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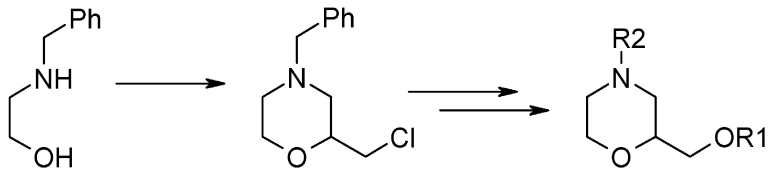

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Efficient and general procedures have been developed for the solution-phase preparation of substituted morpholine derivatives, and a library has been produced around generic structure **1**. This library was designed with proprietary modeling software for use as a general screening library. The 30 R1 reagents were phenols, and the 275 R2 reagents were taken from five different reagent classes, giving a variety of product classes in the final library of 8250 potential products. All of the library members were generated from a common intermediate, mesylate (**5**), which was synthesized efficiently, in bulk, in three steps from *N*-benzylethanolamine (**2**). High-throughput chemistry using robotics was carried out to produce the 7907 library members, which were individually characterized by reversed-phase LC/MS analysis.

Introduction

The morpholine moiety has been utilized extensively by the pharmaceutical industry in drug design, often because of the improvement in pharmacokinetic properties it can confer. The World Drug Index contains well over 100 drugs incorporating this structural feature, including its presence as a side-chain, scaffold, and within fused-ring systems. The biological utility of molecules containing the morpholine moiety is wide-ranging, including antidepressant activity, tachykinin receptor antagonist, serotonin agonist, NK-1 receptor antagonist, and antifungal activity.[1] Hence, it was attractive to design a diverse and general screening library that incorporated this structural feature.[2] The design and synthesis of such a library, with an integral substituted morpholine as the scaffold, is presented here. The morpholine core was decorated as shown in Figure 1.

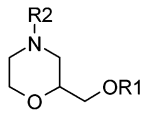

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Figure 1. Morpholine template showing the position of R1 and R2 substitution.

Library Design. ChemSpace technology[3a] was applied to the whole library design process. Starting with the construction of the virtual library, suitable building blocks were taken from our in-house cheminformatics system, ChemCore. Using 7185 phenols for the R1 position and 23192 reagents (carboxylic acids, aldehydes, isocyanates, isothiocyanates, and sulfonyl chlorides) for the R2 position, the virtual library had a size of more than 160 million products. The virtual compounds of this library were taken through several reagent filtering steps in which the structures were checked for druglikeness properties, the availability of building blocks,

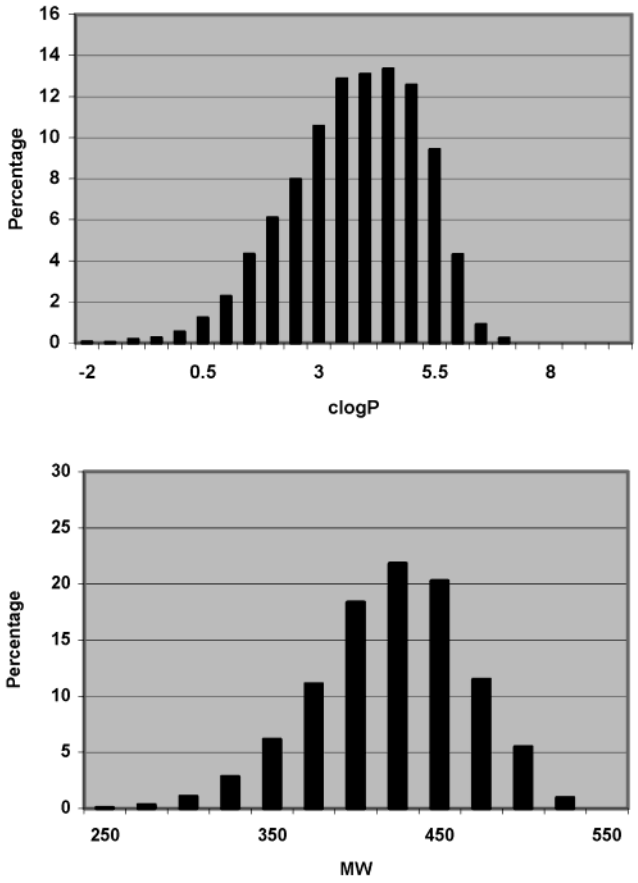

Figure 2. Distribution of the clogP (top) and the molecular weight (bottom) of the compounds in the design set.

and other criteria. For the druglikeness properties, the molecular weight was limited to a value of 550 Da, and the clogP[3b] was allowed a range of −5 to 7.5. In addition, all virtual structures were checked against a list of structural queries derived from general toxicological information and

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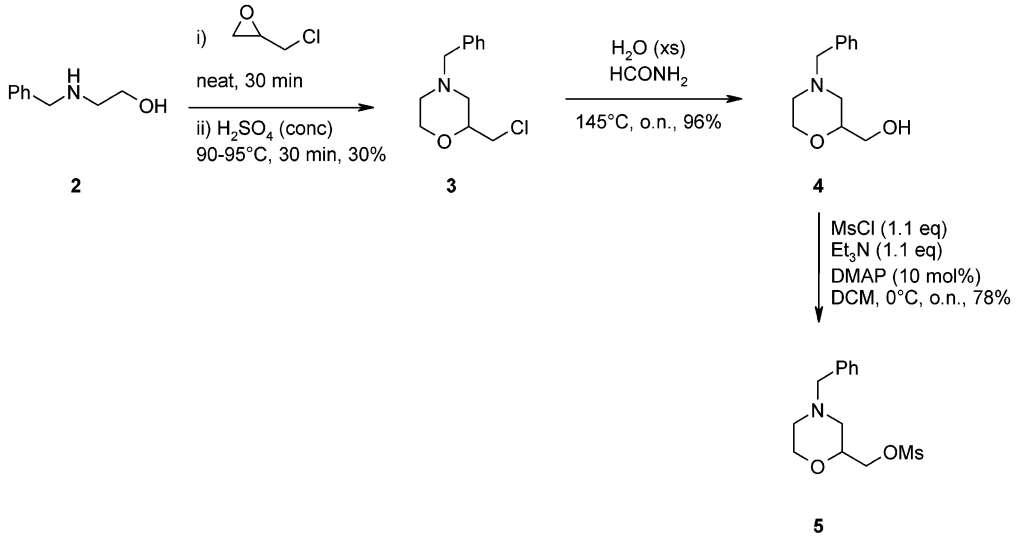
Scheme 1



from reaction-specific information generated through validation of this reaction. At the end of this filtering process, 168 phenols for R1 and 1775 R2 reagents remained. For the design of the products to be synthesized, a selection was carried out using validated molecular descriptors (Unity-2D fingerprints and topomeric fields)[4a] together with the OptiSim algorithm[4b] to identify the maximum diverse set of virtual products under the constraint of a full matrix design. The first designed set was modified through several iterations of reagent replacements, and the final designed library was then composed of 32 phenols, 205 carboxylic acids, 32 aldehydes, 22 isocyanates, 19 isothiocyanates, and 27 sulfonyl chlorides. Figure 2 shows the distribution of the molecular weight and the clogP of the compounds in this design set. The difference in the size of the designed library (9760) and the potential synthesis set (8250) is ~15%. This can be explained mainly by shortages in the supply of commercially available reagents and the decision to use 30 out of the 32 R1 reagents examined in validation chemistry.

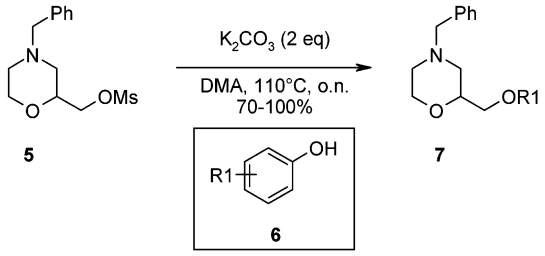
Results and Discussion

Preparation of the Bulk Common Intermediate. The starting material for the library synthesis was *N*-benzylethanolamine (**2**), which was converted into the chloromethyl-morpholine derivative (**3**) via the reported method.[5] This utilizes the epoxide ring opening of (±)-epichlorohydrin by the amine and subsequent sulfuric acid-catalyzed dehydration of the resulting intermediate diol. Prior to acid treatment, it was essential that all traces of excess epichlorohydrin were completely removed, or the ring-closure step would be compromised.

During the validation process, the chloromethyl substrate (**3**) proved to be too unreactive to allow the chlorine to be displaced by the phenoxides generated from various phenols. All efforts to effect this transformation proved unsuccessful,[6] and starting material was recovered unchanged. In addition, attempts to use the corresponding (±)-epibromohydrin in the hope of utilizing the bromide as a better leaving group were also unsatisfactory, since no cyclized product was obtained.

As a solution, it was decided to synthesize the more reactive mesylate. Hence, the chloromethyl compound (**3**) was hydrolyzed into the corresponding hydroxyl compound (**4**) using aqueous formamide at elevated temperatures.[5] The resulting hydroxyl compound (**4**) was then converted into the corresponding mesylate (**5**) using standard conditions. A small amount of the chloride byproduct **(3)** was formed during the reaction. However, its formation can be suppressed by lowering the reaction temperature, reducing the reaction time and by working up as soon as the reaction is complete according to TLC analysis. The mesylate was subsequently synthesized on a kilogram scale, sufficient for full production of the library. These synthetic steps are summarized in Scheme 1.

Scheme 2



Although for this study, racemic (±)-epichlorohydrin was used, both individual enantiomers are commercially available if a chiral library synthesis is required. In this study, it was ensured that all the designed R2 reagents were achiral. The library products (**1**) contain an unresolved chiral center as a result of the use of racemic (±)-epichlorohydrin, and it was advantageous to avoid formation of diastereomeric products.

Preparation of Chemset 8. The mesylate in compound (**5**) proved to be a more satisfactory leaving group and was reacted with each of the phenoxides generated from the phenols **6**{*1*−*30*} and potassium carbonate,[1a] to produce the R1 intermediates of chemset **7**{*1*−*30*} (Scheme 2). The structures of the phenols **6**{*1*−*30*} are given in Figure 3. However, the mesylate was observed to be unusually stable, presumably because of the β-effect, since the introduction of the R1 reagent required heating at 110 °C in DMA in order to afford product formation. The identity of each compound in chemset **7**{*1*−*30*} was confirmed by ^{1}H NMR and LC/MS analysis.

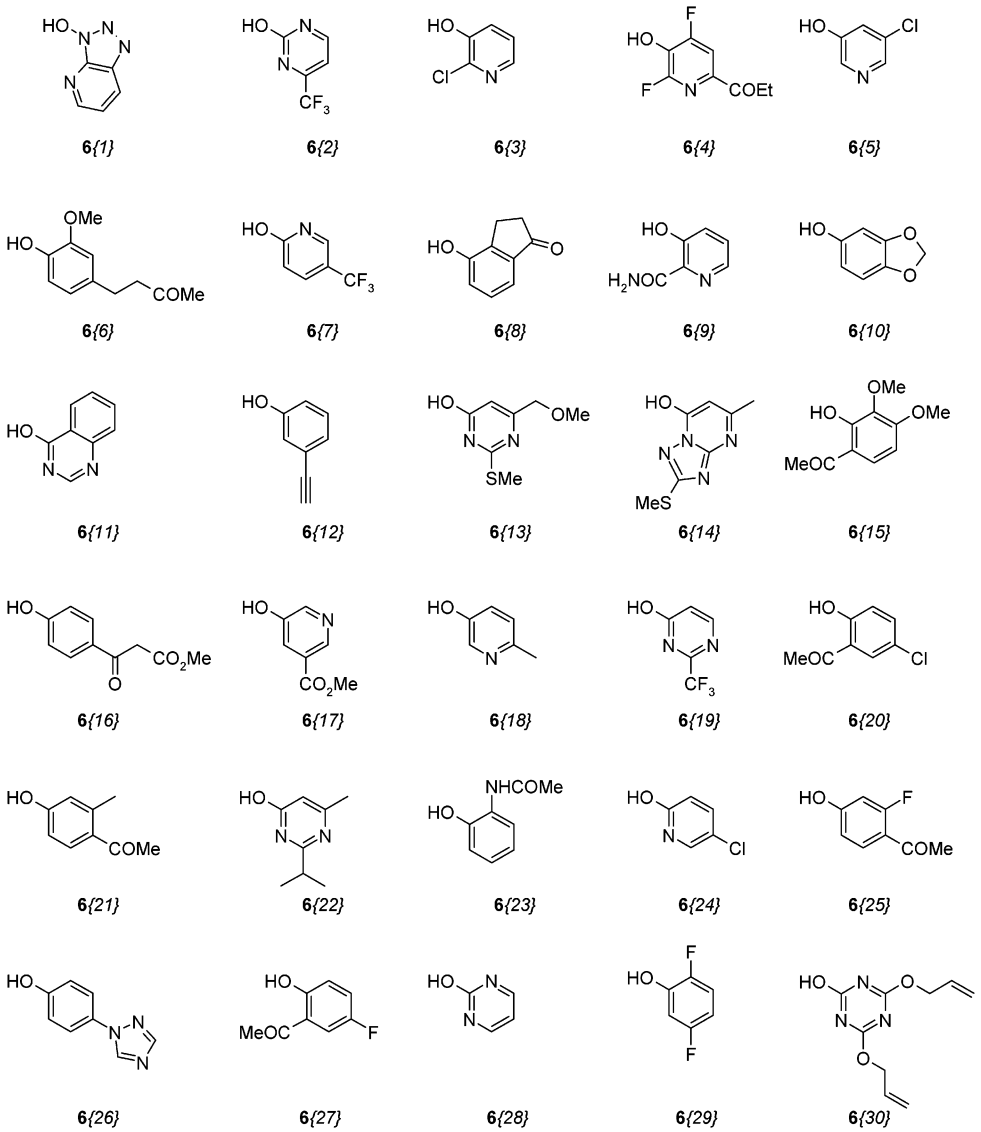
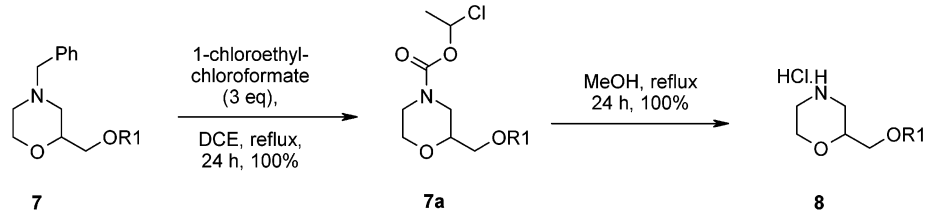


Figure 3. Structures of the phenols **6**{*1*−*30*}

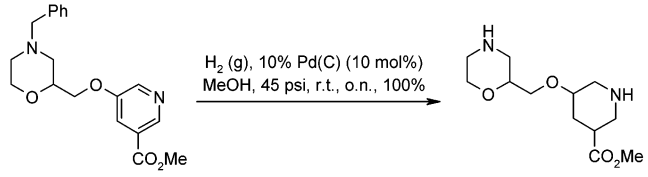
Scheme 3



Debenzylation of the morpholine nitrogen in chemset **7** was carried out using a two-step, one-pot procedure.[7] Thus, the *N*-benzylmorpholine derivatives were heated to reflux in 1,2-dichloroethane for 24 h with an excess of 1-chloroethyl chloroformate to generate a carbamate intermediate (**7a**). Hydrolysis was then achieved by refluxing in methanol, to give the free secondary amines as their HCl salts (**8**) (Scheme 3). The identity of each compound in chemset **8**{*1*−*30*} was confirmed by ^{1}H NMR and LC/MS analysis.

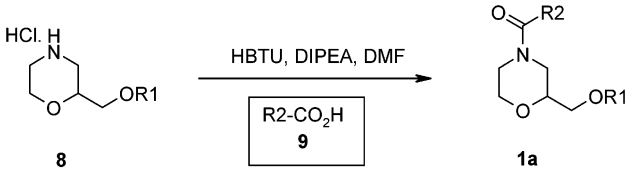
Initially, hydrogenation[8] in methanol was envisaged as the method of choice for the N-debenzylation of chemset **7**. However, this method proved to be unsatisfactory for those derivatives in which the R1 group contained a heterocycle

Scheme 4

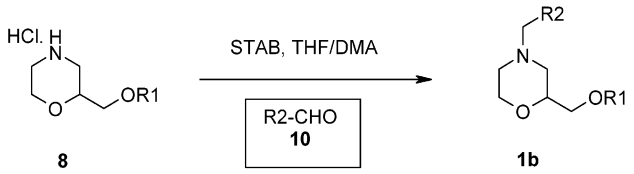


(such as a pyridine or pyrimidine ring). The hydrogenation conditions gave over-reduction in these cases, as in example **7**{*17*} which gave the over-reduced product **8a** (Scheme 4). Similar results were obtained even when the reaction pressure, the reaction time, and the amount of catalyst was

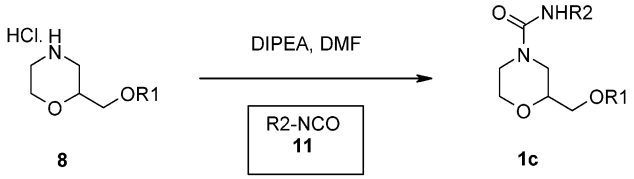
Scheme 5



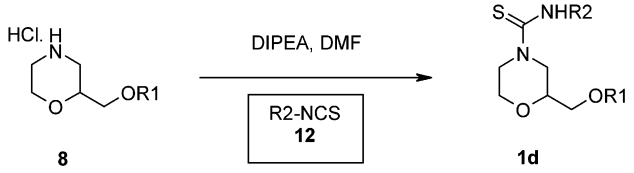
Scheme 6



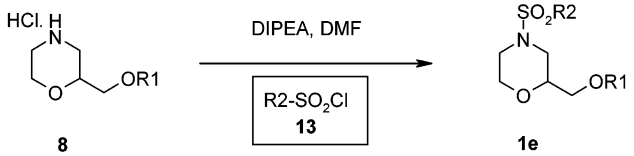
Scheme 7



Scheme 8



Scheme 9



reduced. As a result, the alternative conditions given above were adopted for all the members of chemset **7**, since these conditions gave high yields of the desired products **8** and were easier to implement on a large scale in comparison to high-pressure hydrogenation. Incidentally, the hydrogenation reaction in ethanol (instead of methanol) was sluggish, and unreacted starting material was recovered when this solvent was utilized.

Elaboration of Chemset 8 to the Library Products 1. Schemes 5−9 detail the high-throughput conversion of chemset **8** via five different reagent classes (chemsets **9**−**13**) into the final library products of chemset **1**. The first reagent set **9** consisted of 180 R2 carboxylic acids, which were reacted with the R1 amines of chemset **8** using HBTU and DIPEA in DMF to produce amide products **1a**. (Scheme 5)

The second reagent class, chemset **10**, consisted of 31 R2 aldehydes, which were reacted with the R1 amines of chemset **8** using a reductive amination procedure utilizing sodium triacetoxyborohydride (STAB) to reduce the preformed imines,[9] giving tertiary amine products of chemset **1b** (Scheme 6).

The next two reagent classes, chemsets **11** and **12**, consisted of 22 R2 isocyanates and 16 R2 isothiocyanates, respectively, which were both reacted with the R1 amines of chemset **8** using DIPEA in DMF to give ureas **1c** and thioureas **1d** as the products (Schemes 7 and 8).

The final reagent class, chemset **13**, consisted of 26 R2 sulfonyl chlorides, which were also reacted with the R1 amines of chemset **8** using DIPEA in DMF to form sulfonamide products **1e** (Scheme 9).

Reagents for the full matrix of 8250 reactions (30 R1 × 275 R2) were prepared and ordered. In practice, a library of 7907 members was synthesized according to the above protocols. This shortfall can be explained by logistical reasons, such as running out of reagents and decisions not to carry out anticipated unsuccessful reactions. The distribution of the total number of 7907 reactions by product class and percentage purity of compounds obtained directly from the robot is given in Figure 4.

Although the sulfonamides showed a large proportion of less pure products, the prepurification success rate across all reagent classes of products that were ≥70% pure is still 38%. The original procedure for sulfonamide formation involved dissolving the sulfonyl chlorides in DMF/DIPEA,

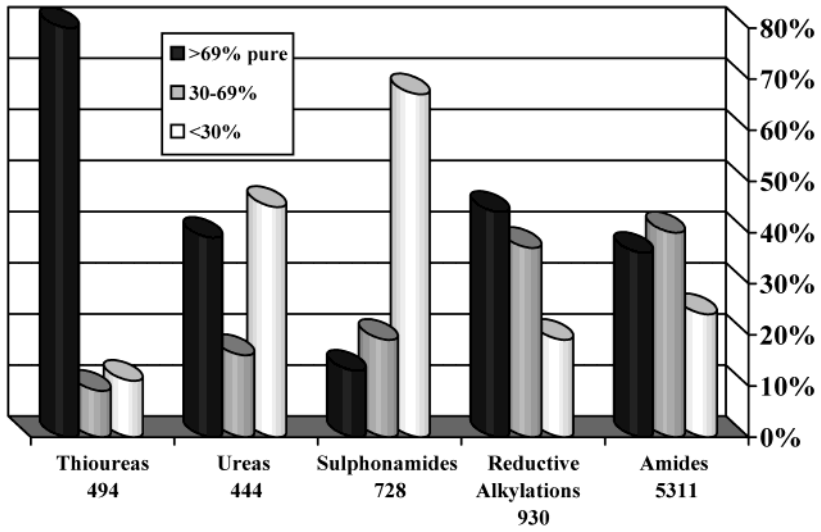


Figure 4. Profile of the library products by R2 reagent class and percentage purity of compounds obtained directly from the robot.

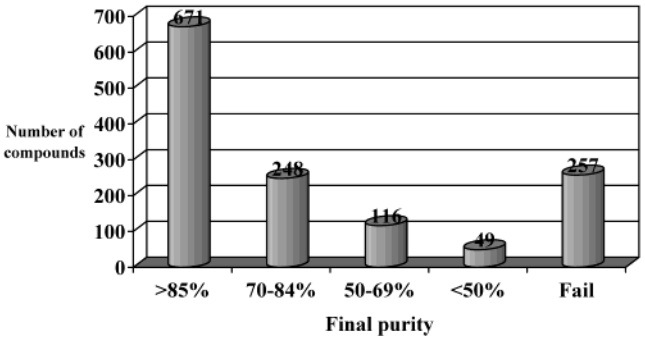


Figure 5. Breakdown of the final purities of 1341 library products submitted for purification.

as for the other R2 reagent classes, but poor initial purities of the products from the robot prompted the development of the alternative MeCN/pyridine protocol given in the Experimental Section. This modification significantly improved the initial purities, although the final figures quoted do not necessarily reflect this, since they encompass the combined results from both procedures. Adoption of the MeCN/pyridine protocol resulted in an 11-fold improvement in the percentage of products obtained in the ≥70% purity range and a >2-fold improvement in the percentage of products obtained in the 30−69% purity range.

Purification. After the high-throughput synthesis was complete, every library member was analyzed by reversed-phase LC/MS with monitoring at 210 and 254 nm and by ELS. Compounds which were ≥70% pure were accepted without further purification. Compounds with purities in the 50−69% range were selected for purification, which was carried out using a FractionLynx system, with collection triggered by detection of mass ion. Purity is defined from LC as the relative area under the curve.

The average quantity put onto the columns was 69 mg with the average prepurification purity being 60%. Recovery was up to 42 mg, with an average recovery of 15 mg and the average postpurification purity being 79%. Thus, after purification, the number of compounds ≥70% pure was increased from 2984 to 3903. For 257 compounds, no significant improvement in purity was achieved. This is often due to precipitation caused by insolubility before chromatography can be completed. A more detailed breakdown is given in Figure 5.

Figure 6 shows a typical example of a library compound before and after FractionLynx purification was carried out.

Conclusion

Efficient and general protocols have been developed for the solution-phase preparation of substituted morpholine derivatives, and a library has been produced around generic structure **1**. This library was designed with proprietary modeling software for use as a general screening library. The R1 reagents were phenols, and the R2 reagents were taken from five different reagent classes, giving a variety of product classes in the final library. All library members were generated from a common intermediate, mesylate (**5**), which was synthesized efficiently in bulk in three steps from *N*-benzylethanolamine (**2**). High-throughput chemistry using robotics was carried out to produce the final library products. The process used has been developed to enable the rapid production of large compound libraries with thousands of members. In this case, 7907 compounds were made, the average amount of each compound being 39 mg (0.09 mmol).

A notable feature of our compound libraries is that the quality of each member is ensured by individual characterization by reversed-phase LC/MS analysis. Purification is

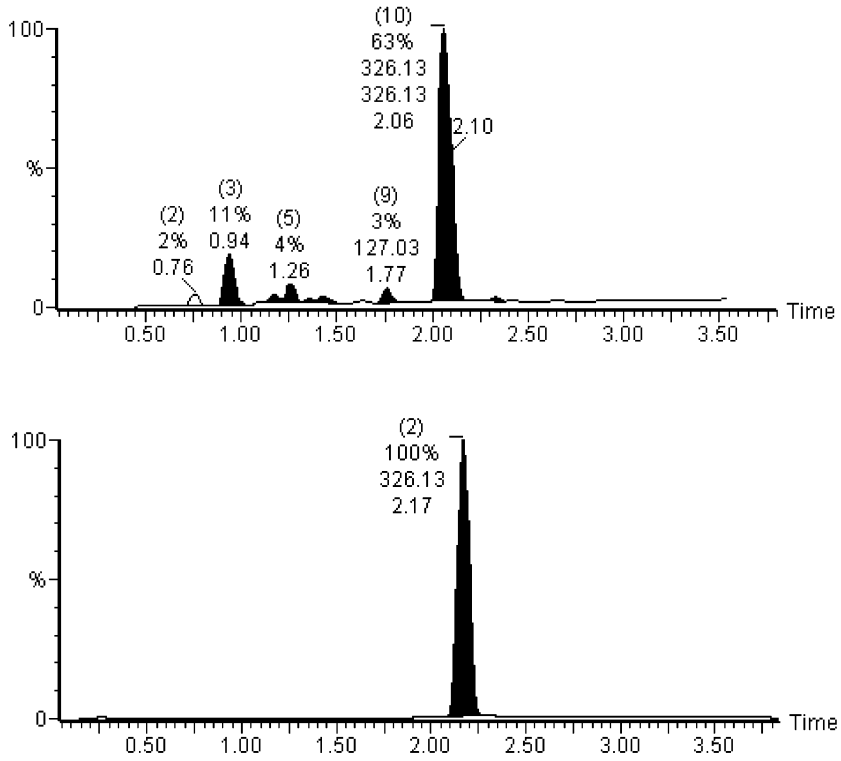


Figure 6. DAD at 254 nm for the same library compound before (top) and after (bottom) purification.

carried out where required, and compounds are then re-analyzed by LC/MS to record the improved purity. In addition, each compound is a product of our proprietary design process, which results in an optimal reagent selection. Overall, the process results in maximizing diversity around a single generic core through intelligent use of varied chemistries and design-led selection of diverse reagents.

Experimental Section

General. All solvents were anhydrous HPLC grade. All non-high-throughput chemistry reactions were carried out under an inert atmosphere of nitrogen. Analytical thin-layer chromatography (TLC) was performed on Merck silica gel (60 F_{254}) plates. Visualization was effected with ultraviolet light or any of the following reagents: ninhydrin, phosphomolybdic acid, anisaldehyde or iodine. Column chromatography was carried out on Merck silica gel 60 (particle size 35−70 μm, 60 Å). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 400 MHz spectrometer. Chemical shifts were measured in parts per million (δ) relative to tetramethylsilane (TMS) or chloroform as the internal standard. Coupling constants (J values) are in hertz (Hz). Infrared spectra (IR) were obtained on a Nicolet Avatar 360 FT-IR spectrometer. Absorptions are reported in wavenumbers (cm^{-1}). All high-throughput reactions and workups were carried out on a Packard MPII liquid handling robot. Mass-selective preparative LC/MS used a Waters LCZ mass spectrometer, Waters 600 HPLC controller, Waters 2700 sample manager, Waters reagent manager, and Gilson 204 fraction collector. Compounds (∼50 mg) were dissolved in methanol to a total volume of 1 mL. These solutions were injected onto a high-resolution preparative reversed-phase column (Phenomenex Luna 60 × 21.2 mm, 5-μm particle size). Chromatography was performed with a binary gradient of solvent A (water + acid modifier) and solvent B (acetonitrile + acid modifier). Waters FractionLynx operating software (version 3.4) was used throughout.

(±)-*N*-Benzyl-2-chloromethylmorpholine (3). *N*-Benzylethanolamine (**2**) (10 g, 66 mmol) was dissolved in neat (±)-epichlorohydrin (5 equiv, 330 mmol, 30.59 g), and the resulting mixture was stirred and heated to 40 °C for 30 min. The reaction mixture was then cooled, and excess epichlorohydrin was exhaustively removed in vacuo to give the intermediate diol as a pale yellow viscous oil (17.09 g, 0.70 mmol, 100%). The diol was treated with concentrated sulfuric acid, and the resulting yellow-orange mixture was heated to 95 °C for 30 min, during which time the reaction mixture turned brown in color. The reaction mixture was cooled and quenched with ice. The aqueous layer was then basified (pH 14) using 5 M aqueous sodium hydroxide solution and extracted into toluene portions (×4). The organic extracts were combined, washed (water, brine), dried ($MgSO_4$), filtered, and concentrated in vacuo to give the desired chloride as a yellow oil (4.25 g, 18.83 mmol, 29%). ^{1}H NMR analysis indicated that this material was sufficiently pure for use without further purification. ^{1}H NMR ($CDCl_3$): δ 7.36−7.21 (m, 5H), 3.92−3.91 (m, 1H, C*H*H), 3.82−3.70 (m, 2H, C*H*H; C*H*O), 3.57−3.49 (m, 4H, CH_2Ph(s); CH_2Cl(m)), 2.88−2.85 (m, 1H, C*H*H), 2.69−2.66 (m, 1H, C*H*H), 2.24−2.22 (m, 1H, C*H*H), 2.03−2.01 (m, 1H, C*H*H). LC/MS: ES^+ 226 [M + 1].

(±)-*N*-Benzyl-2-hydroxymethylmorpholine (4). (±)-*N*-Benzyl-2-chloromethylmorpholine (**3**) (1 g, 4.4 mmol) was dissolved in formamide (10 mL). An excess of water (3 mL) was added, and the resulting reaction mixture was heated to 145 °C overnight. TLC analysis indicated that all of the starting chloride had been consumed, and a new, polar component had been formed in the reaction mixture. The reaction mixture was cooled to room temperature and diluted with water (100 mL) before being basified (to pH 12−14) using 5 M aqueous sodium hydroxide solution. The aqueous formamide layer was extracted into toluene portions, which were combined, washed (brine), dried ($MgSO_4$), filtered, and concentrated in vacuo to give the desired alcohol **4** as a viscous yellow oil (878 mg, 4.24 mmol, 96%). ^{1}H NMR analysis indicated that this material was sufficiently pure for use without further purification. ^{1}H NMR ($CDCl_3$): δ 7.26−7.16 (m, 5H), 3.81−3.79 (m, 1H, C*H*H), 3.64−3.41 (m, 6H, C*H*H; C*H*O, CH_2O CH_2Ph), 2.62−2.57 (m, 2H, 2 × C*H*H), 2.40 (br s, 1H, OH), 2.10−2.04 (m, 1H, C*H*H), 1.94−1.88 (m, 1H, C*H*H). LC/MS: ES^+ 208 [M + 1].

(±)-*N*-Benzyl-2-(methylsulfonato)methylmorpholine (5). (±)-*N*-Benzyl-2-hydroxymethylmorpholine (**4**) (870 mg, 4.2 mmol) was dissolved in dry dichloromethane (10 mL) under an inert atmosphere. This solution was cooled to 0 °C in an ice-bath. Methanesulfonyl chloride (1.1 equiv, 4.62 mmol, 529 mg), triethylamine (1.1 equiv, 4.62 mmol, 467 mg), and a catalytic quantity of 4-(dimethylamino)pyridine (DMAP, 10 mol %, 0.42 mmol, 51 mg) were added to the reaction mixture, which was left to stir at 0 °C for 3−4 h and then warmed to room temperature overnight. The reaction mixture was diluted with dichloromethane (20 mL), and the organic layer was washed (water, brine), dried ($MgSO_4$), filtered, and concentrated in vacuo to give a crude product which was purified by flash chromatography (silica gel; eluant, 75% ethyl acetate in hexane) to give the desired mesylate **(5)** as a viscous yellow oil (831 mg, 2.91 mmol, 70%). IR (neat): 1352, 1174. ^{1}H NMR ($CDCl_3$): δ 7.37−7.26 (m, 5H), 4.23−4.21 (m, 2H, CH_2OMs), 3.91−3.84 (m, 2H, C*H*H, C*H*O), 3.74−3.54 (m, 1H, C*H*H), 3.54−3.53 (s, 2H, CH_2Ph), 3.05 (s, 3H, SO_2Me), 2.76−2.67 (m, 2H, 2 × C*H*H), 2.25−2.22 (m, 1H, C*H*H), 2.06−2.01 (m, 1H, C*H*H). ^{13}C NMR ($CDCl_3$): δ 139.4, 131.2, 130.5, 129.5, 75.4, 72.4, 68.7, 67.7, 65.3, 56.1, 54.8. LC/MS: ES^+ 286 [M + 1].

General Procedure for Preparation of Chemset 7. (±)-*N*-Benzyl-2-(methylsulfonato)methylmorpholine (**5**) (1 g, 3.5 mmol) was dissolved in dry dimethylacetamide (10 mL) under an inert atmosphere and combined with potassium carbonate (2 equiv, 3.15 mmol, 969 mg) and each phenol **6** (0.9 equiv, 3.15 mmol). The resulting reaction mixture was heated to 110 °C overnight, and the course of the reaction was followed by TLC analysis. The reaction mixture was cooled and poured onto water (60 mL), and the aqueous dimethylacetamide layer was extracted with ethyl acetate portions. Addition of brine was required to break up the emulsion formed. The combined organic layers were washed (water, brine), dried ($MgSO_4$), filtered, and concentrated in vacuo to give a crude product that was purified by flash

chromatography (silica gel; eluant, ethyl acetate/hexane mixtures) to give the desired ether **7** as a viscous oil.

General Procedure for Preparation of Chemset 8. Each *N*-benzyl intermediate (**7**) was dissolved in dry 1,2-dichloroethane under an inert atmosphere and treated with an excess (3 equiv) of 1-chloroethylchloroformate. The resulting mixture was heated to reflux (95 °C) for 24 h. When no trace of starting material remained by TLC analysis, the formation of the intermediate carbamate (**7a**) was deemed to be complete. The reaction mixture was evaporated to dryness in vacuo. The resulting residue was taken up in methanol, and the resulting mixture was again heated to reflux (75 °C) overnight. The course of the reaction was followed by TLC analysis until all the intermediate carbamate (**7a**) had been consumed and a polar, baseline component had been formed, corresponding to the HCl salt of the debenzylated material (**8**). The reaction mixture was concentrated in vacuo to remove the methanol and give the desired debenzylated product. The majority of the examples validated were viscous oils. Purification by recrystallization from methanol−ether mixtures was attempted on several examples, but this was successful only for compounds that were solids before purification.

General Procedure for Preparation of Amides Chemset 1a. Stock solutions of each R1 amine hydrochloride (0.38 M) and DIPEA (2 equiv, 0.76 M) in anhydrous DMF and each R2 carboxylic acid (0.66 M) and DIPEA (2 equiv, 1.3 M) in anhydrous DMF were prepared. For those acids that were available as a hydrohalide salt, the stock solutions were of each R2 carboxylic acid (0.66 M) and DIPEA (3 equiv, 2 M) in anhydrous DMF. A stock solution of HBTU (0.4 M) in anhydrous DMF was also prepared. Aliquots (330 μL, 0.22 mmol) of each R2 acid solution were distributed into individual wells of a 2.2-mL 96-deep-well plate. Aliquots (580 μL, 0.22 mmol, 1 equiv) of each R1 amine solution were added to each R2 acid solution. Finally, aliquots (550 μL, 0.22 mmol, 1 equiv) of the HBTU solution were added to each amine/acid mixture. Each deep-well plate was then sealed and left to shake overnight at room temperature. The DMF was removed in vacuo in a Genevac without heat. The dried reaction mixtures were dissolved in DCM (1 mL), and 10% citric acid solution (1 mL) was added. The organic layers were then removed and transferred into another 2.2-mL 96-deep-well plate containing 10% aqueous potassium carbonate solution (1 mL). The organic layers were then removed and transferred into another plate containing deionized water (2 × 1 mL). Finally, the organic layers were then removed and transferred into pretared cube tubes, and a 30-μL aliquot was transferred into a Beckman plate for LC/MS analysis.

General Procedure for Preparation of Tertiary Amines Chemset 1b. Stock solutions of each R1 amine hydrochloride (0.29 M) and DIPEA (0.29 M) in anhydrous DMA and of each R2 aldehyde (0.875 M) in 3:1 anhydrous THF/DMA were prepared. Stock solutions of acetic acid (4.4 M) in anhydrous DMA and of the reducing agent, sodium triacetoxyborohydride (STAB, 0.66 M) in anhydrous DMA, were also prepared. Aliquots (240 μL, 0.21 mmol, 0.95 equiv) of each R2 aldehyde solution were distributed into individual wells of a 5.0-mL, 48-deep-well plate. Aliquots (750 μL, 0.22 mmol, 1 equiv) of each R1 amine solution were added to each R2 aldehyde solution. Aliquots (50 μL, 0.22 mmol, 1 equiv) of the acetic acid solution were added to each amine/aldehyde mixture, and the reaction mixtures were then left to shake for 20 min before addition of the reducing agent to allow formation of the imine. Aliquots (500 μL, 0.33 mmol, 1.5 equiv) of the sodium triacetoxyborohydride solution were then added to the wells. Each deep well plate was then sealed and left to shake overnight at room temperature. The DMA/THF was removed in vacuo using a Genevac without heat. To the dried reaction mixtures, 1 M HCl (1 mL) was added, and the plate was shaken for 5 min. Ethyl acetate (2 mL) was added, followed by saturated aqueous Na_2CO_3 solution (1 mL). The layers were mixed and allowed to settle before removing the aqueous layers. The organic layer was then washed with 20% aqueous Na_2CO_3 solution (1 mL), mixed, and allowed to settle. The aqueous layers were then removed. The organic layer was washed twice further with distilled water (2 × 1 mL) and then transferred into a cube tube plate, and a 30 μL aliquot was transferred to a Beckmann plate for LC/MS analysis.

General Procedure for Preparation of Ureas Chemset 1c. Stock solutions of each R1 amine hydrochloride (0.38 M) and DIPEA (2 equiv, 0.76 M) in anhydrous DMF and of each R2 isocyanate (0.88 M) in anhydrous DMF were prepared. Aliquots (580 μL, 0.22 mmol) of each R1 amine solution were distributed into individual wells of a 2.2-mL 96-deep-well plate. Aliquots (250 μL, 0.22 mmol, 1 equiv) of each R2 isocyanate solution were added to each R1 amine solution. Each deep well plate was then sealed and left to shake overnight at room temperature. The DMF was removed in vacuo in a Genevac without heat. The dried reaction mixtures were dissolved in DCM (1 mL), and 10% citric acid solution (1 mL) was added. The organic layers were then removed and transferred into another 2.2-mL 96-deep-well plate containing 10% aqueous potassium carbonate solution (1 mL). The organic layers were then removed and transferred into another plate containing deionized water (2 × 1 mL). Finally, the organic layers were then removed and transferred into pretared cube tubes, and a 30-μL aliquot was transferred into a Beckman plate for LC/MS analysis.

General Procedure for Preparation of Thioureas Chemset 1d. Stock solutions of each R1 amine hydrochloride (0.38 M) and DIPEA (2 equiv, 0.76 M) in anhydrous DMF and of each R2 isothiocyanate (0.88 M) in anhydrous DMF were prepared. Aliquots (580 μL, 0.22 mmol) of each R1 amine solution were distributed into individual wells of a 2.2-mL 96-deep-well plate. Aliquots (250 μL, 0.22 mmol, 1 equiv) of each R2 isothiocyanate solution were added to each R1 amine solution. Each deep-well plate was then sealed and left to shake overnight at room temperature. The DMF was removed in vacuo in a Genevac without heat. The dried reaction mixtures were then dissolved in DCM (1 mL), and 10% citric acid solution (1 mL) was added. The organic layers were then removed and transferred into another 2.2-mL 96-deep-well plate containing 10% aqueous potassium carbonate solution (1 mL). The organic layers were then removed and transferred into another plate containing deion-

ized water (2 × 1 mL). Finally, the organic layers were then removed and transferred into pretared cube tubes, and a 30-μL aliquot was transferred into a Beckman plate for LC/MS analysis.

General Procedure for Preparation of Sulfonamides Chemset 1e. Stock solutions of each R1 amine hydrochloride (0.38 M) and DIPEA (2 equiv, 0.76 M) in anhydrous DMF and of each R2 sulfonyl chloride (0.82 M) and pyridine (1 equiv, 0.82.M) in anhydrous acetonitrile were prepared. Aliquots (580 μL, 0.22 mmol) of each R1 amine solution were distributed into individual wells of a 2.2 mL 96 deep well plate. Aliquots (268 μL, 0.22 mmol, 1 equiv) of each R2 sulfonyl chloride solution were added to each R1 amine solution. Each deep-well plate was then sealed and left to shake overnight at room temperature. The DMF was removed in vacuo in a Genevac without heat. The dried reaction mixtures were then dissolved in DCM (1 mL), and 10% citric acid solution (1 mL) was added. The organic layers were then removed and transferred into another 2.2-mL 96-deep-well plate containing 10% aqueous potassium carbonate solution (1 mL). The organic layers were then removed and transferred into another plate containing deionized water (2 × 1 mL). Finally, the organic layers were then removed and transferred into pretared cube tubes, and a 30-μL aliquot was transferred into a Beckman plate for LC/MS analysis.

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Supporting Information Available. ^{1}H NMR spectra for compounds **3**, **4**, and **5**; full LC/MS analytical data for 24 final library members. This information is available free of charge via the Internet at http://pubs.acs.org.

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