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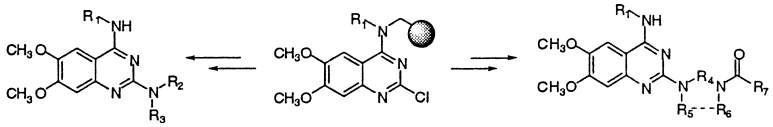

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Solid-Phase Synthesis of 2,4-Diaminoquinazoline Libraries

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A series of libraries containing the 2,4-diaminoquinazoline ring system were prepared, starting from polymer-bound amines. The key steps included reaction of the support-bound amine with 6,7-dimethoxy-2,4-dichloroquinazoline, followed by displacement of the second chlorine with an amine and subsequent TFA-mediated cleavage of the product from the support. When a symmetrical or unsymmetrical diamine was used in the displacement step, the free amine could be acylated with an activated acid to generate another set of compounds. The optimization of conditions for the reductive amination and displacement steps will be discussed as well as the final choice of resin for library production. In addition, quality control methods for library analysis is also described.

Introduction

Combinatorial chemistry has become an important tool for the discovery and optimization of molecules of pharmaceutical interest.[1] Since heterocycles form the basis of many drug classes, combinatorial libraries derived from known heterocyclic core fragments are attractive targets for identifying lead structures.[2,3] While many libraries based on heterocycles have been described in the literature, so far none of these reports have included the 2,4-diaminoquinazoline ring system found in several approved drugs as well as those under development. Examples of these include prazosin (**1**),[4] doxazosin (**2**),[5] and CP-101816-1 (**3**).[6] Herein, we describe a solid-phase approach amenable to preparing combinatorial libraries based on these heterocycles. Specifically, we targeted libraries based on quinazolines **4** and **5**.

Results and Discussion

The application of nucleophilic aromatic substitution (S_NAr) reactions in the synthesis of combinatorial libraries in solution and on solid support has been reported by numerous research groups.[7] We envisioned the S_NAr reaction of quinazoline halides with support-bound amines to be the key step for the preparation of libraries containing **4** and **5**. Specifically, the synthesis of a combinatorial library based on general structure **4** was executed as described in Scheme 1. 2-Methoxy-4-hydroxybenzaldehyde (**7**) was attached to Merrifield resin (**6**) with cesium carbonate in *N*,*N*-dimethylacetamide (DMA), and the resulting aldehyde resin was converted to the secondary amine using a two-step sequence.[8] These conditions offered the advantage of monitoring the success of the imine formation step on support with single-bead FT-IR spectroscopy. The two-step protocol afforded the secondary amine **10**, which was heated with dichloroquinazoline **11** and *N*,*N*-diisopropylamine (DIPEA) to give the (4-amino-2-chloroquinazolinyl)polystyrene derivative **12**. Selective chlorine displacement at the 4-position of **11** by resin **10** was anticipated to occur according to literature precedent for the corresponding solution-phase reaction.[9]

A brief discussion on the choice of reductive amination conditions is necessary. Initial development efforts employed a one-pot reductive amination protocol that proved to be less applicable to the large set of primary amines required for the library.[10] Under such conditions and subsequent reaction with dichloroquinazoline **11**, imine **17** was observed as a contaminant by HPLC−UV and LC−MS analysis after TFA cleavage of the resin (Scheme 2). Furthermore, some resins prepared under these conditions showed the presence of aldehyde carbonyl by single-bead FT-IR analysis. Resin cleavage with TFA in CH_2Cl_2 was used to evaluate the success of both the imine formation/reduction sequence and the attachment of the quinazoline scaffold at this stage. Resins that gave quinazoline **13** of purities greater than 90% by HPLC−UV (area under the curve (AUC) at 214 nm) were used for library production.

The second set of amine building blocks was introduced by heating these resins with primary and secondary amines (**14**) in DMA at 135−140 °C. The library products were then cleaved from the resin using TFA with 2.5% added triethylsilane as cation scavenger. While neat TFA afforded satisfactory results, a slight improvement in product recoveries was observed with the added cation scavenger.

During validation of precursors according to the conditions outlined in Scheme 1, we observed several general limitations of the building blocks (Figure 2). First of all, the preferred reductive amination conditions were not amenable to all classes of amines. Despite literature reports to the contrary, we were not able to get anilines to participate successfully in the reductive amination step.[11] Furthermore, α-branched primary amines and amines containing other basic sites performed poorly in the reductive amination. Other amines,

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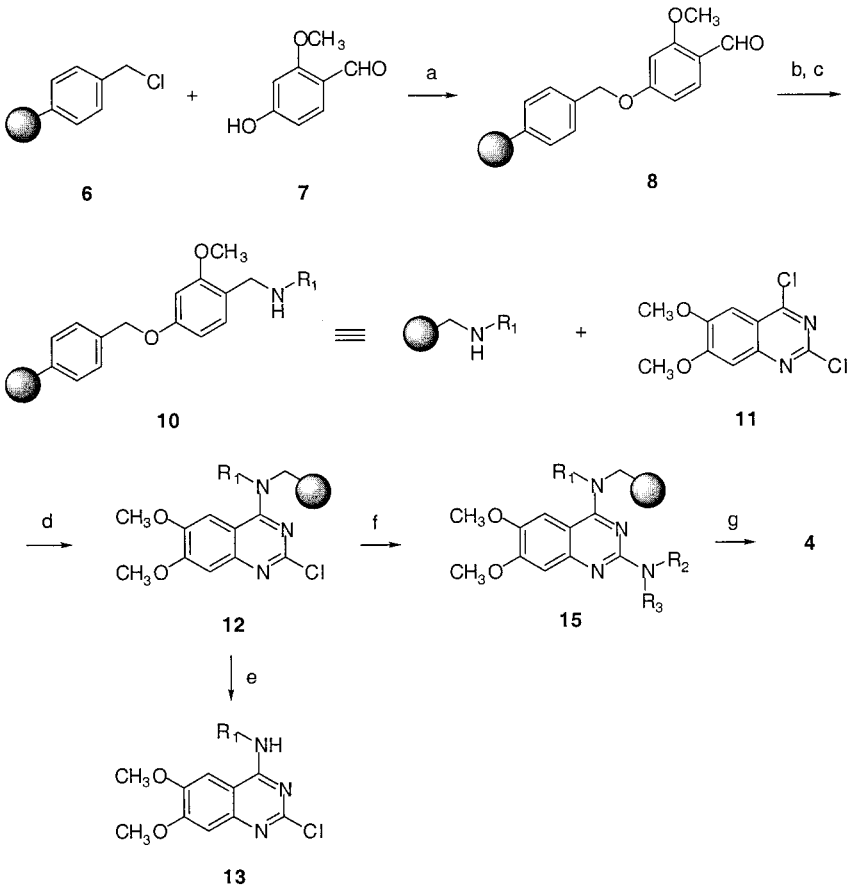
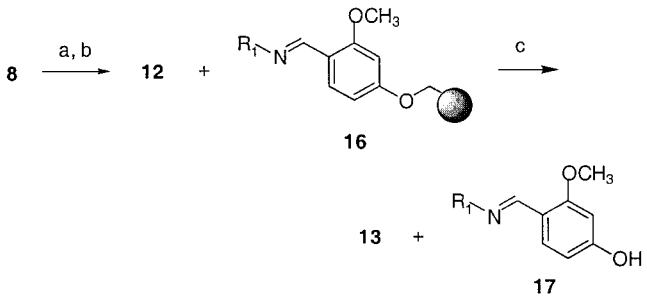
Scheme 1[a]



[a] Reaction conditions: (a) Cs_2CO_3, KI, DMA, 60−65 °C; (b) R_1-NH_2 (**9**), $(MeO)_3CH$, THF; (c) $NaBH_4$, THF/EtOH (3:1); (d) $(i\text{-Pr})_2NEt$, THF, 60 °C; (e) TFA, CH_2Cl_2; (f) R_2R_3NH (**14**), DMA, 135−140 °C; (g) TFA, Et_3SiH.

Scheme 2[a]



[a] Reagents and conditions: (a) R_1-NH_2 (**9**), $NaBH(OAc)_3$, 1% AcOH in DMF; (b) **11**, $(i\text{-Pr})_2NEt$, THF, 50−60 °C; (c) TFA, CH_2Cl_2.

including tryptamine and *tert*-amylamine, gave complex mixtures upon TFA cleavage, indicative of their instability to strong acid required for the cleavage step.

Several classes of amines **14** were found to perform best in the displacement of the support-bound chloride of **12**. Generally, most primary amines and cyclic secondary amines (piperazines and piperidines) provided the cleanest products after TFA cleavage. In contrast, most acyclic secondary amines and primary amines with α-branching afforded complex mixtures in the displacement step.

Other resins were explored during the development of the route described in Scheme 1. For example, Wang resin (**18**) was converted to the known bromide **19** and subsequent displacement with a primary amine afforded the support-bound secondary amine **20** (Scheme 3).[12] However, reaction of this amine with quinazoline **11** and TFA deprotection afforded the expected product **13**, contaminated with 4-hydroxybenzyl derivative **22**, whose formation arises from cleavage of the ether bond of the linker. Similar impurities have been observed with peptides generated from amines derived from Wang resin.[13]

Rink resin (**23**) could also be employed in the generation of quinazoline libraries, allowing for access to library members based on known drugs **1** and **2**. Reaction of dichloride **11** with the free amine, available from simple FMOC deprotection of the commercial resin, afforded the support-bound chloroquinazoline **24** under conditions similar to those described in Scheme 1. Displacement of the support-bound chlorine with primary and cyclic secondary amines followed by TFA-mediated cleavage from the resin as before afforded compound **25**, as described in Scheme 4.

Our approach to libraries of general structure **5** relied upon the reaction of diamines **27** with intermediate **12**, as shown in Scheme 5. Heating these components at 135−140 °C in a mixture of DMA and 1,8-diazabicyclo[5.4.0]unde-7-ene (DBU) afforded free amine **28**. Unlike the conditions described in Scheme 1, the success of this route depended on significantly larger amounts (2000 mol %) of the diamine **27**, as opposed to 600 mol % of amine **14**, and use of DBU as additive. These conditions were necessary to minimize the formation of dimers due to cross-linking of two resin-bound quinazolines with the diamine (vide infra).

When unsymmetrical diamines were employed in the

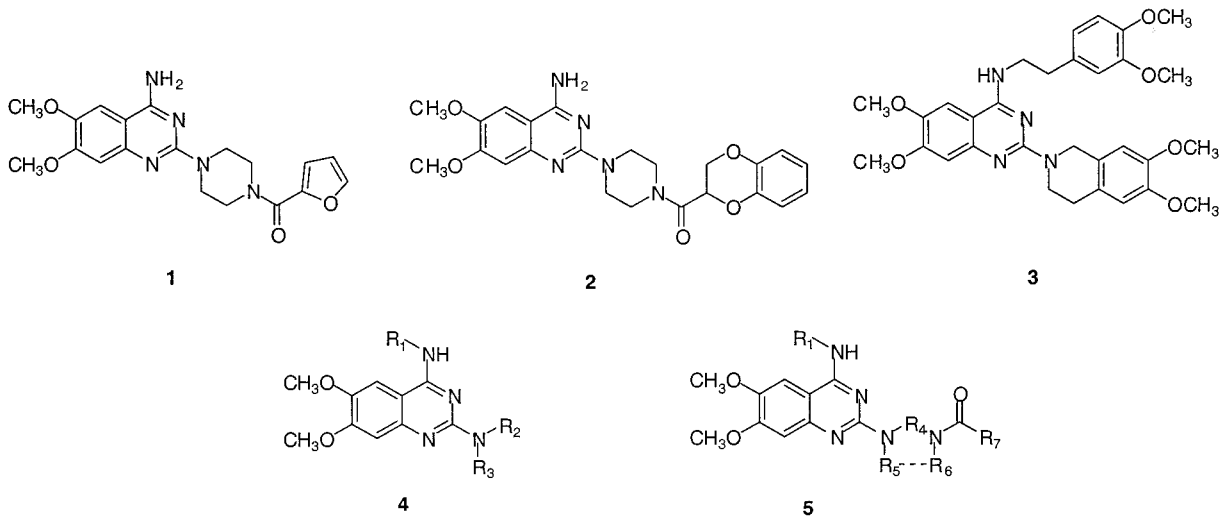


Figure 1. Known quinazoline-2,4-diamine drugs (**1**−**3**) and target library structures (**4** and **5**).

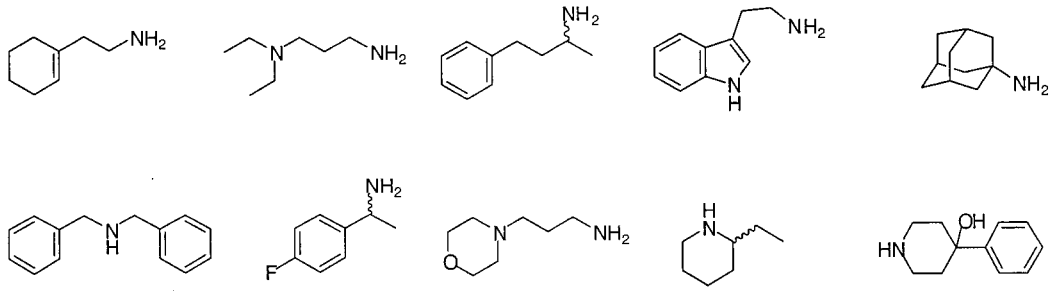
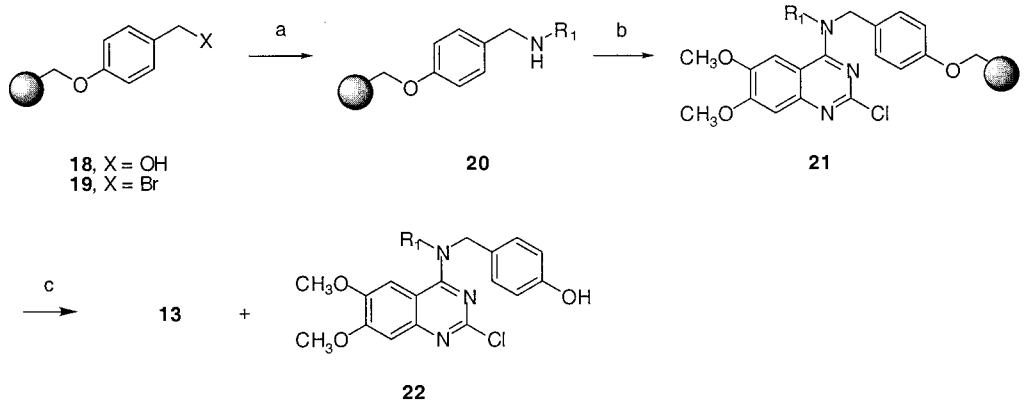


Figure 2. Amines unsuitable for the reductive amination and S_NAr steps outlined in Scheme 1.

Scheme 3[a]



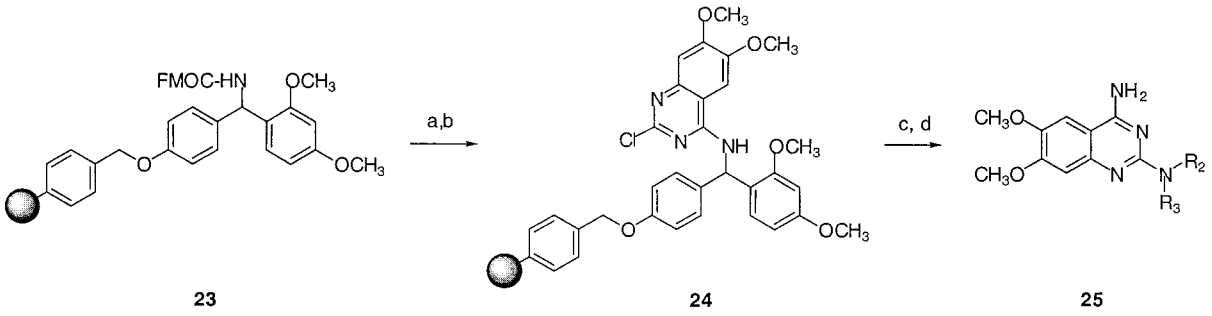
[a] Reagents and conditions: (a) R_1-NH_2 (**9**), CH_2Cl_2; (b) **11**, THF, (*i*-Pr)$_2$NEt, heat; (c) TFA.

displacement step, only one regioisomer was obtained. Generally these diamines contained both a cyclic secondary amine and a primary amine, for example, 4-aminomethylpiperidine. In these cases, the more nucleophilic secondary amine was assumed to displace the chloride of the scaffold, in analogy with other S_NAr reactions employing asymmetric diamines.[14]

The resulting free amine of **28** could be acylated with a variety of carboxylic acid derivatives (**29**). Several popular reagent classes commonly used for carboxylic acid activation were examined, including carbodiimides[15] such as DIC, DCC, EDC, the phosphonium salt PyBOP,[16] and the uronium salt HBTU.[17] While all of these reagents were partially successful for amine acylation, PyBOP performed the best overall and therefore was employed in the synthesis of the library. The acids were preactivated for 5 min by treatment with PyBOP and HOBt in DMF, and then these solutions were added to the resin followed by the addition of the base *N*-methylmorpholine (NMM). As in the previous library chemistry, precursor limitations for the diamines and carboxylic acids were noted. Examples of these are shown in Figure 3.

For many diamines, use of a lower stoichiometry produced dimers resulting from addition to two chloroquinazolines, as illustrated by the reaction of resin **12** (R_1 = 4-trifluoromethylbenzyl) with 600 mol % piperazine (Table 1). We noted a correlation between the resin-swelling ability of the solvents investigated and the amount of dimer formation: dimer formation decreased in the order EtOH > DMSO > DMF = toluene. This order is roughly inverse to the ability

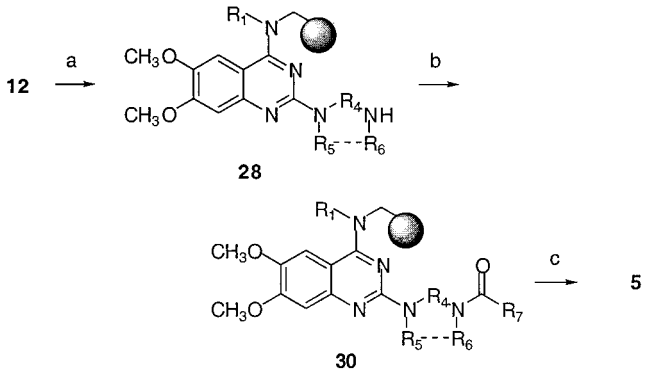
Scheme 4[a]



23 **24** **25**

[a] Reaction conditions: (a) piperidine, DMF; (b) **11**, (*i*-Pr)$_2$NEt, THF, room temp; (c) R_2R_3NH (**14**), DMA, 135−140 °C; (d) TFA, Et_3SiH.

Scheme 5[a]



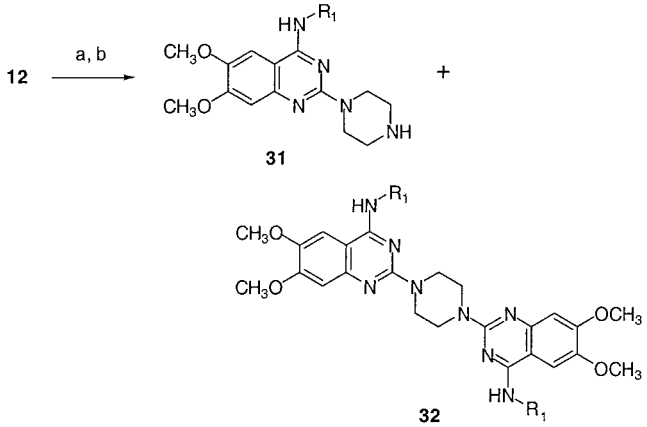
28 **30**

[a] Reaction conditions: (a) diamine (**27**), DMA, DBU, 135−140 °C; (b) R_7CO_2H (**29**), PyBOP, HOBt, NMM; (c) TFA.

of these solvents to swell polystyrene resin. The correlation suggested that when solvents with poor resin-swelling properties were used, the quinazolines were held in sufficient spatial proximity to permit the desired monoaddition product to react with a second quinazoline; better swelling resins separated the quinazoline moieties such that the cross-linking was attenuated. Other factors besides the resin-swelling ability may also have influenced the solvent effect on dimer formation.

Libraries based on structures **4** and **5** were analyzed in the following manner. A percentage of the library (12.5%) was assayed for product identity by flow injection mass spectrometry (FIA-MS). In addition, several wells were removed from the library, accurately weighed, and assayed against purified and fully characterized (NMR, MS, and combustion analysis) samples of the exact same compounds for which quantitative calibration curves were previously generated. This process generates a weight-percent purity value that is more rigorous than HPLC−UV analysis by area-under-the-curve methods. Tables 2 lists weight-percent

Table 1. Dependence of Dimer Formation on Reaction Solvent



31 **32**

Reaction Conditions: (a) piperazine, solvent; (b) TFA.

solvent	temp, °C	% **31**[a]	% **32**[a]
DMF	120	36	16
ethanol	85	47	50
DMSO	120	66	28
toluene	120	81	16

[a] Determined by HPLC−UV analysis [area under the curve at 214 nm]. The ratios reflect the raw HPLC data and are uncorrected for the molar extinction coefficients of **31** and **32**.

purities for library compounds prepared according to the routes outlined in Schemes 1 and 5. Residual solvent and inorganic impurities contributed to low purities in some cases. In the case of **4** (Scheme 1), cross contamination of product wells due to the reaction of volatile amines in adjacent wells was commonly observed.

Summary

We have demonstrated a versatile solid-phase route to prepare libraries of compounds based on the 2,4-diamino-

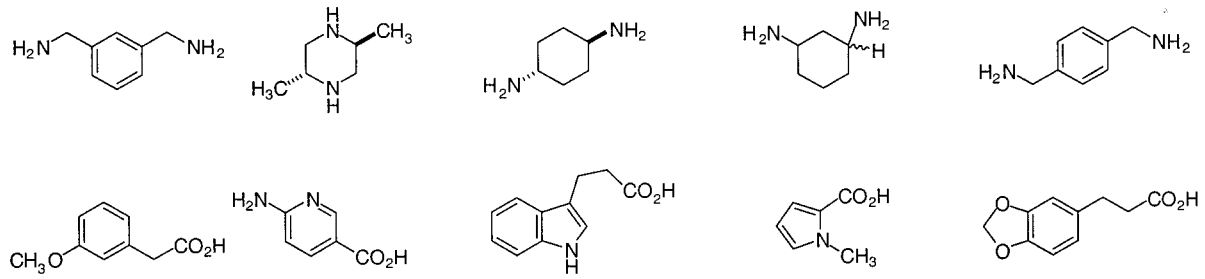
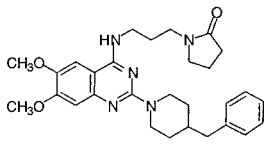
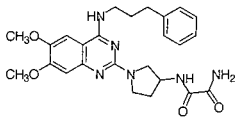
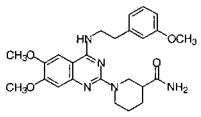
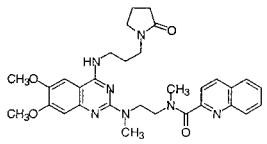
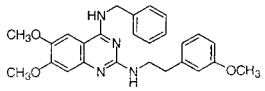
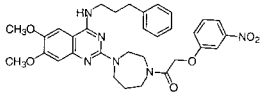
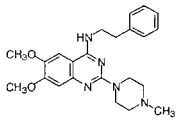
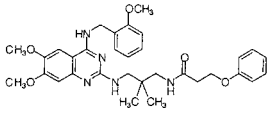
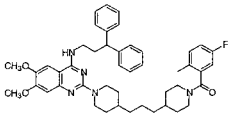
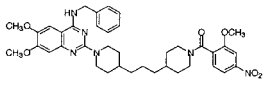
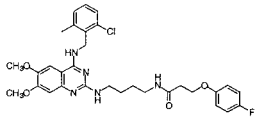
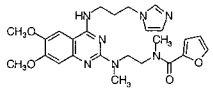


Figure 3. Amines and carboxylic acids unsuitable for the S_NAr and acylation steps outlined in Scheme 5.

Table 2. Structure and Quantitative Purities of Compounds Prepared According to Schemes 1 and 5

	Compound/Structure	Yield (%)[a]	Purity (%)[b]		Compound/Structure	Yield (%)[a]	Purity (%)[b]
4a		31	78	**5c**		56	51
4b		26	70	**5d**		56	51
4c		40	80	**5e**		45	70
4d		17	56	**5f**		46	78
5a		46	73	**5g**		61	67
5b		52	100	**5h**		67	61

[a] Yield of crude material. [b] Determined by quantitation against purified and fully characterized samples; see text for details.

quinazoline ring system. This chemistry features two S_NAr substitutions of 2,4-dichloroquinazoline, one employing a support-bound secondary amine to attach the scaffold to support and another on the support-bound heterocycle. Last, we have shown that diamines can be used and subsequently acylated with carboxylic acids to afford diverse quinazoline libraries.

Experimental Section

General. Chloromethylpolystyrene (Merrifield resin; 100−200 mesh; loading 1.0−1.2 mmol/g) was obtained from Midwest Biotech. 2-Methoxy-4-hydroxybenzaldehyde and 2,4-dichloro-6,7-dimethoxyquinazoline were purchased from Lancaster Synthesis and used as received. FMOC-protected Rink resin was purchased from Advanced Chemtech. All other reagents and library building blocks were commercially available and also used as received. Polypropylene syringe cartridges were purchased from Applied Separations, Allentown, PA.

All library reference standards were purified by reverse-phase HPLC using acetonitrile and water as the mobile phases containing 0.5−1% TFA as acidic buffer. The pure fractions were lyophilized and submitted for analysis and standard curve generation. Library samples were analyzed by HPLC−UV on a Hewlett-Packard HP1100 HPLC with a diode array detector. LC−MS and MS analyses were performed on either a Finnigan TSQ7000 mass spectrometer fitted with a Hewlett-Packard HP1050 HPLC or a Perkin-Elmer Sciex mass spectrometer with a Gilson 215 liquid handler as the sample delivery system. Proton NMR samples were acquired on either a GE QE-300 spectrometer at 300 MHz or a JEOL Eclipse 270 FT-NMR spectrometer at 270 MHz. Elemental analyses were performed by Robertson Microlit, Madison, NJ, or M-H-W Laboratories, Phoenix, AZ.

[(3-Methoxy-4-formylphenoxy)methyl]polystyrene (8). To a nitrogen-purged 5000 mL three-neck flask fitted with an overhead stirrer and stir blade/stir shaft assembly was added a mixture of 2-methoxy-4-hydroxybenzaldehyde (**7**; 71.6 g; 470 mmol), cesium carbonate (296.7 g; 911 mmol), and potassium iodide (25.0 g; 151 mmol) in 2000 mL of anhydrous *N*,*N*-dimethylacetamide. Stirring was initiated, the suspension was heated to ca. 30−35 °C, and then 255.5 g (307 mmol) of chloromethylpolystyrene (**6**; loading 1.2

mmol/g) was added in one portion. The temperature was raised to 50−55 °C and kept at this temperature for 23 h. The suspension was filtered hot into a 3000 mL coarse glass fritted funnel, and the resin was washed according to the following sequence: DMF (2 × 1000 mL), water (2 × 1000 mL), DMF (2 × 1000 mL), water (2 × 1000 mL), DMF (2 × 1000 mL), methanol (2 × 1000 mL), CH_2Cl_2 (2 × 1000 mL), methanol (2 × 1000 mL), 10% acetic acid in CH_2Cl_2 (2 × 1000 mL), methanol (2 × 1000 mL), CH_2Cl_2 (2 × 1000 mL), and finally diethyl ether (3 × 1000 mL). The resin was briefly dried in vacuo in the funnel and then under a stream of nitrogen. The resin was transferred to a 2000 mL round-bottom flask and dried for 36 h under house vacuum. Then the resin was dried to constant weight under high vacuum. Yield: 277 g of tan beads. Single-bead FT-IR: 1678 cm^{-1}. Elemental analysis showed less than 0.05% residual chlorine.

Preparation of Amine Resin 10: General Procedure. A. Imine Formation. To a 500 mL Nalgene polypropylene bottle was added 15.0 g of resin **8** that was suspended in 170 mL of anhydrous THF. This was followed by the addition of the amine (600 mol %) and 42 mL of trimethylorthoformate. The bottle was capped and shaken for 15 h. The resin slurry was filtered and the resin washed according to the following sequence: anhydrous THF (2 × 200 mL), methanol (2 × 200 mL), CH_2Cl_2 (2 × 200 mL), methanol (2 × 200 mL), and finally ethanol (2 × 200 mL). The resin was dried in a vacuum to constant mass and then analyzed by single-bead FT-IR for the presence of the aldehyde stretch at 1675 cm^{-1}. If this absorbance was present, the above procedure was repeated.

B. Imine Reduction. The resin obtained as described above was then suspended in 200 mL of a mixture of anhydrous THF/ethanol (3:1) and treated with 7.2 g (190 mmol; 1270 mol %) of sodium borohydride. The suspension was agitated overnight. The resin was filtered and washed according to the following sequence: THF (2 × 200 mL), ethanol (2 × 200 mL), THF (2 × 200 mL), water (2 × 200 mL), THF (2 × 200 mL), and methanol (2 × 200 mL). The resin was then dried in vacuo to constant weight and then used immediately in the following reaction.

General Procedure: Preparation of Monochloroquinazoline Resin 12. Resin **10** (15 g; 18 mmol) was suspended in anhydrous inhibitor-free THF (150 mL). The resin slurry was then treated with 12.5 g (48.2 mmol) of 2,4-dichloro-6,7-dimethoxyquinazoline (**11**), followed by 16.8 mL (12.5 g; 96.7 mmol) of DIPEA. The resin slurry was heated at 60 °C for 15 h. The reaction mixture was cooled to room temperature and the resin washed according to the following sequence: CH_2Cl_2 (2 × 200 mL), THF (2 × 200 mL), CH_2Cl_2 (2 × 200 mL), and methanol (1 × 200 mL). Resin **12** was then dried in vacuo to constant weight and stored under nitrogen in tightly sealed containers to minimize exposure to the atmosphere. Resins prepared in this manner were subjected to TFA cleavage conditions as described below.

Preparation of Resin 24. Rink resin (**23**; 15.0 g; loading 0.56 mmol/g) was washed with DMF (2 × 150 mL). The resin was then suspended in 120 mL of 20% piperidine in DMF and agitated for 5 min. The solution was drained and the resin exposed to another portion (120 mL) of 20% piperidine in DMF for 10 min. The resin was filtered and washed with DMF (2 × 150 mL), methanol (2 × 150 mL), toluene (2 × 150 mL), methanol (2 × 150 mL), toluene (2 × 150 mL), and diethyl ether (3 × 150 mL).

A total of 12.5 g of the resin was suspended in 120 mL of THF and 7.3 mL (5.41 g; 41.9 mmol) of DIPEA. The resulting slurry was treated with 5.42 g (20.9 mmol) of 2,4-dichloro-6,7-dimethoxyquinazoline (**11**). The mixture was shaken for 18 h and then filtered, and the resin was washed with THF (2 × 150 mL), methanol (2 × 150 mL), CH_2Cl_2 (2 × 150 mL), and finally diethyl ether (3 × 150 mL). The resin was then dried in vacuo to constant mass and analyzed by the procedure given above.

TFA Cleavage of Resins 12 and 24: Validation of Reductive Amination and Scaffold Attachment. A 3 mL polypropylene syringe cartridge was charged with 100 mg of resin **12**. The luer end of the syringe was capped and the resin suspended in about 2 mL of a 1:1 solution (v/v) of TFA in CH_2Cl_2. The suspension was allowed to stand for 1 h, and then the solution was collected and concentrated in vacuo. The residue was dried to constant mass and then analyzed by HPLC−UV and LC−MS or MS. Resins that afforded quinazoline **13**, which possessed the expected molecular ion and HPLC area percent purities of 90% at 214 nm, were then used in the preparation of resin **15**.

Preparation of Resin 15: General Procedure. Resin **12** (100 mg) was suspended in a 0.83 M solution of the amine **14** in *N*,*N*-dimethylacetamide (1.0 mL), and the resulting suspension was heated at 135−140 °C for 16 h. The mixture was cooled to room temperature, and resin **15** was washed according to the following sequence: methanol (2 × 1 mL), CH_2Cl_2 (2 × 1 mL), methanol (2 × 1 mL), CH_2Cl_2 (2 × 1 mL), and methanol (2 × 1 mL).

Quinazoline 4. Resin **15** (100 mg) was treated with a solution of 2.5% triethylsilane in TFA (1 mL). The slurry was allowed to stand for 1−2 h, and the cleavage solutions were collected. The resin was then washed with CH_2Cl_2 (2 × 500 μL). The filtrate and washings were concentrated in vacuo, and the residue was dissolved in acetonitrile/water (3:1). The resulting solutions were frozen and then lyophilized to afford the quinazoline **4**.

Analogously, resin **24** was processed in the same manner as resin **12** to afford quinazoline **25**.

1-{3-[2-(4-Benzylpiperidin-1-yl)-6,7-dimethoxyquinazolin-4-ylamino]propyl}pyrrolidin-2-one (4a). ^{1}H NMR (270 MHz, DMSO-d_6): δ 1.22 (br q, 2H), 1.66−1.95 (m, 8H), 2.18 (t, 2H), 2.55 (d, 2H), 3.06 (t, 2H), 3.26 (t, 2H), 3.48−3.58 (m, 2H), 3.84 (s, 3H), 3.88 (s, 3H), 4.48 (br d, 2H), 7.12−7.35 (m, 6H), 7.62 (s, 1H), 9.04 (br s, 1H), 11.57 (br s, 1H), 11.95 (br s, 1H). MS (ESI): *m*/*z* 504.2 $[M + H]^+$. Anal. Calcd for $C_{29}H_{37}N_5O_3 \cdot C_2HF_3O_2$: C, 60.28; H, 6.28; N, 11.34. Found: C, 60.43; H, 6.19; N, 11.13.

1-{6,7-Dimethoxy-4-[2-(3-methoxyphenyl)-ethylamino]-quinazolin-2-yl}piperidine-3-carboxylic Acid Amide (4b). ^{1}H NMR (270 MHz, DMSO-d_6): δ 1.42−1.86 (m, 3H), 1.94−2.04 (m, 1H), 2.36−2.46 (m, 1H), 2.92 (t, 2H), 3.13−3.30 (m, 2H), 3.69−3.79 (m, with s at δ 3.71, 5H), 3.83 (s,

3H), 3.88 (s, 3H), 4.36−4.50 (br s, 2H), 6.80 (br t, 4H), 7.00 (br s, 1H), 7.15 (s, 1H), 7.21 (t, 1H), 7.45 (br s, 1H), 7.64 (s, 1H), 9.24 (br s, 1H), 11.62 (br s, 1H). MS (ESI): *m*/*z* 466.1 $[M + H]^+$. Anal. Calcd for $C_{25}H_{31}N_5O_4 \cdot C_2HF_3O_2$: C, 55.95; H, 5.57; N, 12.08; F, 9.83. Found: C, 55.74; H, 5.70; N, 11.88; F, 9.66.

***N*-4-Benzyl-6,7-dimethoxy-*N*2-[2-(3-methoxy-phenyl)-ethyl]quinazoline-2,4-diamine (4c).** ^{1}H NMR (270 MHz, CD_3OD): δ 2.83 (br t, $J = 6.93$ Hz, 2H), 3.68 (t, $J = 7.18$ Hz, 2H), 3.70 (s, 3H), 3.90 (s, 3H), 3.95 (s, 3H), 6.69−6.76 (m, 3H), 6.87 (br s, 1H), 7.14 (t, $J = 7.43$ Hz, 1H), 7.23−7.41 (m, 5H), 7.58 (s, 1H). MS (ESI): *m*/*z* 445.1 $[M + H]^+$. Anal. Calcd for $C_{26}H_{28}N_4O_3 \cdot C_2HF_3O_2$: C, 60.21; H, 5.23; N, 10.03; F, 10.20. Found: C, 60.08; H, 5.12; N, 9.84; F, 10.31.

[6,7-Dimethoxy-2-(4-methylpiperazin-1-yl)quinazolin-4-yl]phenethylamine (4d). ^{1}H NMR (270 MHz, CD_3OD): δ 2.98 (s, 3H), 3.03 (t, $J = 7.18$ Hz, 2H), 3.46 (br s, 4H), 3.80 (br t, 2H), 3.90−3.99 (m, with two s's at 3.93 and 3.96, 8H), 3.96 (s, 3H), 4.18 (br s, 2H), 7.12 (s, 1H) 7.16−7.31 (m, 5H), 7.54 (s, 1H). MS (ESI): *m*/*z* 408.1 $[M + H]^+$. Anal. Calcd for $C_{23}H_{29}N_5O_2 \cdot 2C_2HF_3O_2$: C, 51.02; H, 4.92; N, 11.02; F, 17.94. Found: C, 51.00; H, 4.99; N, 10.91; F, 17.79.

Solid-Phase Synthesis of Diamino Quinazoline 5. Preparation of Support-Bound Amine 28. A mixture of resin **12** (200 mg), diamine **27** (4.0 mmol), *N*,*N*-dimethylacetamide (2 mL), and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU; 600 μL, 4.0 mmol) was heated to 135 °C for 14 h. After cooling to room temperature the resin was washed with methanol, dichloromethane, methanol, and dichloromethane (2 × 3 mL each).

Acylation of Support-Bound Amine 28. Solutions of PyBOP (0.8 mL *x* 1.0 M in *N*,*N*-dimethylformamide, 0.80 mmol) and HOBt (0.8 mL *x* 1.0 M in *N*,*N*-dimethylformamide, 0.80 mmol) were added to a solution of a carboxylic acid (0.96 mmol) in *N*,*N*-dimethylformamide (1.6 mL). The mixture was shaken for 10 min. Resin **28** (200 mg) and 4-methylmorpholine (110 μL, 1.0 mmol) were added, and the mixture was shaken overnight. The resulting resin (**30**) was washed with methanol, dichloromethane/*N*,*N*-diisopropylethylamine (4:1), methanol, *N*,*N*-dimethylformamide, methanol, and dichloromethane (2 × 3 mL each).

Quinazoline 5. Trifluoroacetic acid (2 mL) was added to resin **30** isolated from the previous step. After 1 h the solution was drained and the resin was washed with trifluoroacetic acid (2 × 1 mL). The combined filtrate and washings were concentrated to afford the product. Representative compounds prepared in this manner are shown in Table 1.

Analytical data for compounds cited in Table 1 are given below:

[4-(3-{1-[4-(3,3-Diphenylpropylamino)-6,7-dimethoxyquinazolin-2-yl]piperidin-4-yl}-propyl)piperidin-1-yl]-(5-fluoro-2-methylphenyl)methanone (5a). ^{1}H NMR (270 MHz, CD_3OD) δ 7.45 (s, 1H), 7.27 (m, 10H), 7.17−6.88 (m, 5H), 4.66 (d, $J = 12.9$ Hz, 1H), 4.39 (d, $J = 13.4$ Hz, 2H), 4.06 (t, $J = 7.7$ Hz, 2H), 3.94 (s, 3H), 3.90 (s, 3H), 3.64 (t, $J = 7.4$ Hz, 2H), 3.40 (m, 1 H), 3.05 (t, $J = 13.0$ Hz, 3H), 2.83 (t, $J = 12.8$ Hz, 1H), 2.5 (m, 2H), 2.24 (d, 19.1 Hz, 3H), 1.72 (m, 5 H), 1.21 (m, 10H). MS (ESI): *m*/*z* 744 $[M + H]^+$. Anal. Calcd for $C_{46}H_{54}FN_5O_3 \cdot 2C_2HF_3O_2$: C, 61.98; H, 5.83; N, 7.24. Found, C, 62.35; H, 6.08; N, 7.41.

1-(3-{2-[4-(3-{1-[(2,5-Dimethoxyphenyl)acetyl]piperidin-4-yl}-propyl)piperidin-1-yl]-6,7-dimethoxyquinazolin-4-ylamino}propyl)pyrrolidin-2-one (5b). ^{1}H NMR (270 MHz, CD_3OD): δ 7.52 (s, 1H), 7.08 (s, 1H), 6.78 (m, 3H), 4.54 (m, 3H), 3.98 (m, 2H), 3.95 (s, 3H), 3.92 (s, 3H), 3.77 (s, 3H), 3.72 (s, 3H), 3.66 (m, 4H), 3.45 (m, 6H), 3.14 (m, 2H), 3.01 (m, 1H), 2.62 (m, 1H), 2.38 (t, $J = 8.1$ Hz, 2H), 1.99 (m, 6H), 1.66 (m, 2H), 1.52 (m, 1H), 1.27 (m, 10H), 0.96 (m, 1H). MS (ESI): *m*/*z* 717 $[M + H]^+$. Anal. Calcd for $C_{40}H_{56}N_6O_6 \cdot 2C_2HF_3O_2$: C, 55.93; H, 6.19; N, 8.89. Found, C, 56.15; H, 6.37; N, 9.17.

***N*-{4-[4-(2-Chloro-6-methylbenzylamino)-6,7-dimethoxyquinazolin-2-ylamino]butyl}-3-(4-fluorophenoxy)propionamide (5b).** ^{1}H NMR (270 MHz, CD_3OD): δ 7.62 (s, 1H), 7.22 (m, 4H), 6.91 (m, 6H), 5.0 (s, 2H), 4.16 (m, 3H), 3.95 (s, 3H), 3.82 (s, 3H), 3.55 (s, 2H), 2.70 (t, 3H), 2.41 (s, 3H), 1.69 (m, 4H). MS (ESI): *m*/*z* 596 $[M + H]^+$. Anal. Calcd for $C_{31}H_{35}ClFN_5O_4 \cdot C_2HF_3O_2 \cdot H_2O$: C, 54.44; H, 5.26; N, 9.62. Found: C, 54.11; H, 5.28; N, 9.34.

***N*-{1-[6,7-Dimethoxy-4-(3-phenylpropylamino)quinazolin-2-yl]pyrrolidin-3-yl}oxalamide (5c).** ^{1}H NMR (270 MHz, CD_3OD): δ 7.50 (s, 1H), 7.14 (m, 6H), 4.56 (m, 1H), 3.95 (s, 3H), 3.91 (s, 3H), 3.85 (s, 1H), 3.69 (m, 4 H), 3.55 (m, 1H), 2.72 (t, $J = 7.2$ Hz, 2H), 2.37 (s, 1H), 2.20 (s, 1H), 2.06 (m, 2H). MS (ESI): *m*/*z* 479 $[(M + H)^+]$. Anal. Calcd for $C_{25}H_{30}N_6O_4C_2HF_3O_2 \cdot H_2O$: C, 53.11; H, 5.45; N, 13.76. Found: C, 53.25; H, 5.26; N, 13.97.

Quinoline-2-carboxylic Acid [2-({6,7-Dimethoxy-4-[3-(2-oxo-pyrrolidin-1-yl)propylamino]quinazolin-2-yl}methyl-amino)ethyl]methylamide (5d). ^{1}H NMR ($CDCl_3$): δ 8.18 (d, $J = 8.7$ Hz, 0.5H, amide rotamer), 7.97 (m, 1.5H, amide rotamer), 7.82−7.36 (m, 5.5H, amide rotamer), 6.99 (s, 0.5H, amide rotamer), 6.6 (br s, 1H), 4.09 (m, 1H), 3.98 (s, 6H), 3.87 (m, 2H), 3.79 (m, 1H), 3.60 (m, 1H), 3.36 (m, 3H), 3.26 (s, 6H), 3.13 (m, 2H), 2.43 (m, 2H), 2.04 (m, 2H), 1.80 (m, 1H), 1.62 (m, 1H). MS (ESI): *m*/*z* 572 $[M + H]^+$. Anal. Calcd for $C_{31}H_{37}N_7O_4 \cdot 0.50\ H_2O$: C, 64.12; H, 6.60; N, 16.88. Found: C, 63.82; H, 6.63; N, 16.70.

1-{4-[6,7-Dimethoxy-4-(3-phenylpropylamino)quinazolin-2-yl]-[1,4]diazepan-1-yl}-2-(3-nitrophenoxy)ethanone (5e). ^{1}H NMR ($CDCl_3$): δ 7.65 (m, 2H), 7.23 (m, 6 H), 6.98 (m, 1H), 6.84 (m, 1H), 6.62 (m, 1H), 5.28 (br s, 1H), 4.81 (s, 0.3 H, amide rotamer), 4.67 (s, 0.7H, amide rotamer), 3.93 (m, 12H), 3.58 (m, 4H), 2.76 (m, 2H), 2.04 (m, 4H). MS (ESI): *m*/*z* 601 $[M + H]^+$. Anal. Calcd for $C_{32}H_{36}N_6O_6 \cdot 0.50\ H_2O$: C, 63.04; H, 6.12; N, 13.78. Found: C, 63.08; H, 5.86; N, 13.72.

***N*-{3-[6,7-Dimethoxy-4-(2-methoxybenzylamino)-quinazolin-2-ylamino]-2,2-dimethylpropyl}-3-phenoxypropionamide (5f).** ^{1}H NMR ($CDCl_3$): δ 7.23 (m, 4H), 6.88 (m, 7H), 4.77 (d, $J = 5.4$ Hz, 2H), 4.28 (t, $J = 6.6$ Hz, 2H), 3.87 (s, 9H), 3.33 (d, $J = 6.9$ Hz, 2H), 3.11 (d, $J = 6.4$ Hz, 2H), 2.79 (m, 2 H), 0.93 (s, 6H). MS (ESI): *m*/*z* 574 $[M + H]^+$. Anal. Calcd for $C_{32}H_{39}N_5O_5 \cdot 0.50\ H_2O$: C, 65.96; H, 6.92; N, 12.02. Found: C, 65.73; H, 6.68; N, 11.95.

(4-{3-[1-(4-Benzylamino-6,7-dimethoxyquinazolin-2-yl)-piperidin-4-yl]propyl}piperidin-1-yl)-(4-nitro-2-methoxyphenyl)methanone (5g). ^{1}H NMR ($CDCl_3$): δ 7.83 (d, J = 8.2 Hz, 1H), 7.72 (s, 1H), 7.29 (m, 6H), 6.91 (s, 2H), 4.72 (m, 5H), 3.89 (s, 6H), 3.83 (s, 3H), 3.31 (m, 1H), 2.99−2.72 (m, 4H), 1.82−1.00 (m, 17H). MS (ESI): *m*/*z* 683 $[M + H]^+$. Anal. Calcd for $C_{38}H_{46}N_6O_6 \cdot H_2O$: C, 65.12; H, 6.90; N, 11.99. Found: C, 65.34; H, 6.51; N, 11.98.

Furan-2-carboxylic Acid (2-{[4-(3-Imidazol-1-yl-propylamino)-6,7-dimethoxyquinazolin-2-yl]methylamino}-ethyl)methylamide (5h). ^{1}H NMR (270 MHz, $CDCl_3$): δ 7.47 (m, 2H), 7.03−6.91 (m, 5H), 6.42 (m, 1H), 6.0, (br s, 1H), 4.04 (m, 2H), 3.93 (s, 6H), 3.86 (s, 6H), 3.9−3.6 (m, 4H), 3.53 (m, 1H), 3.29−3.12 (m, 3H), 2.14 (m, 1H). MS (ESI): *m*/*z* 494 $[M + H]^+$. Anal. Calcd for $C_{25}H_{31}N_7O_4 \cdot H_2O$: C, 58.70; H, 6.50; N, 19.17. Found: C, 58.65; H, 6.20; N, 18.93.

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