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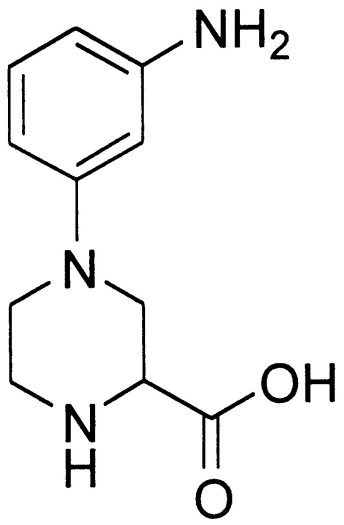

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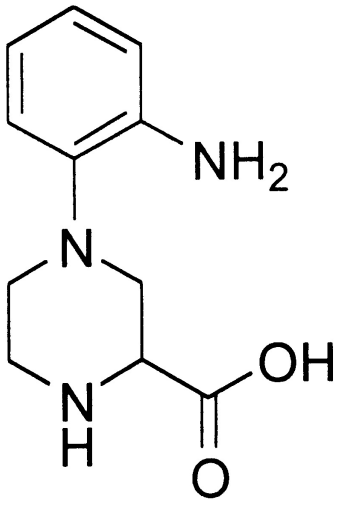

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Solid-Phase Synthesis of Libraries Generated from a 4-Phenyl-2-carboxy-piperazine Scaffold†

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Strategies for finding novel structures of therapeutical interest are discussed. The rationale for the selection of the two scaffolds *N*4-(*m*-aminophenyl)-piperazine-2-carboxylic acid **E** and *N*4-(*o*-aminophenyl)-piperazine-2-carboxylic **F** is described. The synthesis of the appropriate precursors to scaffold **E** and **F** and their use in solid-phase chemistry are described. A 160-member library was produced combining these novel piperazine scaffolds with eight sulfonyl chlorides/acid chlorides and 10 amines. The compound library prepared was analyzed using LC-MS, showing the expected base peak in all wells at an average purity of 82%.

Introduction

The pharmaceutical industry is under continuous pressure to prepare and evaluate novel structural motifs to meet an ever-increasing number of new protein targets being discovered and evaluated for therapeutic use. The chemistry goal is to find structural motifs with broad applications for drug targets in different therapeutic areas. 1,4-Benzodiazepines belong to a well-known class of bioactive compounds that are anxiolytics and antihypnotics,[1] cholecystokinin receptor A and B antagonists,[2] and opioid receptor ligands,[3] that show several other activities,[4] and which have been successfully developed into marketed drugs. Not surprisingly, the synthesis of 1,4-benzodiazepines libraries was explored very early using combinatorial chemistry.[5] More recently, biphenyl structural motifs have been incorporated into molecules showing broad biological activity including antihypertensive (antagonists of the angiotensin II receptor),[6] antihyperglycemic,[7] endothelin-A (ET_A) receptor antagonists,[8] and cyclooxygenase-2 (COX-2) inhibitor[9] activity.

The advent of combinatorial chemistry has revolutionized drug discovery making large, diverse and drug-like compound libraries available for screening against new protein targets in a rapid and cost efficient manner. Numerous recent publications have highlighted this development, describing the synthesis of compound libraries based on novel scaffolds.[10] However, the initial efforts in combinatorial chemistry mainly focused on large and diverse libraries primarily driven by chemistry has so far had limited success. Notably, the current trend is directed toward the design and synthesis of smaller and target based iterative libraries.

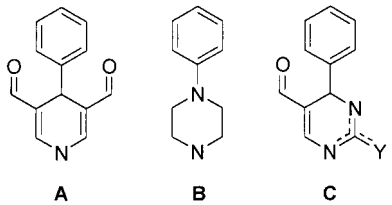

Figure 1. Structural motifs frequently observed in biologically active compounds.

Not withstanding the current focus based on the latter approach, there is a need for exploring ideas for general lead generation libraries, thus discovering hitherto unexplored structural classes with useful biological activities. As part of an effort to develop novel drug-like motifs amenable for combinatorial diversification, we have searched for biologically relevant templates in the MDDR[11] (MACCS-II Drug Data Report) database, by defining small sets of structural motifs attributed to broad biological activities. Three such motifs frequently observed in biologically active compounds were annotated (Figure 1). Template **A** was found in 673 dihydropyridines, template **B** in 2271 phenyl-piperazines, and template **C** in 140 other compounds. Drugs or drug candidates incorporating these three templates show a very wide range of pharmacological activities. These are presented in Table 1, and summarized as follows: 15 dihydropyridines are marketed drugs, while 11 are in phase II or III, covering a total of five therapeutic areas; 16 phenyl-piperazines are marketed drugs, while 23 phenyl-piperazines are currently in phase II or III, covering 18 therapeutic indications. In total, there are 65 structures in phase II (or higher), covering 23 therapeutic areas. Ten structures containing the template **C** are in the preclinical evaluation stage, covering three therapeutic areas. The absence of phase I (or higher) status for compounds having the template **C** is indicative of the

† This is the first publication in a series of scaffolds generated around this theme.

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Table 1. Structure−Therapeutic Activity Profile for the Three Templates Discussed in Figure 1[a]

class	example	main therapeutic activity	nr. str.[b]	status
template **A** (dihydropyridines)	Felodipine	Ca-channel blocker (antihypertensive)	14	launched
	Nimodipine	neuronal injury inhibitor	1	launched
	Furaldipine	Ca-channel blocker (antihypertensive)	3	phase III
	Cronidipine	Ca-channel blocker (antihypertensive)	4	phase II
	Modipafant	PAF antagonist	2	phase II
	YM-15430-1	β-1 adrenergic blocker	1	phase II
	Niguldipine	antineoplastic enhancer	1	phase II
template **B** (phenyl piperazines)	Norfloxacin	antibacterial-quinolone	6	launched
	Naftopidil	α-1 adrenergic blocker (prostate)	2	launched
	Trazodone	antidepressant	2	launched
	Nefazodone	5 HT2A antagonist (antidepressant)	1	launched
	Vesnarinone	phosphodiesterase III inhibitor (cardiotonic)	1	launched
	Levodropropizine	antitussive	1	launched
	Itraconazole	antifungal	1	launched
	Dapiprazole	α-2 adrenergic agonist (glaucoma)	1	launched
	Oxypertine	anxiolytic	1	launched
	Arpiprazole	antipsychotic	1	phase III
	Rifalazil	antimycobacterial	1	phase III
	Fananserin	antipsychotic	4	phase II
	Upidosin	α-1 adrenergic blocker (prostate)	3	phase II
	Flivanserin	antidepressant	3	phase II
	Ensaculin	cognition disorders	2	phase II
	Saperconazole	antifungal	2	phase II
	Ro-23-9424	antibacterial-quinolone	1	phase II
	R-68151	lipooxygenase inhibitor (antipsoriatic)	1	phase II
	R-61837	antiviral	1	phase II
	UP-5222-04	analgesic	1	phase II
	AZ01279880	gpIIb/IIIa antagonist (antiaggregant)	1	phase II
	TAK-044	endothelin antagonist (renal failure)	1	phase II
	CGP-43371	hypolipidemic	1	phase II
template **C**	SQ-32321	Ca-channel blocker (antihypertensive)	5	preclinical
	SNAP-6145-(+)	α-1 adrenergic blocker (prostate)	4	preclinical
	MDDR_266261	antiinflammatory	1	preclinical

[a] Based on the 3084 compounds that contain these scaffolds retrieved from the February 2000 version of the MDDR database. Compounds in phase II (or higher) are shown for templates **A** and **B**, but only compounds in preclinical testing are disclosed for template **C**. [b] "nr. str." is the number of structures in each category. A representative for each class is given in the "example" column. See text for details.

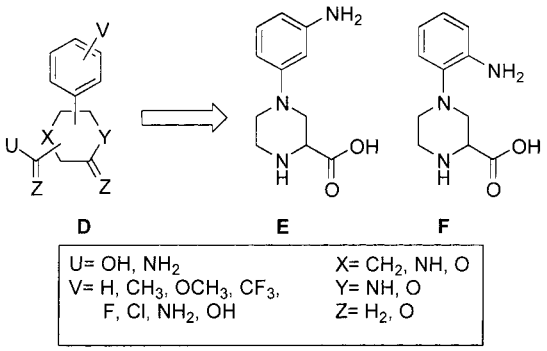


Figure 2. Generic structure and the two 4-phenyl-2-carboxy-piperazine scaffolds used.

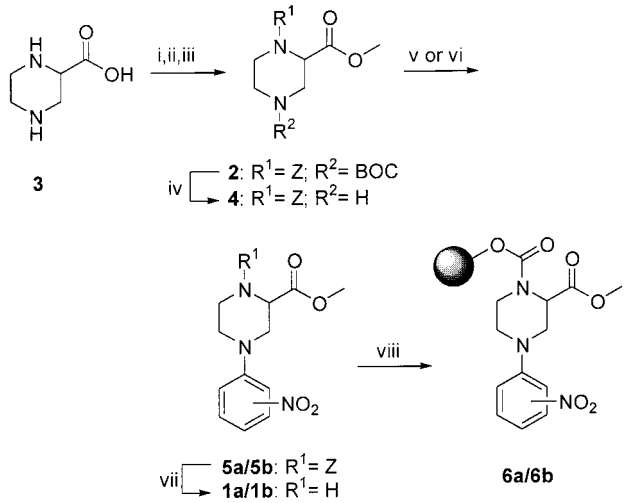
novelty of this particular class of structures for pharmaceutical applications. All three templates have been shown to block Ca-channels.

On the basis of these findings, we have therefore reasoned that derivatives of the generic structure **D** (Figure 2) would be of general interest due to their structural similarity to the bioactive templates shown in Figure 1. The goal is to explore spatially defined structures having ring heteroatoms and appropriately located functional groups that allow for diversification in well-defined directions. This will immediately translate into a good understanding of the pharmacophore, and the interactions with the biological target once activity is obtained. Consequently, we have undertaken the synthesis of several scaffolds derived from the general template **D**, and subsequently developed a synthesis strategy for production of libraries around these scaffolds. In this paper, we report on the synthesis of two of the selected scaffolds (**E** and **F**) and their exploration using solid-phase chemistry. The selection of scaffolds **E** and **F** was made on the basis of synthetic feasibility and provides three points of diversification and furthermore provides appealing prospects for libraries with different directional vectors. Gratifyingly, this structural motif appears in compounds possessing antibacterial[12] and oxytocin receptor antagonist[13] activities but most importantly remains an unexplored framework for therapeutic exploration.

Results and Discussion

These novel scaffolds (**E** and **F**) provide a fairly rigid framework, with well-defined directional vectors of the functional groups where diversity can be introduced, thus providing straightforward information for structure−activity relationships. The strategy adopted for the test library was to prepare the regioisomers **1a**/**1b** (Scheme 1) in solution and subsequently attach and derivatize these scaffolds on solid support. The immobilized scaffolds were subsequently reacted with 8 different electrophiles (acid chlorides and sulfonyl chlorides) and 10 different amines (primary and secondary) to produce the 160 members in this library.

Scheme 1. Synthesis of Scaffolds[a]



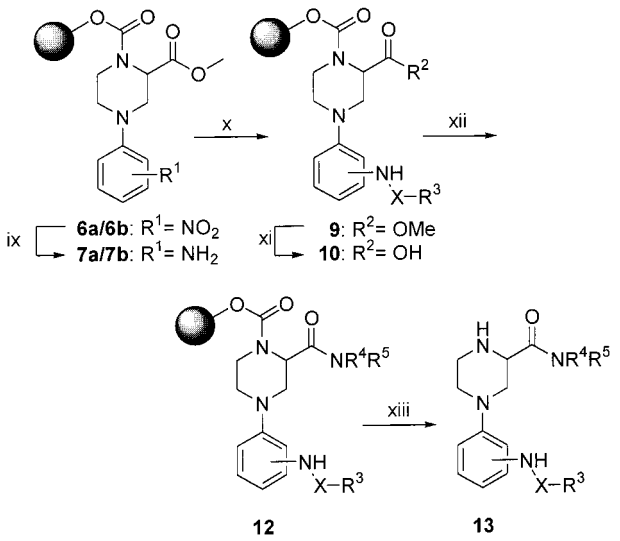
[a] Reagents and conditions: (i) BOC-ON, pH 11, dioxane/H_2O 1:1; (ii) Z-Cl, pH 9.5; (iii) CH_3I, $NaHCO_3$ (aq), adogen 464, DCM; (iv) HCl, dioxane; (v) 2-fluoronitrobenzene, TEA, 60 °C to give **5a** (*o*-NO_2); (vi) $Pd(OAc)_2$, BINAP, $CsCO_3$, 3-bromonitrobenzene, toluene, 100 °C to give **5b** (*m*-NO_2); (vii) TFMSA, anisole, DCM; (viii) *p*-nitrophenyl carbonate Wang resin,[16] DIPEA, DMF, 80 °C.

Synthesis and Immobilizing of the Scaffolds. For the synthesis of the scaffold **2**, piperazine-2-carboxylic acid **3** (Scheme 1) was selectively monoprotected with 2-(*tert*-butoxycarbonyloxyimino)-2-phenylacetonitrile (BOC-ON) in dioxane/water at pH 11 adjusted with aqueous sodium hydroxide. The pH was then lowered with hydrochloric acid to 9.5, and benzyl chloroformate (Z-Cl) was added. The diprotected piperazine-2-carboxylic acid was then esterified using iodomethane and aqueous sodium bicarbonate under phase transfer conditions in DCM (dichloromethane) to yield the orthogonally protected piperazine-2-carboxylic acid **2** in **78**% yield.[14] The *tert*-butoxycarbonyl group was cleaved to yield **4** by treating **2** with hydrochloric acid in dioxane. Reacting Z-protected piperazine **4** with *o*-fluoro-nitrobenzene for 5 days gave **5a** in 95% yield. However, direct aromatic substitution using the corresponding *m*-fluoro-nitrobenzene failed as expected due to the less activating effect of *m*-nitro substituent. Instead **5b** was synthesized in 78% yield using palladium acetate, BINAP ((*R*)-(+)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl), *m*-bromo-nitrobenzene, and cesium carbonate in toluene at 100 °C.[15] Deprotection of **5a**/**5b** using trifluoromethanesulfonic acid (TFMSA) in DCM gave the free amines **1a** and **1b** in 92% and 85% yields correspondingly.

The scaffolds **1a**/**1b** were immobilized onto the *p*-nitrophenyl carbonate activated Wang resin[16] using DIPEA (diisopropylethylamine) in DMF (dimethylformamide). The loading (81% for **6a** and 61% for **6b**) was surprising considering the poor nucleophililicity of the *N*1 of piperazine-2-carboxylates.[17] Longer reaction times did not improve loadings.

Solid-Phase Reactions. There are several methods reported for reduction of nitro compounds on solid support,[18−20] and $CrCl_2$ (chromium(II)chloride)[19] in DMF and $SnCl_2 \cdot H_2O$ (tin(II)chloride monohydrate)[18] in DMF were examined. Very slow reaction was observed using the former.[21] Premature cleavage of the Wang-linker has been reported using $SnCl_2 \cdot H_2O$ due to formation of hydrogen chloride and/or Sn(IV) Lewis acid capabilities.[22,18] However, reduction of **6a**/**6b** using $SnCl_2 \cdot H_2O$ in DMF for 18 h at room temperature produced a clean reduction to the anilines **7a**/**7b** (Scheme 2) with no resin cleavage observed.[23] Subsequently **7a**/**7b** were coupled in DCM/pyridine with the acid chlorides and sulfonyl chlorides in chemset **8** (Figure 3). The esters **9** were hydrolyzed to the corresponding carboxylic acids using potassium trimethylsilanoate in THF (tetrahydrofuran). The free acids **10** were then coupled with the amines in chemset **11** (Figure 4) using pyBOP (benzotriazol-1-yl-oxytripyrrolidino-phosphonium hexafluorophosphate) and *N*-methylmorpholine (NMM) in DMF to yield the amides **12**. The resin bound products were cleaved from the resin with 40% trifluoroacetic acid (TFA) in DCM to provide the TFA salts **13** of the 160-member library.

Scheme 2. Chemistry on Solid Phase[a]



[a] Reagents and conditions: (ix) $SnCl_2 \cdot H_2O$, DMF; (x) R^3XCl, X = SO_2 or CO (**8**), pyridine, DCM; (xi) TMSOK, THF; (xii) NHR^4R^5 (**11**), PyBOP, NMM, DMF; (xiii) TFA, 30% in DCM.

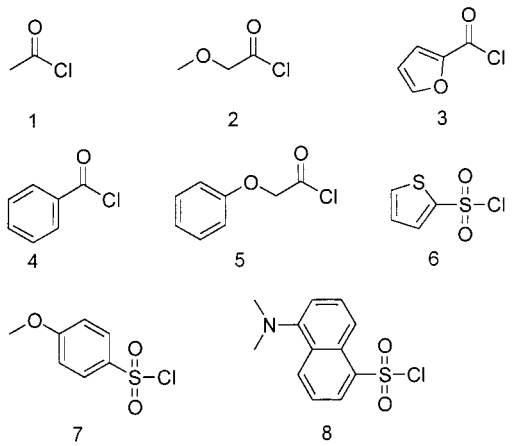


Figure 3. Diversity reagents **8**{*1*−*8*}.

Quality Assessment and Purification. The library was analyzed for every compound using HPLC/UV/ESIMS. All wells showed a base peak consistent with the expected product (MS). The initial analysis showed a purity of above 80% for 126 of the 160 members based on UV light absorption.[24] To further raise the quality of the library, 39

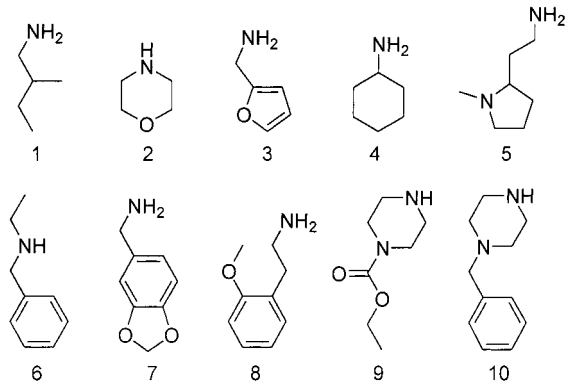


Figure 4. Diversity reagents **11**{*1*−*10*}.

Table 2. Amount of *p*-Hydroxy Benzylated Product in Different Sets/Subsets

set/subset	13-(Bn-OH)$_n$[a]
13a	7.9%
13a{*1*−*8*,*3*}	25.0%
13a{*1*−*8*,*7*}	13.1%
13b	19.6%
13b{*1*−*8*,*8*}	43.6%

[a] The average percentage of sets/subsets of **13** converted to the impurity in which electrophilic substitution with *p*-hydroxy benzyl cation has taken place.

members were subjected to preparative HPLC purification using mass-triggered fraction collection. After purification, a second more thorough analysis[25] of the entire library showed that only 96 of 160 members had purity above 80%. However, 134 of 160 of the compounds showed purity above 70%, and in no case the purity was less than 40%. The library showed an average purity of 82%. Notable is that almost all of the impurities could be identified by their mass.

The most prominent impurities (10% out of 18%) could be assigned to molecules with a mass 106 or 212 more than the expected mass. A plausible explanation for this is that during the cleavage of **12**, some of the Wang-linker is liberated as *p*-hydroxy benzyl cation, which could add to the members of **13**, by electrophilic substitution. In accordance with that **13b**, which is more prone to electrophilic aromatic substitution than **13a**, also shows a higher amount of this impurity. Some impurity trends depending on the reacted amines (chemset **11**) are also evident. The products resulting from the more activated aromatic amines **11**{*3*}, **11**{*7*}, and **11**{*8*} **(**Figure 4) show impurities above average (Table 2).

The other identified impurities (4% out of 18%) consist of *p*-hydroxy aniline, acylated by chemset **8 (**Figure 3). These correspond to the reduced version of *p*-nitrophenyl carbonate Wang-resin that has been acylated during the conversion of **7a**/**7b** to **9**, and then released from the resin at the cleavage step (**12** to **13**). The remaining impurities (4% out of 18%) were not characterized.

Treating the resins **6a**/**6b** with a good nucleophile after the immobilization and before the reduction step (**6a**/**6b** to **7a**/**7b**) could eliminate the *p*-hydroxy aniline impurity by minimizing the unreacted *p*-nitrophenyl carbonate Wang-resin. Furthermore, the cleavage step (**12** to **13**) could include some cation scavenger to minimize adduct to the target molecules.

Table 3. Purity and Yields for a Selection of the Library

compd	purity (%)	yield (%)[a]	pur.[b]	compd	purity (%)	yield (%)[a]	pur.[b]
13a{*1*,*2*}	87	58		**13a**{*7*,*10*}	85	74	
13a{*1*,*5*}	92	63		**13a**{*8*,*10*}	79	63	
13a{*2*,*3*}	71	18		**13b**{*1*,*2*}	64	45	
13a{*3*,*1*}	91	67		**13b**{*2*,*2*}	77	49	
13a{*3*,*4*}	91	70		**13b**{*3*,*2*}	69	41	
13a{*3*,*6*}	100	38	yes	**13b**{*4*,*5*}	84	62	
13a{*3*,*10*}	87	75		**13b**{*5*,*9*}	75	58	
13a{*4*,*5*}	97	63		**13b**{*6*,*1*}	72	46	
13a{*4*,*10*}	93	73		**13b**{*6*,*8*}	85	11	yes
13a{*5*,*3*}	70	30		**13b**{*7*,*9*}	58	64	
13a{*5*,*7*}	84	51		**13b**{*8*,*5*}	78	60	
13a{*6*,*2*}	94	80		**13b**{*8*,*8*}	88	19	yes
13a{*7*,*5*}	94	84		**13b**{*8*,*10*}	76	33	

[a] Yield based on NMR integrals with hexamethyldisiloxane as standard. [b] Indicates whether the compound was purified on preparative HPLC or not.

A selection of the library was subjected to yield determination using NMR. This selection of 20 members was made on basis of evenly distributed compounds from a PCA analysis including 60 chemical descriptors.[26] The results from the NMR analysis are summarized in Table 3.

Library Profiling. Virtual and/or existing compound collections (10^2−10^6 compounds) are screened for their content in druglike[27,28] and permeable[29] compounds. Two druglike scoring schemes, one based on Daylight fingerprints[30] and one based on estimated physicochemical properties,[31] have been implemented in-house.[32] Briefly, a druglike molecule is assigned a value closer to 1 (i.e., it is classified as belonging to the MDDR[11] database), whereas a nondruglike compound is assigned a value closer to 0 (i.e., it is classified as belonging to the ACD[33] database). A value of 0.5 in the druglike scores denotes an equal probability to be classified as "drug" and "nondrug".

Lipinski and co-workers[29] suggested, after studying a subset of 2245 drugs from the World Drug Index, that poor passive permeability is more likely when a chemical structure exhibits more than 5 hydrogen bond donors (HDO, expressed as the sum of O−Hs and N−Hs), when the molecular weight (MW) is over 500, when the calculated logarithm of the octanol/water partition coefficient[34] (CLOGP) is over 5, and when there are more than 10 H-bond acceptors (HAC, expressed as the sum of Ns and Os). Any pairwise combination of the following conditions: MW > 500, CLOGP > 5, HDO > 5, and HAC > 10, may result in compounds with poor permeability. We recently suggested[35] that leadlike libraries should include small, polar compounds with MW below 350 and CLOGP below 3.0.

Within this framework, we have analyzed the contents of the 4-phenyl-2-carboxy-piperazine library to evaluate its contents in terms of druglike and leadlike compounds, as follows: This library was deemed to contain only druglike compounds, since all of them have DFPS ≥ 0.7 and PPFS ≥ 0.7, where DFPS and PPFS are the Daylight-FingerPrint-Score and the Property-and-Pharmacophore-Feature-Score, that evaluate the druglike quality of a compound.[32] All the compounds in the 4-phenyl-2-carboxy-piperazine library have a probability higher than 0.7 to be assigned to the MDDR database, as opposed to the ACD database. Furthermore, 152

out of 160 compounds (95%) are within the "rule-of-5" cutoff, i.e., they do not violate more than one of the "rule of 5" criteria. Also, 118 compounds (73.75%) do not violate any of the "rule of 5" criteria, whereas 34 (21.25%) violate one of the rules. In conclusion, the 4-phenyl-2-carboxy-piperazine library contains at least 95% druglike structures that do not violate the "rule of 5", therefore are expected to yield a good percentage of good-permeability compounds.

We note that only 36 compounds (22.5%) satisfied the leadlike criteria (CLOGP ≤ 4.0, and MW ≤ 400), in addition to being druglike. This is due to the inherent nature of this library, expected to be druglike, but not leadlike according to the previous definition,[35] for the following reason: The scaffolds depicted in Figure 2 have low MW (205 Da) and CLOGP (−0.04), allowing for diverse alterations in the substitution pattern at the disconnection moieties, i.e., at the amine and at the keto groups in Figure 2. Therefore, large variations in MW and CLOGP are permitted in the final compounds. These alterations can furthermore be chosen to meet the "rule-of-5" and druglike criteria, implying that this library is both "druglike" and "leadlike" in the same time.

Conclusions

This paper demonstrates one approach to enrich a compound collection to be used in biological screening in the early lead discovery phase. The focus of this test library is not directed toward a given drug target but rather toward the discovery of novel fairly rigid frameworks with diversity functions that cover a pre-defined structural space. We have also emphasized the concept of leadlike and druglike molecules (e.g., within the constraints imposed by the "rule of 5",[29] but less stringent with respect to "leadlike"[35]), to provide good starting points for lead exploration once a compound is confirmed as a hit in biological screens. A screening library composed of 160 spatially separated compounds[36] has been generated using two regioisomers of the scaffold diversified at two positions with eight electrophiles and 10 amines. The methodology is well adapted for creating larger libraries as well as for using other sets of electrophiles and nucleophiles. The further exploration of the scaffolds **E** and **F** and other modifications of the general scaffold **D** are ongoing.

Experimental Section

General. Toluene was distilled over calcium hydride prior to use. TLC analysis was performed on Merck precoated 60 F_{254} plates. Column chromatography was performed using silica gel 60 (0.040−0.063 mm, Merck). Organic phases were dried over magnesium sulfate monohydrate. Concentrations were performed by rotary evaporation. NMR spectra were recorded on a Bruker AC-F 250 instrument using chloroform-d_3 as solvent and tetramethylsilane as an internal standard. HPLC/MS analyses of all samples were performed on a VG Fisons ESI Platform 2 (MassLynx) equipped with positive (ES+) and negative (ES−) electrospray detection and with a photodiode array detector. Samples (∼1 mM, 5 μL) were injected on a reversed-phase column (Waters Xterra MS C8 2.5 μm, 4.6 × 50 mm), with a linear gradient of 0.1 M NH_4OAc/CH_3CN going from 95/5 to 0/100 for 4 min with a flow rate of 1.5 mL/min. Mass spectra were collected from 100 to 800 au for both ES+ and ES−, and UV spectra were recorded between 220 and 350 nm. Quantifications were based on the total absorption in the range 220−250 nm. Purification was performed on a semipreparative HPLC system with mass trace triggered fraction collection (Micromass, model LCZ 2000, Fraction Lynx). Samples were separated on a Waters Xterra C8 5 μm, 20 × 100 mm column with 0.1 M NH_4OAc/CH_3CN through a linear generic gradients going from 95/5 to 0/100 for 8 min with a flow rate of 25 mL/min. High-resolution mass spectrometry (HRMS) was run on a Finnigan MAT900 equipped with an electrospray ion source. Samples were infused at 1 μL/min.

Synthesis of Scaffolds: Racemic *N*1-(Benzyloxycarbonyl)-*N*4-(*tert*-butoxycarbonyl)-piperazine-2-carboxylic Acid, Methyl Ester[14] (2). Piperazine-2-carboxylic acid dihydrochloride (20.5 g, 101 mmol) was dissolved in a 1:1 mixture of water and 1,4-dioxane (660 mL). Using 50% aqueous sodium hydroxide, the solution was adjusted to pH 11. BOC-ON (27.4 g, 111 mmol) dissolved in 1,4-dioxane (160 mL) was slowly added during a period of 1 h. The pH was kept constant at 11 during the addition. The solution was then stirred for three additional hours, during which the pH was again kept constant at 11. The resulting solution was then cooled with an ice bath, and the pH was lowered to pH 9.5 using aqueous hydrochloric acid (6 M). The solution was kept at pH 9.5 during a dropwise addition of benzyl chloroformate (21.4 mL, 152 mmol) over a period of 45 min. After approximately 4 h, the temperature was raised to ambient. The solution was left stirring overnight (16 h). The solution was washed with diethyl ether (4 × 200 mL), acidified to pH 1−2, and extracted with ethyl acetate (4 × 200 mL). The combined ethyl acetate extracts were dried, filtered, and concentrated. The resulting yellow oil was dissolved in saturated aqueous sodium bicarbonate (200 mL) and treated with a solution of 40 g of Adogen 464 and 15 mL of iodomethane in 200 mL of DCM. The mixture was stirred for 48 h and was then extracted with DCM (2 × 200 mL). The combined organic extracts were washed with water (200 mL), dried, and evaporated. The resulting oil was dissolved again in DCM (100 mL) and left to crystallize. Several recrystallizations from DCM gave **2** as pure crystals (29.2 g, 78%). Melting point and NMR was in accordance with litterature.[14] A more extensive NMR analysis is given. ^{1}H NMR (250.13 MHz) δ 7.42−7.21 (m, 5H), 5.24−5.06 (m, 2H), 4.81−4.33 (m, 2H), 4.15−3.81 (m, 2H), [3.74 and 3.69][37] (s, 3H), 3.38−3.21 (m, 1H), 3.18−3.02 (dd, J = 3.6, 11.4 Hz, 1H), 2.97−2.79 (m, 1H), 1.55−1.38 (m, 9H). ^{13}C NMR (62.90 MHz) δ 170.1, 155.8, 153.8, 136.2, 128,5, 128,2, 127.9, 80.3, [67.7 and 67.6],[3737] [54.6 and 54.1],[37] 52.4, 44.6, 42.4, [41.2 and 40.9].[37]

Racemic *N*1-(Benzyloxycarbonyl)-piperazine-2-carboxylic Acid, Methyl Ester (4). Compound **2** (20 g, 53 mmol) was dissolved in 1,4-dioxane (100 mL). To this solution was added dropwise 60 mL of concentrated hydrochloric acid (12 M). After 1 h the solvents were evaporated, and the residue was taken up in water and washed with toluene. The aqueous phase was extracted once with 500 mL of DCM with 5% triethylamine and then thrice with DCM. The

combined organic extracts were dried, filtered, and concentrated to afford **4** (14.7 g 100%) as an oil. ^{1}H NMR (250.13 MHz) δ 7.38−7.22 (m, 5H), 5.20−5.05 (m, 2H), 4.80−4.60 (m, 1H), 3.90−3.82 (m, 1H), [3.77 and 3.72][37] (s, 3H), 3.59−3.42 (m, 1H), 3.25−3.02 (m, 1H), 3.00−2.81 (m, 2H), 2.79−2.62 (m, 1H), 1.82 (bs, 1H). ^{13}C NMR (62.90 MHz) δ 171.2, [156.3 and 155.8],[37] 136.5, 128.9, 128.3, 128.1, 127.9, 127.6, [67.1 and 66.9],[37] [55.2 and 54.7],[37] 52.0, [47.1 and 47.0],[37] 45.1, [42.3 and 42.0].[37]

Racemic *N*1-(Benzyloxycarbonyl)-*N*4-(*o*-nitrophenyl)-piperazine-2-carboxylic Acid, Methyl Ester (5a). Amine **4** (14.7 g, 53 mmol) was dissolved in triethylamine (14.7 mL, 106 mmol), *o*-nitro-fluorobenzene (11.3 mL, 106 mmol) was added, and the solution was heated at 60 °C for 5 days. Excess reagent was removed under reduced pressure, and the resulting yellow-red oil was purified with flash chromatography (toluene/ethyl acetate 9:1) to yield **5a** (20.1 g, 95%) as a yellow oil. ^{1}H NMR (250.13 MHz) δ 7.68−7.65 (m, 1H), 7.49−7.46 (m, 1H), 7.37−7.33 (m, 5H), 7.20−7.11 (m, 2H), 5.19−5.17 (m, 2H), 4.89−4.76 (m, 1H), 4.08−3.96 (m, 1H), [3.78 and 3.72][37] (s, 3H), 3.75−3.66 (m, 1H), 3.61−3.42 (m, 1H), 3.19−3.09 (m, 2H), 2.95−2.81 (m, 1H). ^{13}C NMR (62.90 MHz) δ [170.3 and 170.1],[37] [156.4 and 155.7],[37] 145.3, 144.9, 136.3, 133.1, 128.6, 128.2, 127.9, 125.1, 123.9, 122.5, 67.7, [55.2 and 54.8],[37] 53.2, 52.6, 51.8, [41.9 and 41.6].[37] HRMS *m*/*z* 422.1339 [(M + Na)$^+$ calcd for $C_{20}H_{21}N_3O_6Na^+$ 422.1328].

Racemic *N*1-(Benzyloxycarbonyl)-*N*4-(*m*-nitrophenyl)-piperazine-2-carboxylic Acid, Methyl Ester (5b). An oven-dried (130 °C, 6 h) Schlenktube was charged with anhydrous toluene (5 mL), amine **4** (104 mg, 374 μmol), 1-bromo-3-nitrobenzene (50.0 mg, 249 μmol), palladium(II)-acetate (0.56 mg, 2.5 μmol), and (*R*)-(+)-2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl (BINAP) (2.21 mg, 3.74 μmol) under argon. After 30 min of complex formation, oven-dried (130 °C, 6 h) cesium carbonate (122 mg, 374 μmol) was added, and the tube was heated at 100 °C for 20 h. The solution was allowed to cool to room temperature, diluted with diethyl ether (20 mL), and washed twice with water. The organic phase was dried and concentrated. The reaction mixture was purified with flash column chromatography (toluene/ethyl acetate 9:1) to give (**5b**) as a yellow oil (71.2 mg, 178 μmol, 72% yield). ^{1}H NMR (250.13 MHz) δ 7.78−7.61 (m, 2H), 7.46−7.28 (m, 5H), 7.25−7.19 (m, 2H), 5.35−5.10 (m, 2H), 5.03−4.90 (m, 1H), 4.30−4.08 (m, 2H), [3.77 and 3.72][37] (s, 3H), 3.62−3.31 (m, 2H), 3.15 (dd, J = 3.93, 12.55 Hz, 1H), 2.96−2.82 (m, 1H). ^{13}C NMR (62.90 MHz) 170.3, [155.7 and 155.2],[37] 151.4, 149.2, 136.2, 129.9, 128.6, 128.2, 128.0, 125.3, 122.6, 115.0, 110.7, [67.8 and 67.7],[37] 55.2, 54.8, 52.7, [50.9 and 50.6],[37] 47.8, [41.3 and 41.1].[37] HRMS *m*/*z* 422.1340 [(M + Na)$^+$ calcd for $C_{20}H_{21}N_3O_6Na^+$ 422.1328].

Racemic *N*4-(*o*-Nitrophenyl)-piperazine-2-carboxylic Acid, Methyl Ester (1a). Anisole (22 mL, 201 mmol) was added to a solution of **5a** (20.1 g, 50 mmol) in 500 mL of DCM. A solution of TFMSA (44.4 mL, 502 mmol), in 200 mL of DCM, was added dropwise to the reaction mixture. After 10 min the reaction mixture was gently poured into a vigorously stirred aqueous solution of sodium dihydrogen phosphate monohydrate (137 g, 1.01 mol). The resulting mixture was extracted thrice with diethyl ether/triethylamine (2:1, 3 × 100 mL), and the combined organic phases were dried and concentrated. Purification by flash column chromatography (ethanol/ethyl acetate 1:1) gave **1a** as a yellow oil (12.2 g, 46 mmol, 92% yield). ^{1}H NMR (250.13 MHz) δ 7.73 (dd, J = 1.5, 8.1 Hz, 1H), 7.54−7.47 (m, 1H), 7.22 (dd, J = 0.9, 7.7 Hz, 1H), 7.14−7.07 (m, 1H), 4.12 (bs, 1H), 3.73 (dd, J = 3.2, 7.7 Hz, 1H), 3.76 (s, 3H), 3.45 (dd, J = 3.1, 11.7 Hz, 1H), 3.23−2.87 (m, 5H). ^{13}C NMR (62.90 MHz) δ 171.8, 145.8, 144.3, 133.4, 125.6, 122.7, 121.9, 57.0, 54.0, 52.5, 52.2, 44.4. The pure free base **1a** was dissolved in methanol, treated with 1.5 equiv of concentrated hydrochloric acid, concentrated, and recrystallized from methanol to give **1a**·HCl as a yellow solid, suitable for storing: mp 198 °C (dec, darkens at 80 °C). ^{1}H NMR (250.13 MHz, D2O, shifts relative to HDO = 4.75 ppm) δ 7.80 (dd, J = 1.5, 8.4 Hz, 1H), 7.62−7.56 (m, 1H), 7.33 (d, J = 8.1 Hz, 1H), 7.26−7.20 (m, 1H), 4.44 (dd, J = 3.7, 7.7 Hz, 1H), 3.81 (s, 3H), 3.67−3.51 (m, 2H), 3.44−3.12 (m, 4H). ^{13}C NMR (62.90 MHz, D_2O, shifts relative to acetone = 30.9 ppm) δ 168.5, 144.8, 144.6, 135.4, 126.3, 125.9, 123.7, 56.1, 54.5, 51.5, 49.3, 43.2. HRMS *m*/*z* 266.1137 [(M + H)$^+$ calcd for $C_{12}H_{16}N_3O_4$+ 266.1141].

Racemic *N*4-(*m*-Nitrophenyl)-piperazine-2-carboxylic Acid, Methyl Ester (1b). Synthesis was performed using the same method as for *o*-nitro compound **1a**. Purification by flash column chromatography (ethanol/ethyl acetate 1:1) gave **1b** as a yellow oil (85% yield). ^{1}H NMR 7.62 (s, 1H), 7.55 (d, J = 1.46 Hz, 1H), 7.38−7.25 (m, 1H), 7.15 (dd, J = 1.8, 8.4 Hz, 1H), 3.78 (s, 3H), 3.67−3.52 (m, 2H), 3.40−3.15 (m, 3H), 3.13−2.87 (m, 2H), 2.62 (bs, 1H). ^{13}C NMR (62.90 MHz) 171.1, 151.1, 148.4, 129.0, 120.9, 113.1, 109.1, 56.1, 51.5, 50.0, 47.8, 43.1. HRMS *m*/*z* 266.1139 [(M + H)$^+$ calcd for $C_{12}H_{16}N_3O_4$+ 266.1141].

General Remarks for Solid-Phase Reactions. All solid-phase reactions were checked for completion by taking small samples of the resin, which was subsequently rinsed and cleaved with 30% TFA in DCM. The cleavage solution was evaporated and subjected to reversed-phase HPLC analysis. In those cases where the amount of solvent is not explicitly stated, the minimal amount to achieve good swelling was used. Glassware was silylated by treatment with a 10% solution of dichlorodimethylsilane in DCM followed by rinsing with DCM.

Racemic *N*1-(PS-Wang)-*N*4-(*o*/*m*-Nitrophenyl)-piperazine-2-carboxylic Acid, Methyl Esters (6a/6b). PS-Wang resin (2.5 g, 0.89 mmol/g, 2.23 mmol) was suspended in DCM (18 mL). The suspension was cooled on an ice bath, and *p*-nitrophenyl chloroformate (1.35 g, 6.68 mmol) dissolved in DCM (5 mL) was added. After mixing, the suspension was treated with NMM (0.73 mL, 6.68 mmol). The mixture was shaken in an ice bath for 2 h, and then overnight at room temperature. The suspension was transferred to a fritted reservoir. The supernatant was removed with applied pressure of nitrogen gas, and the resin was rinsed three times with DCM. The treatment with *p*-nitrophenyl chloroformate and NMM was repeated once. The resin was then rinsed alternating with DCM and diethyl ether

(repeated three times) and then with DMF (five times). DMF was then added until the resin was swelled, and the suspension was transferred to a silylated round-bottomed flask. This was then treated with either a solution of racemic *N*4-(*o*-nitrophenyl)-piperazine-2-carboxylic acid, methyl ester hydrochloride salt **1a**·HCl (2.02 g, 6.68 mmol) and DIPEA (1.16 mL, 6.68 mmol) in DMF (5 mL) or a solution of racemic *N*4-(*m*-nitrophenyl)-piperazine-2-carboxylic acid, methyl ester (**1b**) (1.77 g, 6.68 mmol) in DMF (5 mL). To the scaffold treated resin was then added additional DIPEA (1.16 mL, 6.68 mmol). The flask was heated at 80 °C and shaken for 20 h. The resin was then transferred to a fritted reservoir and the supernatant was removed by applied nitrogen gas. The resin was rinsed once with DMF. The supernatant and first rinse were collected, evaporated, and purified on column chromatography to isolate excess scaffolds **1a**/**1b**. Then the resin was rinsed with DMF four times, then alternating with DCM and diethyl ether (five times), and finally with diethyl ether three times. The resin was then dried under vacuum for several days. The loading was 0.57 mmol/g (81%) for *o*-substituted (**6a**) and 0.43 mmol/g (61%) for *m*-substituted (**6b**).[17]

Racemic *N*1-(PS-Wang)-*N*4-(*o*/*m*-Aminophenyl)-piperazine-2-carboxylic Acid, Methyl Esters (7a/7b). Racemic *N*1-(PS-Wang)-*N*4-(*o*/*m*-nitrophenyl)-piperazine-2-carboxylic acid, methyl esters (**6a**/**6b**) (10 g, loading 0.43−0.57 mmol/g) were each suspended in DMF in a fritted reservoir and treated with a solution of $SnCl_2 \cdot H_2O$ (26.7 g, 118 mmol, 21−27 equiv) in DMF (15 mL). After shaking for 18 h, the supernatants were removed with applied nitrogen pressure, and the resin was rinsed with DMF (five times), methanol (two times), DCM (two times), and diethyl ether (two times). The resin was then dried under vacuum for several days and then stored under argon.

Library Synthesis. Racemic *N*1-(PS-Wang)-*N*4-(*o*-aminophenyl)-piperazine-2-carboxylic acid, methyl ester (**7a**) and racemic *N*1-(PS-Wang)-*N*4-(*m*-aminophenyl)-piperazine-2-carboxylic acid, methyl ester (**7b**) were each divided onto a plate with 96 fused fritted 1 mL reservoirs. A total of 80 reservoirs were used on each plate with an average of 56 mg resin per reservoir for **7a** and 65 mg for **7b**. This resulted in a typical loading of about 30 μmol scaffold per reservoir. The resin was swelled in DCM and sucked dry, then rinsed with DCM:pyridine (2:1) (2 × 400 μL) and sucked dry. Eight different electrophiles (diversity reagents **8)** in DCM (300 μL, 1.27 M, 380 μmol, 12 equiv) were added in 10 reservoirs each on both plates. More DCM:pyridine (2:1) was added until good swelling (approximately 200 μL). Mixing was achieved by rotating the closed plates for 15 h. The supernatants were removed by suction, and the resin was rinsed with DCM (5 × 400 μL), methanol (2 × 400 μL), DCM (5 × 400 μL), and tetrahydrofuran (THF) (4 × 400 μL). This furnished the amides and sulfonyl amides **9**. The resin was sucked dry, and potassium trimethylsilanoate in THF (600 μL, 0.625 M, 380 μmol, 12 equiv) was added. After mixing for 4 h, the resin was sucked dry and rinsed with THF (5 × 800 μL), THF:acetic acid (3:1) (4 × 800 μL), and DMF (5 × 400 μL). This yielded the methylester deprotected **10**. The resin was again sucked dry. PyBOP in DMF (562 μL, 0.333 M, 187 μmol, 6 equiv) was added. Ten different amines (diversity reagents **11**) (200 μL, 0.95 M, 190 μmol, 6 equiv) were added to eight reservoirs each on both plates orthogonal to the electrophile addition. Finally NMM in DMF (90 μL, 4.22 M, 380 μmol, 12 equiv) was added, and the plates were rotated for 10 h to give **12**. After sucking dry and washing with DMF (5 × 800 μL), methanol (3 × 800 μL), and DCM (5 × 800 μL), cleavage was performed by adding 400 μL of DCM and 300 μL of TFA and mixing for 10 min. The cleavage solutions were collected in two 96-well plates. Residual products were rinsed of the resin with DCM (3 × 200 μL) and also collected. Solvents were evaporated in a vacuum centrifuge at 45 °C and 5 mbar overnight, and **13** were collected.

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