82-99%, and compounds **4** wherein R_1 = NHR (**4Ba-g** and **4Da-g**) were generally of somewhat lower purity than the other analogs, having HPLC purities in the 30-87% range. Only three compounds from



R_1 \ R_2	a	b	c	d	e	f	g
A	92 (70)	93 (48)	95 (60)	89 (71)	92 (47)	89 (41)	91 (82)
B	48 (36)	69 (23)	74 (32)	75 (27)	73 (31)	69 (15)	76 (62)
C	93 (47)	95 (72)	98 (60)	97 (66)	99 (75)	82 (44)	99 (89)
D	31 (20)	75 (23)	73 (16)	78 (13)	68 (22)	30 (16)	87 (29)
E	88 (65)	93 (76)	91 (55)	83 (42)	84 (85)	86 (49)	90 (114)

Table 3. Yields[a] and HPLC[b] purities of benzoxazinone products **6**.
[a]Yields are based on mass recovery. [b]HPLC conditions: ODS Hypersil 5um 125x4 mm C18 column, 5-95% acetonitrile/1.0% TEA, 0.5% H_3PO_4, 30 min.

the entire grid afforded HPLC purities less than 50%. The yields were good to excellent for compounds **6** with R_1 = alkyl (**6Ca-g** and **6Ea-g**) or alkoxy (**6Aa-g**). Compounds **4Ba-g** and **4Da-g** exhibited lower yields largely due to incomplete reaction at step 1 (*vide supra*, Scheme 2). Considering that this is a five-step synthesis, with a portion of the sample taken for characterization of each intermediate and the physical manipulation of the reaction mixtures to and from the reaction block, these are quite acceptable overall yields (i.e. 90% yield for each reaction of a 5 step synthesis affords an overall 59% yield).

In conclusion, a solution-phase library synthesis of benzoxazinones has been developed wherein the only purification techniques employed were those based on our recently reported CMR/R technology. Specifically, all intermediates and final products were purified by the *post-reaction* use of reactant-sequestering resins, reagent-sequestering resins, *in situ* tagging by sequestration-enabling-reagents, and reaction-quenching resins. This purification strategy is highly amenable to automation; indeed the reactions were performed in our robotic laboratory reaction block apparatus. This five-step solution-phase synthesis of benzoxazinones demonstrates that CMR/R purification technology can be used even for multi-step library syntheses, previously thought to be the exclusive domain of solid phase organic synthesis.

EXPERIMENTAL SECTION

General: ^{1}H NMR spectra were recorded using 360 and 400 MHz NMR spectrometers. Elemental analyses were performed by Atlantic Microlab Inc., Atlanta, GA. HPLC purities were determined with a Hewlett Packard HP1100 and a ODS Hypersil 5um 125 x 5 mm C18 column, eluting with a gradient system of 5/95 to 95/5 acetonitrile/H_2O with a buffer consisting of 1.0% TEA/0.50% H_3PO_4 over 30 min at 1 mL/min, and detected by UV at 254 nm using a diode array detector. Column chromatography was performed on a Waters preparative liquid chromatography Model 500, using silica gel columns. Reported yields are unoptimized with emphasis on purity of products rather than quantity.

6-amino-3-[[(1,1-dimethylethoxy)carbonyl]amino]2-methylbenzoic, 2-(trimethylsilyl)ethyl ester (1). 2-(Trimethylsilyl)ethyl alcohol (12.0 g, 0.10 mol) and potassium carbonate (9.4 g, 0.067 mol) were refluxed in THF for 3 hours. 1,1-Dimethylethyl(1,4-dihydro-5-methyl-2,4-dioxo-2H-3,1-benzoxazin-6yl)carbamate[2] (10.0 g, 0.034 mol) was added and the solution stirred for four days at reflux. Upon completion of the reaction, the solution was cooled to room temperature and diluted with water and ethyl acetate. The organic layer was washed with water and brine. The solution was dried over magnesium sulfate, filtered and the solvent was removed to give the crude product. The product was purified by column chromatagraphy (25% ethyl acetate-hexane) to give 5.9 g (48%) of a white solid of **1**; ^{1}H NMR ($CDCl_3$) ppm 0.09 (s, 9H), 1.13 (m, 2H), 1.51 (s, 9H), 2.29 (s, 3H), 4.41 (m, 2H), 4.68 (bs, 2H), 5.98 (bs, 1H), 6.56 (d, 1H), 7.31 (bs, 1H); Anal. Calcd for $C_{18}H_{30}O_4N_2Si$: C, 58.98; H, 8.25; N, 7.64. Found: C, 59.05; H, 8.20; N, 7.58.

General Procedure A. Amide/carbamate formation from Scaffold 1 to afford compounds (2a,c,e). The aniline **1** (158.53 mM) (946 uL, 0.15 mmol) in anhydrous dichloromethane was added to a reaction vessel containing 2 mL of dichloromethane. A solution of pyridine **9** (180 mM) (1 mL, 0.180 mmol) in dichloromethane was added followed by addition of the electrophile **7a** (neat) (0.17 mmol) (benzoyl chloride, N-p-tosyl-L-phenylalaninlyl chloride, and benzyl chloroformate) and the solution was agitated on an orbital shaker at room temperature for 22 hours. Upon completion of the reaction, the CMR/R polyamine resin **13** (~2.98 meq/g) (300 mg, 0.894 mmol) was added followed by addition of 2 mL of dichloromethane and the suspension was agitated on an orbital shaker for 1 hour. The solution was filtered and the polymer was rinsed with four 1 mL portions of dichloromethane. The combined filtrate and washings are evaporated to afford the pure product **2**.

2A: general procedure A; ^{1}H NMR ($CDCl_3$) ppm 0.09 (s, 9H), 1.14 (m, 2H), 1.53 (s, 9H), 2.29 (s, 3H), 4.44 (m, 2H), 5.20 (s, 2H), 6.15 (bs, 1H), 7.38 (m, 5H), 7.71 (bd, 1H), 7.94 (bd, 1H), 8.24 (bs, 1H); HPLC purity (retention time): 98.6% (23.9 min); HRMS calcd for $C_{26}H_{36}O_6N_2Si$ ($M^+ + NH_4$) 518.2686, found 518.2685.

2C: general procedure A; ^{1}H NMR ($CDCl_3$) ppm 0.08 (s, 9H), 1.13 (m, 2H), 1.54 (s, 9H), 2.36 (s, 3H), 4.46 (m, 2H), 6.22 (bs, 1H), 7.55 (m, 3H), 7.73 (m, 1H), 7.93 (dd, 2H), 8.36 (d, 1H), 9.95 (bs, 1H); HPLC purity (retention time): 99.3% (22.2 min); HRMS calcd for $C_{25}H_{34}O_5N_2Si$ ($M^+ + NH_4$) 488.2581, found 488.2581.

2E: general procedure A; ^{1}H NMR ($CDCl_3$) ppm 0.09 (s, 9H), 1.13 (m, 2H), 1.54 (s, 9H), 2.28 (s, 3H), 2.39 (s, 3H), 3.03 (m, 2H), 3.96 (bs, 1H), 4.46 (m, 2H), 5.02 (bs, 1H), 6.24 (bs, 1H), 6.96 (m, 2H), 7.19 (m, 5H), 7.55 (d, 2H), 7.57 (bd, 1H), 7.94 (d, 1H), 9.50 (bs, 1H); HPLC purity (retention time): 100% (23.6 min); HRMS calcd for $C_{34}H_{45}O_7N_3SSi$ ($M^+ + NH_4$) 685.3091, found 685.3081.

General Procedure B. Urea formation from Scaffold 1 to afford compounds (2b,d).
The aniline **1** (158.53 mM) (946 uL, 0.15 mmol) in anhydrous dichloromethane was added to a reaction vessel containing 2 mL of anhydrous dichloromethane. The isocyanate **7b** (neat) (0.30 mmole) (isopropyl isocyanate and (R)-(+)-α-methylbenzyl isocyanate) was added followed by addition of a catalytic amount of polymer-bound DMAP **8** and the solution stirred at 55° C for 49 hours. Tetrafluorophthalic anhydride **11** (22 mg, 0.10 mmoles) was added and the solution stirred at room temperature for 1 hour. The CMR/R polyamine resin **13** (500 mg, 1.49 mmoles, ~2.98 meq/g) was added followed by addition of 2 mL of anhydrous DCM and the solution stirred at room temperature for 1 hour. The solution was filtered and the polymer was rinsed with four 1 mL portions of dichloromethane. The combined filtrate and washings are evaporated to afford the pure product **2**.

4-(N-Benzyl-N-methylamino)pyridine polymer supported (P-DMAP), (8).
The polymer-bound DMAP **8** was purchased from Aldrich Chemical Company. The polymer **8** was rinsed three times with DMF, two times with DCM, soaked in DCM for 30 minutes, rinsed two times with DCM, three times with THF, and three times with ether. The polymer **8** was dried under vacuum to a constant weight. Anal. Obsd: Cl, 1.25, N, 7.20.

2B: general procedure B; ^{1}H NMR ($CDCl_3$) ppm 0.09 (s, 9H), 1.11 (m, 2H), 1.50 (d, 3H), 1.52 (s, 9H), 2.26 (s, 3H), 4.37 (m, 2H), 4.88 (bs, 1H), 4.98 (quintet, 1H), 6.16 (bs, 1H), 7.34 (m, 5H), 7.66 (m, 2H), 7.74 (bs, 1H); HPLC purity (retention time): 97.1% (21.8 min); HRMS calcd for $C_{27}H_{39}O_5N_3Si$ ($M^+ + H$) 514.2737, found 514.2758.

2D: general procedure X; ^{1}H NMR ($CDCl_3$) ppm 0.10 (s, 9H), 1.19 (d, 6H), 1.53 (s, 9H), 2.28 (s, 3H), 3.96 (octet, 1H), 4.37 (m, 1H), 4.43 (m, 2H), 6.17 (bs, 1H), 7.72 (s, 1H); HPLC purity (retention time): 99.1% (19.9 min); HRMS calcd for $C_{22}H_{37}O_5N_3Si$ ($M^+ + H$) 452.2581, found 452.2582.

General Procedure C. Deprotection of the Boc group of compounds 2 to afford the aniline hydrochloride salts (3).
Six mL of 2 N HCl in 1,4-dioxane was added to the Boc protected aniline **2** (0.15 mmoles, 25 mM solution) in a reaction vessel and the solution was agitated on an orbital shaker at room temperature for 17 hours. Evaporation of the solvents afforded the product **3**.

3A: general procedure C; ^{1}H NMR ($CDCl_3$) ppm 0.03 (s, 9H), 1.02 (m, 2H), 2.22 (s, 3H), 4.27 (m, 2H), 5.10 (s, 2H), 7.35 (m, 7H), 9.28 (bs, 1H); HPLC purity (retention time): 97.0% (19.6 min); HRMS calcd for $C_{21}H_{28}O_4N_2Si$ ($M^+ + H$) 401.1897, found 401.1901.

3B: general procedure C; ^{1}H NMR ($CDCl_3$) ppm 0.05 (s, 9H), 1.11 (m, 2H), 1.38 (d, 3H), 2.26 (s, 3H), 4.41 (m, 2H), 4.79 (m, 2H), 7.34 (m, 6H), 7.69 (m, 1H), 7.96 (d, 1H); HPLC purity (retention time): 42.5% (17.37 min); HRMS calcd for $C_{22}H_{31}O_3N_3Si$ ($M^+ + H$) 414.2213, found 414.2213.

3C: general procedure C; ^{1}H NMR ($CDCl_3$) ppm 0.06 (s, 9H), 0.88 (m, 2H), 2.28 (s, 3H), 4.20 (m, 2H), 7.51 (m, 5H), 7.92 (d, 2H), 10.15 (s, 1H); HPLC purity (retention time): 87.7% (17.4 min); HRMS calcd for $C_{20}H_{26}O_3N_2Si$ (M^+ + H) 371.1791, found 371.1781.

3D: general procedure C; ^{1}H NMR ($CDCl_3$) ppm 0.05 (s, 9H), 1.09 (d, 6H), 2.21 (s, 3H), 3.70 (m, 1H), 4.40 (m, 2H), 7.32 (m, 1H), 7.78 (m, 2H); HPLC purity (retention time): 50.0% (14.6 min); HRMS calcd for $C_{17}H_{29}O_3N_3Si$ (M^+ + H) 352.2056, found 352.2077.

3E: general procedure C; ^{1}H NMR ($CDCl_3$) ppm 0.00 (s, 9H), 1.07 (m, 2H), 2.23 (s, 3H), 2.33 (s, 3H), 2.66 (m, 1H), 2.88 (m, 1H), 4.17 (m, 1H), 4.37 (m, 2H), 7.00 (d, 1H), 7.20 (m, 6H), 7.45 (m, 4H), 8.21 (d, 1H), 9.74 (s, 1H); HPLC purity (retention time): 73.4% (20.1 min); HRMS calcd for $C_{29}H_{37}O_5N_3SSi$ (M^+ + H) 568.2301, found 568.2289.

General Procedure D. Reaction of the aniline 3 with electrophiles to afford compounds (4).
The aniline hydrochloride **3** (0.15 mmol) was dissolved into a solution of pyridine **9** in DCM (180 mM) (2 mL, 0.36 mmol) followed by an additional 1 mL of DCM (a couple of drops of DMF was added to compounds **3B** and **3D** for solubility). The electrophile **18** (0.17 mmol) (benzoyl chloride, hydrocinnamoyl chloride, carbobenzyloxy-L-valine anhydride, benzyl chloroformate, benzene sulfonyl chloride, or benzyl isocyanate) was added neat and the solution was agitated on an orbital shaker at room temperature for 16 hours. Upon completion of the reaction, the CMR/R polyamine resin **13** (~2.98 meq/g) (300 mg, 0.894 mmol) was added followed by addition of 2 mL of dichloromethane and the suspension was agitated on an orbital shaker for 1 hour. The solution was filtered and the polymer was rinsed with four 1 mL portions of dichloromethane. The combined filtrate and washings are evaporated to afford the pure product **4**.

Carbobenzyloxy-L-valine anhydride (18a).
Carbobenzyloxy-L-valine acid **21a** (113 mg, 0.45 mmol) was added to a suspension of P-EDC **22** (1.01 mmol/g, 0.22 g, 0.22 mmol) in DCM (2 mL) at room temperature. After the mixture stirred at room temperature for 30 minutes, the slurry was filtered directly into the reaction vessel and rinsed with 1 mL of DCM.

4Aa: general procedure D; ^{1}H NMR ($CDCl_3$) ppm 0.09 (s, 9H), 1.04 (m, 6H), 1.14 (m, 2H), 2.23 (s, 3H), 2.32 (m, 1H), 4.12 (t, 1H), 4.44 (m, 2H), 5.15 (s, 2H), 5.20 (s, 2H), 5.38 (bd, 1H), 7.36 (m, 10H), 7.60 (m, 2H), 7.98 (d, 1H), 8.39 (bs, 1H); HPLC purity (retention time): 95.6% (23.4 min); HRMS calcd for $C_{34}H_{43}O_7N_3Si$ (M^+ + NH_4) 651.3214, found 651.3220.

4Ab: general procedure D; ^{1}H NMR ($CDCl_3$) ppm 0.09 (s, 9H), 1.14 (m, 2H), 2.37 (s, 3H), 5.22 (s, 2H), 7.35 (m, 5H), 7.55 (m, 4H), 7.79 (d, 1H), 7.90 (d, 2H), 8.06 (d, 1H), 8.41 (bs, 1H); HPLC purity (retention time): 94.5% (22.1 min); HRMS calcd for $C_{28}H_{32}O_5N_2Si$ (M^+ + NH_4) 522.2424, found 522.2404.

4Ac: general procedure D; ^{1}H NMR ($CDCl_3$) ppm 0.08 (s, 9H), 1.11 (m, 2H), 2.09 (s, 3H), 2.72 (t, 2H), 3.09 (t, 2H), 4.41 (m, 2H), 5.20 (s, 2H), 6.77 (bs, 1H), 7.35 (m, 10H), 7.55 (d, 1H), 7.95 (d, 1H), 8.35 (bs, 1H); HPLC purity (retention time): 97.0% (22.7 min); HRMS calcd for $C_{30}H_{36}O_5N_2Si$ (M^+ + NH_4) 550.2737, found 550.2742.

4Ad: general procedure D; ^{1}H NMR ($CDCl_3$) ppm 0.06 (s, 9H), 1.09 (m, 2H), 2.10 (s, 3H), 4.40 (m, 2H), 5.19 (s, 2H), 6.62(bs, 1H), 7.15 (d, 1H), 7.41 (m, 7H), 7.70 (d, 2H), 7.92 (d, 1H), 8.41 (bs, 1H); HPLC purity (retention time): 95.9% (22.5 min); HRMS calcd for $C_{27}H_{32}O_6N_2SiS$ (M^+ + NH_4) 558.2094, found 558.2091.

4Ae: general procedure D; ^{1}H NMR ($CDCl_3$) ppm 0.08 (s, 9H), 1.12 (m, 2H), 2.28 (s, 3H), 4.44 (m, 2H), 5.20 (s, 2H), 5.22 (s, 2H), 6.36 (bs, 1H), 7.36 (m, 10H), 7.73 (m, 1H), 7.98 (d, 1H), 8.30 (bs, 1H); HPLC purity (retention time): 98.7% (23.8 min); HRMS calcd for $C_{29}H_{34}O_6N_2Si$ (M^+ + NH_4) 552.2530, found 552.2552.

4Af: general procedure D; ^{1}H NMR ($CDCl_3$) ppm 0.08 (s, 9H), 1.13 (m, 2H), 2.28 (s, 3H), 4.43 (m, 4H), 4.93 (bt, 1H), 5.18 (s, 2H), 6.08(s, 1H), 7.30 (m, 11H), 7.98 (d, 1H), 8.36 (bs, 1H); HPLC purity (retention time): 95.7% (21.5 min); HRMS calcd for $C_{29}H_{35}O_5N_3Si$ ($M^+ + NH_4$) 551.2690, found 551.2691.

4Ba: general procedure D; ^{1}H NMR ($CDCl_3$) ppm 0.08 (s, 9H), 1.03 (m, 8H), 1.52 (d, 3H), 2.19 (s, 3H), 2.23 (m, 1H), 4.31 (m, 2H), 4.78 (m, 1H), 4.96 (m, 1H), 5.12 (s, 2H), 5.41(m, 1H), 5.62 (bd, 1H), 7.14 (m, 2H), 7.29 (m, 10H), 7.57 (m, 1H), 8.03 (bs, 1H); HPLC purity (retention time): 66.0% (21.5 min); HRMS calcd for $C_{35}H_{46}O_6N_4Si$ ($M^+ + NH_4$) 664.3530, found 664.3528.

4Bb: general procedure D; ^{1}H NMR ($CDCl_3$) ppm 0.07 (s, 9H), 1.13 (m, 2H), 1.49 (d, 3H), 2.28 (s, 3H), 4.35 (m, 2H), 4.97 (quintet, 1H), 5.34 (bd, 1H), 7.37(m, 10H), 7.47 (m, 4H), 7.90 (m, 6H); HPLC purity (retention time): 54.8% (20.2 min); HRMS calcd for $C_{29}H_{35}O_4N_3Si$ ($M^+ + NH_4$) 535.2741, found 535.2749.

4Bc: general procedure D; ^{1}H NMR ($CDCl_3$) ppm 0.04 (s, 9H), 1.03 (m, 2H), 1.43 (t, 2H), 1.58 (d, 3H), 2.39 (s, 3H), 2.66 (t, 2H), 4.21 (m, 2H), 4.97 (m, 1H), 6.12 (m, 1H), 6.91(m, 1H), 7.24 (m, 12H), 7.77 (bs, 1H); HPLC purity (retention time): 58.7% (20.8 min); HRMS calcd for $C_{31}H_{39}O_4N_3Si$ ($M^+ + NH_4$) 563.3054, found 563.3067.

4Bd: general procedure D; ^{1}H NMR ($CDCl_3$) ppm 0.08 (s, 9H), 1.07 (m, 2H), 1.52 (d, 3H), 2.08 (s, 3H), 4.32 (m, 2H), 4.78 (m, 1H), 4.94 (m, 1H), 6.97(d, 1H), 7.14 (m, 1H), 7.34 (m, 8H), 7.68 (m, 2H), 7.87 (m, 1H), 8.17 (bs, 1H); HPLC purity (retention time): 57.0% (20.7 min); HRMS calcd for $C_{28}H_{35}O_5N_3SiS$ ($M^+ + NH_4$) 571.2410, found 571.2451.

4Be: general procedure D; ^{1}H NMR ($CDCl_3$) ppm 0.08 (s, 9H), 1.03 (m, 2H), 1.50 (d, 3H), 2.22 (s, 3H), 4.31 (m, 2H), 4.96 (m, 1H), 5.19 (s, 2H), 5.41(m, 1H), 6.62 (bs, 1H), 7.38 (m, 9H), 7.61 (m, 1H), 7.77 (m, 1H), 7.93 (m, 1H), 8.94 (bs, 1H); HPLC purity (retention time): 69.5% (21.8 min); HRMS calcd for $C_{30}H_{37}O_5N_3Si$ ($M^+ + NH_4$) 565.2846, found 565.2891.

4Bf: general procedure D; ^{1}H NMR ($CDCl_3$) ppm 0.01 (s, 9H), 1.07 (m, 2H), 1.38 (d, 3H), 2.08 (s, 3H), 4.02 (m, 2H), 4.18 (m, 1H), 4.35 (d, 2H), 4.67(m, 1H), 4.94 (m, 1H), 6.89 (m, 2H), 7.29 (m, 11H), 7.60 (m, 1H); HPLC purity (retention time): 78.6% (19.8 min); HRMS calcd for $C_{30}H_{38}O_4N_4Si$ ($M^+ + NH_4$) 564.3006, found 564.3038.

4Ca: general procedure D; ^{1}H NMR ($CDCl_3$) ppm 0.08 (s, 9H), 1.12 (m, 2H), 2.35 (s, 3H), 4.45 (m, 2H), 5.23 (s, 2H), 6.44 (bs, 1H), 7.38 (m, 5H), 7.52 (m, 3H), 7.71 (m, 1H), 7.96 (d, 2H), 8.33 (d, 1H), 10.11 (s, 1H); HPLC purity (retention time): 91.2% (21.9 min); HRMS calcd for $C_{33}H_{41}O_6N_3Si$ ($M^+ + NH_4$) 621.3108, found 621.3099.

4Cb: general procedure D; ^{1}H NMR ($CDCl_3$) ppm 0.08 (s, 9H), 1.14 (m, 2H), 2.43 (s, 3H), 4.48 (m, 2H), 7.54 (m, 5H), 7.80 (m, 2H), 7.93 (m, 3H), 8.42 (d, 1H), 10.16 (s, 1H); HPLC purity (retention time): 90.5% (20.3 min); HRMS calcd for $C_{27}H_{30}O_4N_2Si$ ($M^+ + NH_4$) 492.2319, found 492.2308.

4Cc: general procedure D; ^{1}H NMR ($CDCl_3$) ppm 0.08 (s, 9H), 1.12 (m, 2H), 2.16 (s, 3H), 2.74 (t, 2H), 3.10 (t, 2H), 4.45 (m, 2H), 6.85 (bs, 1H), 7.29 (m, 5H), 7.52 (m, 4H), 7.93 (d, 2H), 8.33 (d, 1H), 10.08 (s, 1H); HPLC purity (retention time): 94.4% (21.0 min); HRMS calcd for $C_{29}H_{34}O_4N_2Si$ ($M^+ + NH_4$) 520.2632, found 520.2683.

4Cd: general procedure D; ^{1}H NMR ($CDCl_3$) ppm 0.07 (s, 9H), 1.10 (m, 2H), 2.21 (s, 3H), 4.45 (m, 2H), 6.75 (bs, 1H), 7.22 (d, 1H), 7.30 (m, 1H), 7.56 (m, 4H), 7.70 (m, 2H), 7.92 (m, 2H), 8.29 (d, 1H), 8.62 (bs,

1H), 10.12 (s, 1H); HPLC purity (retention time): 92.4% (21.1 min); HRMS calcd for $C_{26}H_{30}O_5N_2SiS$ ($M^+ + NH_4$) 528.1988, found 528.1990.

4Ce: general procedure D; ^1H NMR ($CDCl_3$) ppm 0.08 (s, 9H), 1.05 (m, 6H), 1.15 (m, 2H), 2.35 (m, 1H), 4.15 (t, 1H), 4.45 (m, 2H), 5.16 (s, 2H), 5.46 (bs, 1H), 7.37 (m, 5H), 7.55 (m, 5H), 7.96 (d, 2H), 8.38 (d, 1H), 10.04 (s, 1H); HPLC purity (retention time): 96.6% (22.2 min); HRMS calcd for $C_{28}H_{32}O_5N_2Si$ ($M^+ + NH_4$) 522.2424, found 522.2426.

4Cf: general procedure D; ^1H NMR ($CDCl_3$) ppm 0.07 (s, 9H), 1.08 (m, 2H), 2.25 (s, 3H), 4.40 (m, 4H), 5.35 (m, 1H), 6.46 (bs, 1H), 7.28 (m, 5H), 7.46 (m, 4H), 7.86 (d, 2H), 8.07 (m, 1H), 9.85 (bs, 1H); HPLC purity (retention time): 93.4% (19.8 min); HRMS calcd for $C_{28}H_{33}O_4N_3Si$ ($M^+ + NH_4$) 521.2584, found 521.2586.

4Da: general procedure D; ^1H NMR ($CDCl_3$) ppm 0.09 (s, 9H), 1.08 (m, 9H), 1.52 (d, 6H), 2.67 (s, 3H), 3.98 (m, 2H), 4.17 (m, 1H), 4.23 (m, 1H), 5.13 (s, 2H), 5.36 (m, 1H), 5.62 (m, 1H), 7.37 (m, 5H), 7.72 (m, 2H), 7.79 (bs, 1H); HPLC purity (retention time): 44.9% (14.7 min); HRMS calcd for $C_{30}H_{44}O_6N_4Si$ ($M^+ + NH_4$) 602.3374, found 602.3385.

4Db: general procedure D; ^1H NMR ($CDCl_3$) ppm 0.10 (s, 9H), 1.15 (m, 2H), 1.20 (d, 6H), 2.36 (s, 3H), 3.98 (m, 1H), 4.41 (m, 2H), 7.55 (m, 3H), 7.90 (m, 2H); HPLC purity (retention time): 63.3% (18.1 min); HRMS calcd for $C_{24}H_{33}O_4N_3Si$ ($M^+ + NH_4$) 473.2584, found 473.2564.

4Dc: general procedure D; ^1H NMR ($CDCl_3$) ppm 0.09 (s, 9H), 1.13 (m, 2H), 1.18 (d, 6H), 1.51 (t, 2H), 2.07 (s, 3H), 2.73 (m, 2H), 3.98 (m, 2H), 4.40 (m, 2H), 4.53 (bd, 1H), 6.83 (bs, 1H), 7.29 (m, 5H), 7.43 (m, 1H), 7.79 (m, 1H), 7.83 (bs, 1H); HPLC purity (retention time): 53.5% (18.8 min); HRMS calcd for $C_{26}H_{37}O_4N_3Si$ ($M^+ + NH_4$) 501.2897, found 501.2918.

4Dd: general procedure D; ^1H NMR ($CDCl_3$) ppm 0.08 (s, 9H), 1.13 (m, 9H), 2.13 (s, 3H), 3.98 (m, 1H), 4.39 (m, 2H), 4.54 (m, 1H), 6.83 (m, 1H), 7.06 (m, 1H), 7.46 (m, 2H), 7.70 (m, 1H), 7.82 (m, 1H), 8.10 (bs, 1H), 8.19 (bs, 1H); HPLC purity (retention time): 34.3% (18.8 min); HRMS calcd for $C_{23}H_{33}O_5N_3Si$ ($M^+ + NH_4$) 509.2254, found 509.2268.

4De: general procedure D; ^1H NMR ($CDCl_3$) ppm 0.09 (s, 9H), 1.17 (m, 8H), 2.27 (s, 3H), 3.98 (m, 1H), 4.43 (m, 2H), 5.19 (s, 2H), 6.22 (m, 1H), 7.40 (m, 6H), 7.87 (m, 1H), 9.42 (m, 1H); HPLC purity (retention time): 47.6% (20.0 min); HRMS calcd for $C_{25}H_{35}O_5N_3Si$ ($M^+ + NH$) 486.2424, found 486.2433.

4Df: general procedure D; ^1H NMR ($CDCl_3$) ppm 0.15 (s, 9H), 0.91 (m, 8H), 1.98 (s, 3H), 3.68 (m, 1H), 4.19 (m, 4H), 5.60 (bd, 1H), 5.83 (m, 1H), 6.16 (m, 1H), 7.06 (m, 6H), 7.41 (m, 1H), 7.82 (bs, 1H); HPLC purity (retention time): 65.8% (17.7 min); HRMS calcd for $C_{25}H_{36}O_4N_4Si$ ($M^+ + NH_4$) 502.2850, found 502.2877.

4Ea: general procedure D; ^1H NMR ($CDCl_3$) ppm 0.07 (s, 9H), 1.06 (m, 8H), 2.18 (s, 3H), 2.39 (s, 3H), 2.60 (m, 1H), 3.01 (m, 2H), 3.96 (q, 1H), 4.19 (t, 1H), 4.42 (m, 2H), 5.17 (s, 2H), 5.43 (bm, 1H), 5.56 (bm, 1H), 6.96 (m, 2H), 7.14 (m, 7H), 7.37 (m, 5H), 7.51 (d, 2H), 7.87 (d, 1H), 9.66 (s, 1H); HPLC purity (retention time): 78.3% (23.2 min); HRMS calcd for $C_{42}H_{52}O_8N_4SSi$ ($M^+ + NH_4$) 818.3619, found 818.3610.

4Eb: general procedure D; ^1H NMR ($CDCl_3$) ppm 0.08 (s, 9H), 1.15 (m, 2H), 2.35 (s, 3H), 2.40 (s, 3H), 3.06 (m, 2H), 3.94 (q, 1H), 4.46 (m, 2H), 5.29 (bd, 1H), 6.96 (m, 2H), 7.15 (m, 6H), 7.52 (m, 5H), 7.94 (m, 4H), 9.75 (s, 1H); HPLC purity (retention time): 83.6% (22.2 min); HRMS calcd for $C_{36}H_{41}O_6N_3SSi$ ($M^+ + NH_4$) 689.2829, found 689.2809.

4Ec: general procedure D; ^{1}H NMR ($CDCl_3$) ppm 0.07 (s, 9H), 1.12 (m, 2H), 2.04 (s, 3H), 2.39 (s, 3H), 2.75 (t, 2H), 3.06 (m, 4H), 3.92 (bm, 1H), 4.46 (m, 2H), 5.36 (bd, 1H), 6.97 (m, 4H), 7.24 (m, 10H), 7.50 (m, 2H), 7.85 (d, 1H), 9.68 (s, 1H); HPLC purity (retention time): 95.2% (22.7 min); HRMS calcd for $C_{38}H_{45}O_6N_3SSi$ ($M^+ + NH_4$) 717.3142, found 717.3153.

4Ed: general procedure D; ^{1}H NMR ($CDCl_3$) ppm 0.06 (s, 9H), 1.10 (m, 2H), 2.07 (s, 3H), 2.40 (s, 3H), 3.01 (m, 2H), 3.87 (q, 1H), 4.20 (m, 2H), 6.91 (d, 2H), 7.18 (m, 6H), 7.48 (m, 5H), 7.59 (t, 1H), 7.74 (d, 2H), 7.90 (d, 1H), 9.72 (bs, 1H); HPLC purity (retention time): 95.3% (22.2 min); HRMS calcd for $C_{35}H_{41}O_7N_3S_2Si$ ($M^+ + NH_4$) 725.2499, found 725.2502.

4Ee: general procedure D; ^{1}H NMR ($CDCl_3$) ppm 0.09 (s, 9H), 1.14 (m, 2H), 2.27 (s, 3H), 2.39 (s, 3H), 3.01 (d, 2H), 3.92 (q, 1H), 4.43 (m, 2H), 5.23 (s, 2H), 6.45 (bs, 1H), 6.95 (m, 2H), 7.20 (m, 5H), 7.38 (m, 6H), 7.54 (d, 2H), 7.96 (d, 1H), 9.55 (bs, 1H); HPLC purity (retention time): 89.3% (23.5 min); HRMS calcd for $C_{37}H_{43}O_7N_3SSi$ ($M^+ + NH_4$) 719.2935, found 719.2940.

4Ef: general procedure D; ^{1}H NMR ($CDCl_3$) ppm 0.04 (s, 9H), 1.11 (m, 2H), 1.99 (s, 3H), 2.38 (s, 3H), 2.98 (m, 2H), 3.98 (m, 1H), 4.34 (d, 2H), 4.39 (m, 2H), 5.82 (bt, 1H), 6.95 (m, 4H), 7.25 (m, 12H), 7.44 (d, 2H), 9.52 (bs, 1H); HPLC purity (retention time): 89.3% (21.7 min); HRMS calcd for $C_{37}H_{44}O_6N_4SSi$ ($M^+ + NH_4$) 718.3095, found 718.3098.

General Procedure E. Deprotection of the 2-(trimethylsily)ethyl ester group of compounds 4 to afford the carboxylic acids (5).

The ester **4** (0.15 mmol) was dissolved into a solution of anhydrous THF (BHT free) (3 mL) followed by addition of tetrabutylammonium fluoride **23** in THF (1N) (170 uL, 0.17 mmol). The solution was agitated on an orbital shaker at room temperature for 16 hours. Upon completion of the reaction, the CMR/R calcium sulfonate resin **28** (~1.76 meq/g of Ca^{2+}) (300 mg, 1.05 mmol) and Amberlyst® A-15 resin **27** (~4.7 meq/g) (300 mg, 1.41 mmol) was added and the suspension was agitated on an orbital shaker for 6 hours. The solution was filtered and the polymer was rinsed with four 1 mL portions of dichloromethane. The combined filtrate and washings are evaporated to afford the pure product **5**. These products were not characterized and carried on to the next step.

Amberlyst® A-15 (27).

Amberlyst® A-15 **27** was purchased from Aldrich Chemical Company. The polymer was rinsed three times with DMF, soaked in DMF for 1.5 hours, rinsed three times with DMF, rinsed three times with DCM, three times with THF, and three times with ether, and dried *in vacuo*.

Preparation of CMR/R calcium sulfonate resin (28).

Amberlyst® A-15 (H) **27** is packed in a column and flushed with deionized water. A saturated solution of calcium hydroxide in deionized water is passed through the column until the eluent is basic (the resin displays a distinct lightening in color as it exchanges with the calcium cation). Upon completion, the resin is rinsed with deionized water until the eluent is neutral. The resin **28** is then removed from the column and rinsed three times with DCM, three times with THF, three times with ether, and dried in vacuo. Anal. Obsd: Ca, 7.06%, 1.76 mmol/g; S, 11.71%, 3.65 mmol/g.

General Procedure F. Cyclization of the carboxylic acid 5 to afford benzoxazinones (6).

The acid **5** (0.15 mmol) was dissolved into a solution of DMF (5 mL) followed by an additional of polymer-bound EDC **22** (1.01 meq/g) (0.30, 0.30 mmol). The solution was agitated on an orbital shaker at room temperature for 12 hours. Upon completion of the reaction, the solution was filtered and the polymer was rinsed with four 1 mL portions of dichloromethane. The combined filtrate and washings are evaporated to afford the pure product **6**.

6Aa: general procedure F; ^{1}H NMR ($CDCl_3$) ppm 1.05 (t, 36H), 2.28 (septet, 1H), 2.63 (s, 3H), 4.28 (t, 1H), 5.10 (s, 2H), 5.48 (s, 2H), 6.94 (d, 1H), 7.39 (m, 7H), 7.79 (d, 1H), 7.97 (m, 2H), 9.62 (s, 1H); HPLC purity (retention time): 92.0% (19.6 min); HRMS calcd for $C_{29}H_{29}O_6N_3$ (M^+) 515.2056, found 515.2094.

6Ab: general procedure F; ^{1}H NMR ($CDCl_3$) ppm 2.78 (s, 3H), 5.50 (s, 2H), 7.38 (m, 4H), 7.54 (m, 5H), 7.79 (bs, 1H), 7.93 (m, 2H), 8.15 (d, 1H); HPLC purity (retention time): 93.4% (17.7 min); HRMS calcd for $C_{23}H_{18}O_4N_2$ (M^+) 386.1267, found 386.1284.

6Ac: general procedure F; ^{1}H NMR ($CDCl_3$) ppm 2.45 (s, 3H), 2.77 (t, 2H), 3.11 (t, 2H), 5.47 (s, 2H), 6.93 (bs, 4H), 7.29 (m, 6H), 7.39 (m, 3H), 7.50 (m, 2H), 7.89 (d, 1H); HPLC purity (retention time): 94.8% (18.5 min); HRMS calcd for $C_{25}H_{22}O_4N_2$ (M^+) 414.1580, found 414.1618.

6Ad: general procedure F; ^{1}H NMR ($CDCl_3$) ppm 2.64 (s, 3H), 5.47 (s, 2H), 7.39 (m, 8H), 7.59 (m, 2H), 7.68 (m, 3H); HPLC purity (retention time): 88.6% (18.6 min); HRMS calcd for $C_{22}H_{18}O_5N_2S$ (M^+) 422.0936, found 422.0934.

6Ae: general procedure F; ^{1}H NMR ($CDCl_3$) ppm 2.65 (s, 3H), 5.47 (s, 4H), 6.77 (bs, 1H), 7.27 (m, 2H), 7.47 (m, 6H), 7.56 (m, 1H), 7.71 (m, 3H); HPLC purity (retention time): 92.4% (20.0 min); HRMS calcd for $C_{24}H_{20}O_5N_2$ (M^+) 416.1372, found 416.1398.

6Af: general procedure F; ^{1}H NMR ($CDCl_3$) ppm 2.65 (s, 3H), 4.43 (d, 2H), 5.49 (s, 2H), 6.98 (bt, 1H), 7.30 (m, 8H), 7.56 (m, 2H), 8.17(m, 2H), 8.27 (d, 1H); HPLC purity (retention time): 89.3% (17.6 min); HRMS calcd for $C_{24}H_{21}O_4N_3$ (M^+) 415.1532, found 415.1557.

6Ag: general procedure F; ^{1}H NMR ($CDCl_3$) ppm 1.55 (s, 9H), 2.71 (s, 3H), 5.47 (s, 2H), 6.37 (bs, 1H), 7.37 (m, 6H), 8.08 (d, 1H); HPLC purity (retention time): 91.4% (20.0 min); HRMS calcd for $C_{21}H_{22}O_5N_2$ (M^+ + H) 383.1607, found 383.1608.

6Ba: general procedure F; ^{1}H NMR ($CDCl_3$) ppm 1.01 (m, 7H), 1.40 (d, 3H), 2.52 (s, 3H), 4.24 (m, 1H), 4.82 (m, 1H), 5.14 (s, 2H), 6.44 (m, 1H), 7.34 (m, 13H), 7.76 (d, 1H); HPLC purity (retention time): 48.1% (18.2 min); HRMS calcd for $C_{30}H_{32}O_5N_4$ (M^+) 528.2373, found 528.2391.

6Bb: general procedure F; ^{1}H NMR ($CDCl_3$) ppm 1.62 (d, 3H), 2.70 (s, 3H), 5.17 (quintet, 1H), 7.38 (m, 6H), 7.52 (m, 3H), 7.79 (bs, 1H), 7.92 (d, 3H), 8.03 (s, 1H); HPLC purity (retention time): 69.4% (16.0 min); HRMS calcd for $C_{24}H_{21}O_3N_3$ (M^+) 399.1583, found 399.1564.

6Bc: general procedure F; ^{1}H NMR ($CDCl_3$) ppm 1.59 (d, 3H), 2.41 (s, 3H), 2.74 (t, 2H), 3.08 (t, 2H), 5.11 (quintet, 1H), 7.04 (d, 1H), 7.28 (m, 12H), 7.66 (d, 1H); HPLC purity (retention time): 73.6% (17.0 min); HRMS calcd for $C_{26}H_{25}O_3N_3$ (M^+) 427.1896, found 427.1876.

6Bd: general procedure F; ^{1}H NMR ($CDCl_3$) ppm 1.62 (d, 3H), 2.26 (s, 3H), 5.14 (m, 1H), 6.31 (bs, 1H), 7.10 (d, 1H), 7.55 (m, 12H); HPLC purity (retention time): 75.1% (17.4 min); HRMS calcd for $C_{23}H_{21}O_4N_3S$ (M^+) 435.1253, found 435.1237.

6Be: general procedure F; ^{1}H NMR ($CDCl_3$) ppm 1.51 (d, 3H), 2.64 (s, 3H), 5.14 (m, 1H), 5.21 (s, 2H), 6.51 (bs, 1H), 7.11 (d, 1H), 7.34 (m, 11H), 7.86 (bs, 1H); HPLC purity (retention time): 72.7% (18.5 min); HRMS calcd for $C_{25}H_{23}O_4N_3$ (M^+) 429.1689, found 429.1678.

6Bf: general procedure F; ^{1}H NMR ($CDCl_3$) ppm 1.42 (d, 3H), 2.61 (s, 3H), 4.41 (m, 3H), 4.81 (m, 1H), 5.10 (m, 1H), 6.45 (bs, 1H), 7.28 (m, 12H); HPLC purity (retention time): 69.0% (16.0 min); HRMS calcd for $C_{25}H_{24}O_3N_4$ (M^+) 428.1848, found 428.1852.

6Bg: general procedure F; ^{1}H NMR ($CDCl_3$) ppm 1.59 (d, 3H), 1.63 (s, 9H), 2.45 (s, 3H), 5.27 (quintet, 1H), 7.52 (m, 4H), 7.60 (d, 1H), 8.05 (d, 1H), 8.21 (s, 1H), 8.37 (s, 1H), 8.69 (bs, 1H); HPLC purity (retention time): 76.2% (18.3 min); HRMS calcd for $C_{22}H_{25}O_4N_3$ (M^+) 395.1845, found 395.1827.

6Ca: general procedure F; ^{1}H NMR ($CDCl_3$) ppm 1.02 (t, 6H), 2.12 (septet, 1H), 2.65 (s, 3H), 4.14 (t, 1H), 5.08 (s, 2H), 7.38 (m, 5H), 7.57 (m, 4H), 7.82 (d, 1H), 7.95 (s, 1H), 8.18 (d, 2H), 9.80 (bs, 1H); HPLC purity (retention time): 93.3% (19.2 min); HRMS calcd for $C_{28}H_{27}O_5N_3$ (M^+) 485.1951, found 485.1964.

6Cb: general procedure F; ^{1}H NMR ($CDCl_3$) ppm 2.93 (s, 3H), 7.76 (m, 6H), 8.12 (m, 2H), 8.27 (m, 2H), 8.43 (m, 2H), 10.44 (s, 1H); HPLC purity (retention time): 95.4% (17.0 min); HRMS calcd for $C_{22}H_{16}O_3N_2$ (M^+ + H) 357.1219, found 357.1248.

6Cc: general procedure F; ^{1}H NMR ($CDCl_3$) ppm 2.51 (s, 3H), 2.73 (t, 2H), 2.97 (t, 2H), 7.29 (m, 5H), 7.62 (m, 4H), 7.82 (d, 1H), 8.17 (m, 2H), 9.71 (s, 1H); HPLC purity (retention time): 98.0% (18.1 min); HRMS calcd for $C_{24}H_{20}O_3N_2$ (M^+) 384.1474, found 384.1482.

6Cd: general procedure F; ^{1}H NMR ($CDCl_3$) ppm 2.52 (s, 3H), 7.61 (m, 10H), 7.74 (m, 2H), 8.24 (m, 2H), 9.88 (bs, 1H); HPLC purity (retention time): 96.8% (18.3 min); HRMS calcd for $C_{21}H_{16}O_4N_2S$ (M^+ + H) 393.0909, found 393.0910.

6Ce: general procedure F; ^{1}H NMR ($CDCl_3$) ppm 2.91 (s, 3H), 5.34 (s, 2H), 7.51 (m, 4H), 7.69 (m, 3H), 8.14 (m, 3H), 8.37 (d, 2H), 9.40 (bs, 1H); HPLC purity (retention time): 98.9% (19.9 min); HRMS calcd for $C_{23}H_{18}O_4N_2$ (M^+ + H) 387.1345, found 387.1349.

6Cf: general procedure F; ^{1}H NMR ($CDCl_3$) ppm 2.32 (s, 3H), 4.20 (d, 2H), 7.08 (m, 5H), 7.42 (m, 4H), 7.78 (s, 2H), 7.98 (m, 1H), 8.13 (s, 1H), 8.21 (d, 1H); HPLC purity (retention time): 82.3% (17.2 min); HRMS calcd for $C_{23}H_{19}O_3N_3$ (M^+ + H) 386.1505, found 386.1488.

6Cg: general procedure F; ^{1}H NMR ($CDCl_3$) ppm 1.56 (s, 9H), 2.79 (s, 3H), 6.52 (bs, 1H), 7.55 (m, 4H), 8.29 (m, 3H); HPLC purity (retention time): 99.5% (20.0 min); HRMS calcd for $C_{20}H_{20}O_4N_2$ (M^+ + H) 353.1501, found 353.1495.

6Da: general procedure F; ^{1}H NMR ($CDCl_3$) ppm 0.91 (m, 7H), 1.51 (d, 6H), 2.52 (s, 3H), 4.14 (m, 1H), 5.12 (s, 2H), 5.24 (m, 1H), 5.79 (bd, 1H), 6.40 (bd, 1H), 7.12 (d, 1H), 7.32 (m, 6H), 9.79 (bs, 1H); HPLC purity (retention time): 30.8% (11.4 min); HRMS calcd for $C_{25}H_{30}O_5N_4$ (M^+) 466.2216, found 466.2208.

6Db: general procedure F; ^{1}H NMR ($CDCl_3$) ppm 1.56 (d, 6H), 2.72 (s, 3H), 5.26 (quintet, 1H), 7.18 (d, 1H), 7.55 (m, 5H), 7.93 (m, 1H), 9.19 (bs, 1H); HPLC purity (retention time): 74.6% (12.8 min); HRMS calcd for $C_{19}H_{19}O_3N_3$ (M^+) 337.1426, found 337.1423.

6Dc: general procedure F; ^{1}H NMR ($CDCl_3$) ppm 1.41 (d, 6H), 2.44 (s, 3H), 2.78 (t, 2H), 3.10 (t, 2H), 4.21 (quintet, 1H), 6.91 (bd, 1H), 7.09 (d, 1H), 7.29 (m, 6H), 7.73 (bs, 1H); HPLC purity (retention time): 73.2% (14.1 min); HRMS calcd for $C_{21}H_{23}O_3N_3$ (M^+) 365.1739, found 365.1725.

6Dd: general procedure F; ^{1}H NMR ($CDCl_3$) ppm 1.27 (d, 6H), 2.30 (s, 3H), 4.14 (m, 1H), 6.61 (bs, 1H), 7.10 (d, 1H), 7.45 (m, 6H), 7.69 (d, 1H); HPLC purity (retention time): 78.2% (14.5 min); HRMS calcd for $C_{18}H_{19}O_4N_3S$ (M^+) 373.1096, found 373.1088.

6De: general procedure F; ^{1}H NMR ($CDCl_3$) ppm 1.28 (d, 6H), 2.66 (s, 3H), 4.14 (m, 1H), 5.20 (s, 2H), 6.45 (bd, 1H), 7.13 (d, 1H), 7.28 (m, 6H), 8.83 (bs, 1H); HPLC purity (retention time): 68.1% (16.0 min); HRMS calcd for $C_{20}H_{21}O_4N_3$ (M^+) 367.1532, found 367.1523.

6Df: general procedure F; ^{1}H NMR ($CDCl_3$) ppm uninterpetable; HPLC purity (retention time): 29.6% (13.8 min); HRMS calcd for $C_{20}H_{22}O_3N_4$ (M^+) 366.1692, found 366.1675.

6Dg: general procedure F; ^{1}H NMR ($CDCl_3$) ppm 1.30 (d, 6H), 1.65 (s, 9H), 2.45 (s, 3H), 4.07 (quintet, 1H), 7.15 (bd, 1H), 7.49 (d, 1H), 8.06 (d, 1H), 8.24 (bs,); HPLC purity (retention time): 86.6% (15.4 min); HRMS calcd for $C_{17}H_{23}O_4N_3$ (M^+) 333.1689, found 333.1675.

6Ea: general procedure F; ^{1}H NMR ($CDCl_3$) ppm 0.95 (m, 6H), 1.38 (septet, 1H), 2.04 (s, 3H), 2.50 (s, 3H), 3.12 (t, 2H), 4.21 (t, 1H), 4.27 (q, 1H), 5.05 (m, 1H), 5.06 (s, 2H), 6.86 (d, 2H), 7.15 (m, 5H), 7.27 (m, 4H), 7.41 (d, 2H), 7.78 (d, 1H), 7.92 (s, 2H), 8.47 (d, 1H), 9.65 (bs, 1H); HPLC purity (retention time): 87.9% (19.3 min); HRMS calcd for $C_{37}H_{38}O_7N_4S$ (M^+ + H) 683.2539, found 683.2587.

6Eb: general procedure F; ^{1}H NMR ($CDCl_3$) ppm 2.20 (s, 3H), 2.71 (s, 3H), 3.19 (m, 2H), 4.47 (q, 1H), 5.70 (d, 1H), 7.09 (m, 5H), 7.24 (m, 3H), 7.58 (m, 4H), 7.96 (m, 3H), 8.09 (d, 1H), 8.47 (bs, 1H); HPLC purity (retention time): 93.4% (17.7 min); HRMS calcd for $C_{31}H_{27}O_5N_3S$ (M^+) 553.1671, found 553.1672.

6Ec: general procedure F; ^{1}H NMR ($CDCl_3$) ppm 2.18 (s, 3H), 2.63 (s, 3H), 2.82 (m, 2H), 3.07 (m, 2H), 3.27 (m, 2H), 4.47 (q, 1H), 5.54 (bd, 1H), 7.06 (m, 6H), 7.27 (m, 6H), 7.61 (m, 4H), 10.14 (bs, 1H); HPLC purity (retention time): 91.0% (18.4 min); HRMS calcd for $C_{33}H_{31}O_5N_3S$ (M^+ + H) 582.2062, found 582.2072.

6Ed: general procedure F; ^{1}H NMR ($CDCl_3$) ppm 2.19 (s, 3H), 2.43 (s, 3H), 3.20 (m, 2H), 4.47 (q, 1H), 5.61 (bd, 1H), 7.04 (m, 3H), 7.18 (m, 6H), 7.48 (m, 3H), 7.56 (m, 2H), 7.78 (m, 2H), 10.34 (bs, 1H); HPLC purity (retention time): 83.1% (17.8 min); HRMS calcd for $C_{30}H_{27}O_6N_3S_2$ (M^+ + H) 590.1420, found 590.1419.

6Ee: general procedure F; ^{1}H NMR ($CDCl_3$) ppm 2.16 (s, 3H), 2.34 (s, 3H), 3.20 (m, 2H), 4.47 (q, 1H), 5.21 (m, 3H), 5.61 (d, 1H), 7.00 (m, 2H), 7.18 (m, 6H), 7.38 (m, 7H), 10.14 (bs, 1H); HPLC purity (retention time): 83.6% (19.5 min); HRMS calcd for $C_{32}H_{29}O_6N_3S$ (M^+ + H) 584.1855, found 584.1860.

6Ef: general procedure F; ^{1}H NMR ($CDCl_3$) ppm 2.19 (s, 3H), 2.59 (s, 3H), 3.18 (m, 2H), 4.42 (m, 3H), 5.61 (bd, 1H), 6.61 (bs, 1H), 7.05 (m, 5H), 7.30 (m, 7H), 7.58 (d, 2H), 7.76 (bs, 1H), 8.28 (d, 2H); HPLC purity (retention time): 86.4% (17.6 min); HRMS calcd for $C_{32}H_{30}O_5N_4S$ (M^+ + H) 583.2015, found 583.2042.

6Eg: general procedure F; ^{1}H NMR ($CDCl_3$) ppm 1.55 (s, 9H), 2.19 (s, 3H), 2.69 (s, 3H), 3.19 (m, 2H), 4.47 (q, 1H), 5.43 (d, 1H), 6.50 (bs, 1H), 7.07 (m, 4H), 7.22 (m, 4H), 7.60 (d, 2H), 8.22 (d, 1H); HPLC purity (retention time): 89.8% (19.5 min); HRMS calcd for $C_{29}H_{31}O_6N_3S$ (M^+ + H) 550.2012, found 550.2007.

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5. The reaction block employed in our robotics synthesis laboratory is a modified version of a commercially-available apparatus from Bohdan, INC, Mundelein, Illinois. The 6X8 array block has 48 medium-fritted pyrex reaction chambers, each capable of handling up to 9 mL total volume. Each row of vessels can be independently manipulated to allow for open valve position rinsing/draining or closed valve position for incubations. The block is equipped with an inert atmosphere manifold and has a performing temperature range of -40C to 120C.

6. Polymeric DMAP is commercially available from Aldrich Chemical Company, Milwaukee, Wisconsin.

7. Column **f** was not treated with the 2N HCl so as not to deprotect the Boc groups from the compounds in that column.

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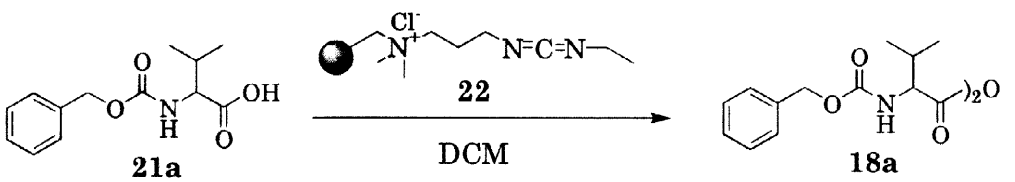
9. The carbobenzyloxy-L-valine anhydride **18a** was prepared directly from the acid **21a** and 1.5 equivalents of polymeric-EDC (Scheme 4). See reference 1g and also: Desai, M. C.; Stramiello S. L. M. *Tetrahedron Lett.* **1993**, *34*, 7685.



Scheme 4. *In situ* preparation of anhydride from acid using P-EDC.

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