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TETRAHEDRON

Libraries of N-Alkylaminoheterocycles from Nucleophilic Aromatic Substitution with Purification by Solid Supported Liquid Extraction

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Abstract: Heterocycles containing 2 or 3 chlorine atoms have been converted to libraries of N-alkylaminoheterocycles by parallel solution phase nucleophilic aromatic substitution. The first chloride displacement was achieved with stoichiometric nucleophilic alcohols, or amines. In the final substitution, excess amine was used to ensure that all active electrophiles were consumed. The excess amine and salts were removed by automated solid supported liquid extraction (SLE). SLE is partition chromatography using buffered water immobilized on a solid support and elution by a water immiscible solvent. This is a high throughput method for liquid-liquid extraction which is easily automated using simple liquid handling robotics.

For the past two years we have been involved in the solution phase synthesis of general screening libraries for drug discovery. Solution methods are complimentary to solid phase methods and for many libraries a combination of solution and solid phase techniques have been used.[1] Solution phase synthesis of libraries is indicated for reactions which are reliable, irreversible and contribute maximal structural diversity in each synthesis step. For these reactions, solution phase library methods have several advantages over solid phase methods. For solution methods, there is no need for a functional group for attachment to the solid support and the synthesis is shortened by elimination of the attachment and cleavage steps. In addition, it is less difficult to develop and to monitor solution phase reactions. Also, solid phase chemistry has some inherent inefficiencies in that extensive washing steps are required and some resins and linkers are expensive. However, for the preparation of large solution phase libraries, purification options are limited.[2] The ideal solution phase library synthetic sequence is 2 or 3 steps. When a particular library synthesis exceeded five steps, we have found that the purity of the products was increased if some of the reactions were performed on solid support.

For screening libraries, we have focused on reactions which produce structures that are constrained to a few major conformations by rings and hindered rotation. The library compounds produced also posses drug-like properties such as heterocyclic cores, molecular weights under 600 and *c*log P values less than 5.[3] Nucleophilic aromatic substitution (NAS) reactions fit these aforementioned criteria for solution phase synthesis of screening libraries. We have focused our efforts on making heteroatom-carbon bonds (rather than carbon-carbon bonds) because of the high reactivity, predictability and the large variety of readily available synthons containing nucleophilic sulfur, nitrogen, or oxygen atoms. Halogenated heterocycles are especially useful in this regard, since each heteroatom in the ring is activating for halide displacement. In addition, the heteroatoms, especially nitrogen, helps to reduce the log P compared to the benzene analogs.

NAS reactions are generally irreversible and can be driven to completion by the use of excess reagents. In addition, a large number of di- or trihalogenated heterocycles are known. Therefore it is possible to develop reaction protocols and automated reaction equipment which can be applied to numerous scaffolds thereby producing an important fraction of the large numbers of compounds (>100,000) needed for a general screening library. Importantly, the leads identified from libraries prepared by aromatic heterocyclic displacement have structures which represent good starting points for further medicinal chemistry. These compounds have many

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sites for additional substituents and the heterocycles themselves are stable to a wide variety of chemical conditions required for side chain modifications. Furthermore, the limited number of conformations likely to be adopted by these molecules makes them amenable to molecular modeling methods.

PURIFICATION

Planning for solution synthesis of libraries often begins with determining the method for purification of the intermediates and final products. Liquid-liquid extraction with an aqueous buffer and an organic solvent is probably the most widely used "clean-up" method in general organic synthesis. It follows that an automated, high throughput extraction method would greatly expand the range of reactions used in the parallel synthesis of libraries. Indeed, a number of groups have reported automated liquid-liquid extraction protocols based on separation by measured volume.[4] However, we found that removal of high concentrations of amine salts in small volumes with this method to be slow, difficult to use and, since a separate drying step was required, generally inefficient. Often times only about half of either layer was removed for further use, and in regards to the robotics, each time a layer was separated a syringe needle wash was required. These limitations, along with emulsions and volume changes that occur upon mixing, are further drawbacks of direct separation by volume. Another liquid-liquid extraction method using phase separation membranes has been reported.[5]

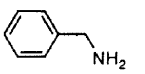
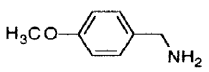
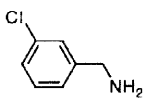
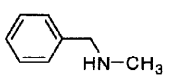
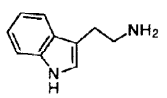
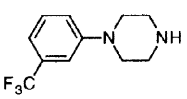
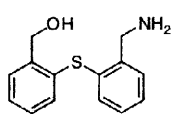
A good high throughput extraction method needs to meet a number of requirements. The method should be solvent efficient, predictable, rapid, inexpensive, scaleable and yield a dried solution. In addition, the ability to readily expand the extraction solvent volume would be useful toward compensating for variation in partition coefficients and thus extraction efficiency. Finally, the materials should be commercially available, and adaptable to a variety of liquid handling robots without the need for specialized equipment (i.e. no phase separation detection).

For library synthesis, we have developed an automated, high throughput solid supported liquid-liquid extraction (SLE) system for the removal of inorganic salts, amines and acids.[6] The SLE format eliminates most of the difficulties of automating liquid-liquid extraction. SLE is "normal" phase liquid-liquid partition chromatography.[7] Aqueous buffer, the more polar solvent, is immobilized on a stationary phase and elution is with a water immisible solvent. Partition chromatography has been used to obtain very high separation selectivities with small particle sizes and large pressure differentials across the columns.[7] However for library purification, we have chosen to optimize for speed and gravity elution rather than for separation capability. Thus, the SLE method gives separations which are essentially the same as liquid-liquid extraction in a separatory funnel. A useful inert stationary phase support is inexpensive, coarse, hydrophilic diatomaceous earth.[8] In practice, the diatomaceous earth is packed in microtiter filter plates or in columns and is treated with buffered water, resulting in a thin aqueous film coating the hydrophilic support. The reaction mixture is added to the column and eluted with a water immiscible solvent. Due to the column format, the stationary aqueous phase at the top of the column is prevented from mixing with the aqueous phase further down the column resulting in an extraction which is more efficient than a single layer separation in a separatory funnel.[7] Gravity elution of the SLE columns allows the method to be automated with simple liquid transfer robotics. The scale and relative proportion of the organic solvent used is easy to adjust (2 mL diatomaceous earth per 0.1 mmol substrate or 60 mL for 15 mmol substrate). During the past two years we have used this SLE method to "clean up" over 60,000 compounds derived both from solution and solid phase syntheses. To date, the SLE method has been used in conjunction with aqueous acid or base to effectively remove water soluble byproducts from libraries based on amide and sulfonamide synthesis, alkylations, reductions and oxidations.

Illustrated in Table 1 are representative examples of the separation of excess amines with 1-naphthalenemethanol as the neutral internal standard. This experiment was conducted using the same volumes as many of the library workups. Additional chloroform elutions would increase the recovery of the neutral internal standard. The test amine (0.1 mmol) and triethylamine (0.1 mmol) in chloroform (1 mL) was added to a 3 mL size Chem Elute Extube® (3 mL diatomaceous earth) pretreated with 2 N hydrochloric acid (300 μL).

The column was eluted with chloroform (< 3 mL), the eluant volume was adjusted to 3 mL, and the component concentrations were measured from the area under the curve (AUC) by HPLC at 214 nm. In general, very hydrophobic amines do not extract well presumably because the amine hydrochloride can partition into chloroform.[9]

Table 1

Amine	Before extraction AUC at 214nm	After extraction (3 fold dilution) AUC at 214nm	% Amine remaining	% standard recovered
	415	0	<1%	72%
	588	0	<1%	85%
	765	0	<1%	78%
	453	0	<1%	82%
	2507	0	<1%	75%
	1227	118	29%	70%
	1822	0	<1%	76%

LIBRARY APPROACH

Our choice of library format was one in which the parallel synthesis of one compound per well occurs in the first 11 columns of the standard 96 deep-well microtiter plate providing 88 spatially separated products per plate. For each plate, a combinatorial matrix was produced by adding eight derivatives of one class of reagents across 8 rows of the microtiter plate and 11 derivatives of a second class of reagent across the 11 columns of the plate. Employing chemistries that can be done in microtiter plates allows for both production and screening without reformatting materials and for ready tracing of the original reagents. Previously, we used 2 mL vials for small solution phase libraries, however for large libraries, deep well microtiter plates are more convenient. A combination of filter bottom plates and standard deep-well plates are used. These are sealed by clamping gaskets onto the 96 well plates between rigid metal plates (Figure 1). A useful technique to avoid product loss when transferring a filter plate from a clamp to a collection plate, is to freeze the reaction in the filter plate. Even if the solvents do not become solid, the increased viscosity at low temperature allows one to unclamp a filter plate and transfer it onto the top of a collection plate without leakage.

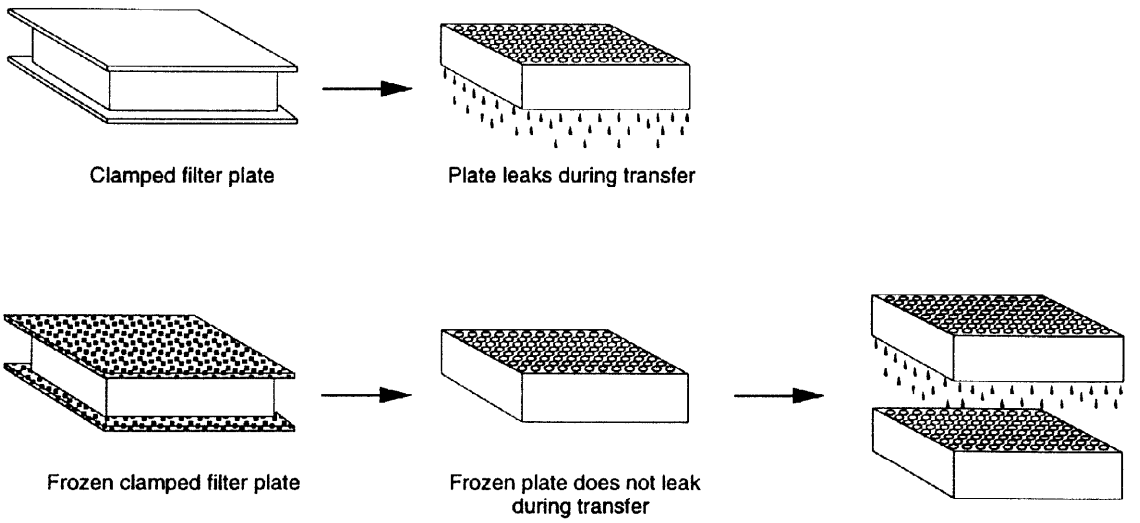


Figure 1

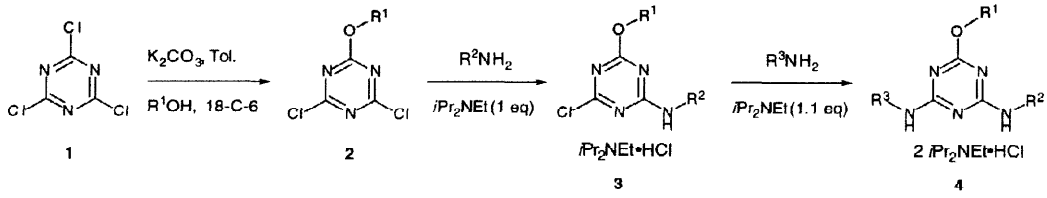
The choice of one compound per well allows us to optimize the chemistry in much the same way that industrial chemical process work is optimized. In each instance the quality of the products was established by producing test libraries. Each of the reagents used to attach pendent side chains to the central scaffold was checked under the synthesis conditions. For example, a library with three side chains requires three test libraries; while two of the positions are held constant with one side chain from each of the respective sets, the third position is allowed to react with each reagent in that third side chain set. When any candidate did not give a clean reaction it was discarded or replaced. Although, the final library matrix may contain failures where side chains were incompatible, the production of test libraries avoids the failure of a full row or column in the final library. It was difficult to predict what factors influence library quality and, therefore, it was important that the test libraries simulated as closely as possible the final synthesis conditions.

CHEMISTRY

For these first libraries, we focused on NAS reactions which were well known and for which there was an adequate literature background. The general scheme for NAS libraries involved addition of the first nucleophile under conditions in which one equivalent gave complete reaction at the most reactive halogen. The final substitution used a large excess of nucleophilic amine and heating to ensure that all active halogens were replaced. Thus, the resulting mixture contained the desired substitution product along with excess amine and amine salts. SLE was used to remove the excess amine and salts.

A library was constructed from sequential substitution of cyanuric chloride (**1**), (Scheme 1).[10] Initial reaction of **1** with an alcohol or phenol (R^1OH) was performed on large scale using conventional glassware according to the procedure of Menicagli.[11] Intermediate **2** was then divided into deep-well microtiter plates and treated with dichloroethane solutions of nucleophilic amine (slight excess) and excess tertiary amine. The plates were sealed and heated. Similarly, the next substitution was achieved with excess nucleophilic and tertiary amines by heating at 95 °C in *n*-butanol over night. The solvent was evaporated and the residue was dissolved in chloroform and separated from the slight excess amine and two equivalents of amine hydrochloride by SLE. In this instance, the diatomaceous earth was simply pretreated with water since most of the excess amines were already hydrochloride salts. When *n*-butanol was used as solvent in the first amine substitution step, both amine diaddition and minor *n*-butanol addition were observed. This problem was even more

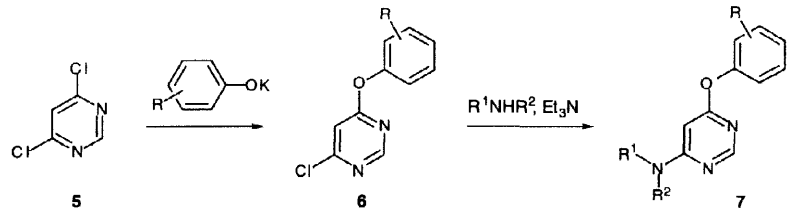
pronounced in the automated synthesis where the time between reagent addition and efficient mixing was increased. Consequently, dichloroethane was chosen as the solvent for the first amine substitution reaction to prevent formation of the amine diaddition side product. For the more reactive phenoxydichlorotriazines (**2**, R^1 = Ar), dichloroethane served as the solvent for both steps.



1 2 3 4

Scheme 1: NAS of cyanuric chloride

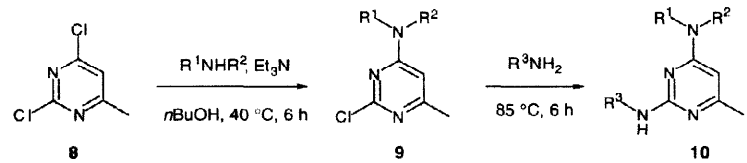
A library was produced from sequential substitution of 4,6-dichloropyrimidine (**5**) (Scheme 2).[12] Potassium phenoxides were prepared on a 15 mmol scale and added to one equivalent of **5**. The addition products **6**, isolated by extraction and used without further purification, were distributed into septum capped vials, treated with nucleophilic amine (2 equiv.), triethylamine (2 equiv.) and heated at 85 °C for 72 hours. Capped vials were used in place of microtiter plates because volatile amines in the diversity set tended to evaporate through the microtiter plate sealing gaskets with prolonged heating. The excess amine was removed by SLE using 1 N hydrochloric acid. Initially, we explored transferring solutions of the potassium phenoxides into solutions of **5**. Experimemts showed that water absorbed during the transfer, hydrolyzed some of **5** to the chloropyrimidinone. After amine substitution and SLE of the reaction mixture, the products **7** were contaminated with excess phenol. Since hydrophobic phenols could not be effectively removed by SLE using aqueous sodium hydroxide, many of the products remained contaminated. Consequently for the library, we used large scale synthesis under nitrogen to provide essentially pure **6** with no left over phenol.



5 6 7

Scheme 2: NAS of 4,6-dichloropyrimidine

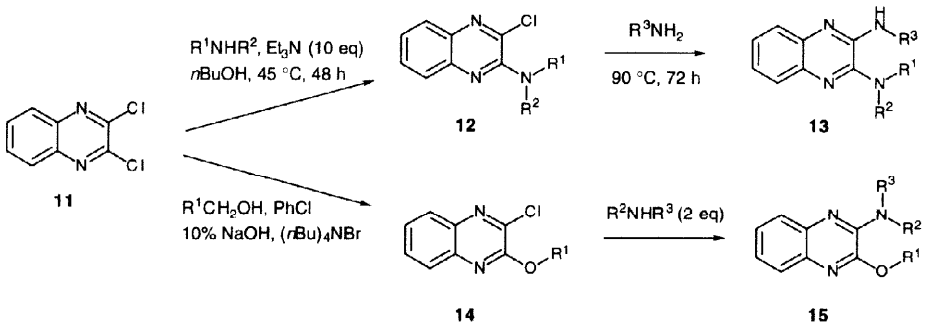
An additional pyrimidine library was produced from 2,4-dichloro-6-methylpyrimidine (**8**) and sequential displacement with amines (Scheme 3).[13]



8 9 10

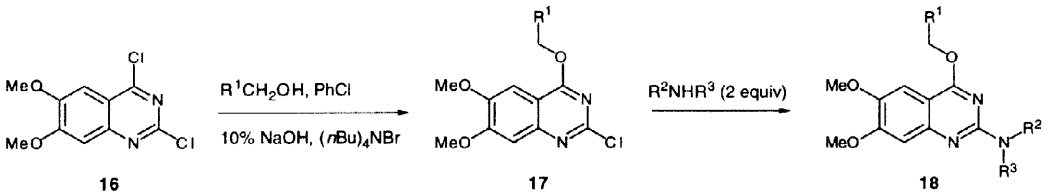
Scheme 3: NAS of 2,4-dichloro-6-methylpyrimidine

The first library prepared from 2,3-dichloroquinoxaline(**11**) involved sequential substitutions first with a secondary amine followed by a primary amine (Scheme 4).[14] The second amine substitution required high temperatures (90 °C) and long reaction times (72 h). The next library used alcohols as the first nucleophile and the second substitution could be effected at lower temperature.[14, 15] As in the triazine and pyrimidine series, an initial substitution with oxygen does not deactivate the ring for the second substitution.



Scheme 4: NAS of 2,3-dichloroquinoxaline

Similarly, alcohol and then amine substitution of 2,4-dichloro-6,7-dimethoxyquinazoline (**16**) produced an additional library (Scheme 5).[16]



Scheme 5: NAS of 2,4-dichloro-6,7-dimethoxyquinazoline

In summary, well known NAS reactions have been adapted for the solution phase, parallel synthesis of large, spatially separated libraries. The use of excess nucleophilic amine in the final substitution ensures that no active electrophiles remain to interfere with biological screening. The excess amines and water soluble impurities were removed by supported liquid extraction (SLE). The SLE procedure achieves the same separation as liquid-liquid extraction with the added advantage that it is easy to automate for high throughput synthesis using simple liquid handling equipment.

EXPERIMENTAL

In each test library, 100% of the compounds were analyzed by HPLC MS. For final library components, 12.5% (11 from each plate of 88) were analyzed by direct injection electrospray MS with a mass range from 200 to 700.

Preparation of substituted 1,3-dichloro-5-aryloxytriazines (2)

A suspension of cyanuric chloride (**1**) (18.44 g, 100 mmol), K_2CO_3 (13.82 g, 100 mmol) and 18-crown-6 (0.79 g, 3 mmol) in toluene (80 mL) was treated dropwise with a solution of one of the selected phenols (100 mmol) in toluene (20 mL). The reaction mixture was stirred at room temperature for 24 h, filtered through celite, and the celite pad washed with EtOAc. The filtrate was concentrated to an oil which, for most phenols, solidified under high vacuum. The resulting aryloxytriazine **2** was triturated with hexane, dried under high vacuum and used without further purification.

Preparation of substituted 1-chloro-3-aryloxy-5-alkylaminotriazines (3)

A set of 16 amine solutions in CH_2Cl_2 (1.0 M) was prepared. A solution of 1,3-dichloro-5-aryloxytriazine (**2**) (20 mmol) and *i*-Pr_2NEt (2.84 g, 22 mmol) was dissolved in $ClCH_2CH_2Cl$ (80 mL). The scaffold solution (0.2 mL, 0.05 mmol, 1.0 eq) was added to 384 wells of 4 Beckman deep well microtiter plates (2 mL per well) by an Eppendorf repeater pipette. A Gilson 215 liquid handler was used to dispense the 16 amine solutions (0.05

mL, 0.05 mmol, 1.0 equiv.). Each amine was added to a row of two plates, the plates were sealed, and allowed to stand at room temperature for 24 h.

Preparation of substituted 1,3-dialkylamino-5-aryloxytriazines (4)

A set of 24 amine solutions in $ClCH_2CH_2Cl$ (1.0 M) was prepared. A solution of *i*-Pr_2NEt in $ClCH_2CH_2Cl$ (1.0 M, 0.055 mmol, 1.1 equiv.) was dispensed to each reaction well followed by 24 amine solutions (0.06 mL, 0.06 mmol, 1.2 equiv.). One amine to each column for each pair of two plates. The plates were sealed by clamps and heated in an oven at 78 °C for 24 h. The reaction mixture from each well was transferred onto the top of a well of a Polyfiltronics Uni-filter® 2 mL capacity 96 well microtiter filter plate which was packed with Varian Sample Preparations Chem Elut® extraction hydromatrix (diatomaceous earth) pretreated with water (0.3 mL). The filter plate was supported on a deep well microtiter plate to collect the products. The hydromatrix columns were then eluted with CH_2Cl_2 (2 X 1 mL) and the collected extracts were concentrated in vacuo.

For a library of 1920 compounds, 74% of the wells analyzed, showed the expected molecular ion at greater than 85% relative ion abundance. 98% of the wells analyzed showed the expected ion at a relative ion abundance greater than 15%.

Preparation of 4-(2-naphthoxy)-6-chloropyrimidine (6, R = fused C_4H_4)

A solution of 2-Naphthol (734 mg, 5.1 mmol) in warm 2-methyl-2-propanol (6 mL) under a nitrogen atmosphere was treated at once with a 1.0 M solution of KO*t*Bu (7.5 mL) in 2-methyl-2-propanol. The opaque reaction mixture was treated with a solution of **5** (775 mg, 5.2 mmol) in warm 2-methyl-2-propanol (8.6 mL) and heated at 35 °C. RP-HPLC or TLC (50% hexane/EtOAc) was used to monitor the reaction. If excess phenol was present after 3 h, additional **5** was added and the mixture stirred over night. The solution was diluted with Et_2O, washed with water (2 X), and the aqueous layers were combined and extracted with Et_2O. The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated in vacuo. Analytical data: ^1H NMR (300 MHz, $CDCl_3$, TMS): δ 6.96 (s, 1 H), 7.29 (d, J = 2.3 Hz, 1 H), 7.48-7.55 (m, 2 H), 7.61 (d, J = 2.2 Hz, 1 H), 7.81-7.90 (m, 2 H), 7.94 (d, J = 8.9 Hz, 1 H), 8.60 (s, 1 H); mass spectrum *m/z* (CI) 257 $(m+1)^+$. A set of 16 phenols was used.

Preparation of substituted 4-aryloxy-6-alkylaminopyrimidines (7)

The library was made in two sets of 384 compounds. Sixteen 4-chloro-6-aryloxypyrimidines **6** (5 mmol) were dissolved in $ClCH_2CH_2Cl$ (10 mL). Insoluble derivatives were dissolved in a mixture of $ClCH_2CH_2Cl$ (6 mL) and CH_3CN (≤ 4 mL) and kept at 35 °C. Each chloropyrimidine solution (200 μL, 0.1 mmol) was transferred to each of 24 septa-capped 2 mL vials held in four racks. The vial caps were loosened and the solvent evaporated in vacuo at 40 °C during 20 h. Each of 24 amines (4 mmol) was combined with Et_3N (556 μL, 4 mmol) and diluted to 5.5 mL with a mixture of 2-methyl-2-propanol/$ClCH_2CH_2Cl$ (9:1). Each amine solution (300 μL, 0.218 mmol) was transferred to 16 vials, each containing a different monochloropyrimidine. The racks were then heated at 85 °C for 72 h then concentrated in vacuo at 40 °C. Chem Elut® extraction columns (3 mL) were treated with 1N aq HCl (300 μL) and supported in test tubes. The reaction mixtures were dissolved in $CHCl_3$ (400 μL) and transferred to the top of the extraction columns. The columns were gravity eluted with CH_2Cl_2 (2 mL) and then concentrated under reduced pressure. For a library of 768 compounds, 86% of the wells analyzed, showed the expected molecular ion at 100% relative ion abundance.

Preparation of 2,4-dialkylamino-6-methylpyrimidines (10)

A set of 24 secondary amine solutions in *n*-BuOH (1.0 M) was prepared. A solution of 2,4-dichloro-6-methylpyrimidine (**8**) (4.8 g, 25 mmol) in Et_3N (17.4 mL) was diluted with *n*-BuOH (82.6 mL) and dispensed (0.2 mL, 0.050 mmol, 1.0 equiv.) into each of 384, 2 mL vials. The secondary amine solutions (0.055 mL, 0.055 mmol, 1.1 equiv.) were each added to 24 vials and heated at 40 °C overnight. A set of 16 primary amine

solutions in *n*-BuOH (1.0 M) was prepared. Each amine solution (0.055 mL, 0.055 mmol, 1.1 equiv.) was dispensed into one each of the 2-chloro-4-alkylamino-6-methylpyrimidine reaction solutions to create a 24 X 16 matrix (4 microtiter plates). The reactions were heated overnight at 85 °C then concentrated in a vacuum oven during 3 h at 65 °C. The residues were dissolved in $CHCl_3$ (0.3 mL) and poured onto 3 mL Chem Elut® extraction columns pretreated with distilled water (0.3 mL). The columns were eluted with CH_2Cl_2 (2 X 1 mL) and the extracts concentrated in a vacuum oven to provide **10**.

Preparation of 2,3-dialkylaminoquinoxalines (13)

A set of 24 secondary amine solutions in *n*-BuOH (1.0 M) were prepared. A solution of 2,3-dichloroquinoxaline(**11**) (3.82 g, 19.20 mmol) in Et_3N (26.13 mL) was diluted with *n*-BuOH (293.87 mL) and aliquots (0.80 mL, 0.050 mmol, 1.0 equiv.) were dispensed into each of 384, 2 mL vials. Each secondary amine solution (0.055 mL, 0.055 mmol, 1.1 equiv.) was added to 24 vials and heated at 45 °C for 48 h. A set of 16 primary amine solutions in *n*-BuOH (1.0 M) were prepared. The amine solutions (0.055 mL, 0.055 mmol, 1.1 equiv.) were each dispensed into one each of the solutions of **12** to create a 24 X 16 matrix (4 microtiter plates). After heating at 90 °C for 72 h, the solutions were concentrated in a vacuum oven during 3 h at 65 °C. The residues were dissolved in $CHCl_3$ (0.3 mL) and transferred on to 3 mL Chem Elut® extraction columns pretreated with distilled water (0.3 mL). The columns were eluted with CH_2Cl_2 (2 X 1 mL) and the extracts were concentrated in a vacuum oven to provide **13**.

Preparation of 2-chloro-3-alkyloxyquinoxaline (14, R^1 = phenoxyethyl)

To a suspension 2,3 dichloroquinoxaline (**11**) (1.5 g, 7.85 mmol) in PhCl (30 mL), was added *n*-Bu_4NBr (130 mg, 390 mmol, 0.05 equiv.), 2-phenoxyethanol (1 mL, 7.85 mmol, 1 equiv.), and 10% aq NaOH (4 mL). The mixture was stirred at room temperature for 18 h, diluted with CH_2Cl_2 (100 mL) and water (10 mL) and the layers separated. The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude solid product was crystallized from warm MeOH (50 mL) by the addition of water to provide **14**.

Preparation of 2-alkyloxy-3-alkylaminoquinoxalines (15)

A set of 96 primary and secondary amine solutions in CH_3CN (1.0 M) were prepared. The 2-chloro-3-alkyloxyquinoxaline **14** (2.88 g, 9.6 mmol) was dissolved in CH_2Cl_2 (48 mL), dispensed (0.50 mL, 0.10 mmol, 1.0 equiv.) into each of 96, 2 mL vials, and concentrated in a vacuum oven during 1 h at 40 °C. The solids were recovered in the amine solutions (0.22 mL, 0.22 mmol, 2.2 equiv.), heated at 80 °C for 48 h, then concentrated in a vacuum oven during 3 h at 80 °C. The residues were dissolved in $CHCl_3$ (0.3 mL) and transferred into 3 mL Chem Elut® extraction columns pretreated with distilled water (0.3 mL). The columns were eluted with CH_2Cl_2 (2 X 1 mL) and the extracts concentrated in a vacuum oven to afford **15**.

Preparation of 2-chloro-4-phenoxyethyl-6,7-dimethoxyquinazolines (17, R^1 = phenoxyethyl)

To a mixture of 2,4-dichloro-6,7-dimethoxyquinazoline (**16**) (1.0 g, 3.86 mmol), *n*-Bu_4NBr (62.2 mg, 0.192 mmol) in PhCl (9.6 mL) were added 20% aq NaOH (4 mL) and a solution of 2-phenoxyethanol (500 mg, 3.975 mmol) in PhCl (6.6 mL). The mixture was stirred at ambient temperature for 18 h, partitioned with 3 portions of CH_2Cl_2, dried (Na_2SO_4), filtered, and concentrated. Crystallization of the resultant solid from acetone by the addition of water provided 1.22 g of a tan solid. Analytical data: ^1H NMR (270 MHz, DMSO-d_6) δ 3.83 (s, 3 H), 3.97 (s, 3 H), 4.47 (t, J = 4.5 Hz, 2 H), 4.85 (t, J = 4.4 Hz, 2 H), 6.96 (t, J = 7.4 Hz, 1 H), 7.04 (m, 2 H), 7.23 (s, 1 H), 7.29 (m, 3 H); mass spectrum *m/z* (ESI) 360.9 (M^+).

Preparation of 2-alkylamino-4-alkoxy-6,7-dimethoxyquinazolines (18)

A set of 96 primary and secondary amine solutions in 2-methyl-1-propanol (0.5 M) were prepared. A solution of 2-alkoxy-4-chloro-6,7-dimethoxyquinazoline **17** (3.74 g, 9.60 mmol) in CH_2Cl_2 (48 mL) was prepared and aliquoted (0.50 mL, 0.10 mmol, 1.0 equiv.) into each of 96, 2 mL vials. The solvent was removed

in vacuo during 1 h at 40 °C, the residue was dissolved in one of the amine solutions (0.44 mL, 0.22 mmol, 2.2 equiv.) and the mixtures were heated at 105 °C for 72 h. The solutions were concentrated in a vacuum oven during 3 h at 100 °C, the residues were dissolved in $CHCl_3$ (0.3 mL) and transferred on to 3 mL Chem Elut® extraction columns pretreated with distilled water (0.3 mL). The columns were eluted with CH_2Cl_2 (2 X 1 mL) and the extracts were concentrated in a vacuum oven to provide **18**.

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