Parallel Solid-Phase Synthesis and High-Throughput ^{1}H NMR Evaluation of a 96-Member 1,2,4-Trisubstituted-pyrimidin-6-one-5-carboxylic Acid Library

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A solid-phase organic synthesis method has been developed for the preparation of trisubstituted pyrimidin-6-one carboxylic acids **12**, which allows elaboration to a 3-dimensional combinatorial library. Three substituents are introduced by initial Knoevenagel condensation of an aldehyde and malonate ester resin **7** to give resin bound **1**. Cyclization of **1** with an N-substituted amidine **10**, oxidation, and cleavage afforded pyrimidinone **12**. The initial solid-phase reaction sequence was followed by gel-phase ^{19}FNMR and direct-cleavage ^{1}H NMR of intermediate resins to determine the optimal conditions. The scope of the method for library production was determined by investigation of a 3 × 4 pilot library of twelve compounds. Cyclocondensation of *N*-methylamidines and **7** followed by CAN oxidation gave mixtures of the resin bound pyrimidin-6-one **11** and the regioisomeric pyrimidin-4-one **15**, which after cleavage from the resin afforded a nearly 1:1 mixture of pyrimidin-6-one and pyrimidin-4-one carboxylic acids **12** and **16**, respectively. The regiochemical assignment was confirmed by ROESY1D and gHMBC NMR experiments. A library was prepared using 8 aldehydes, 3 nitriles, and 4 amines to give a full combinatorial set of 96 pyrimidinones **12**. Confirmation of structural identity and purity was carried out by LCMS using coupled ELS detection and by high-throughput flow ^{1}H NMR.

Introduction

Recent advances in the development of parallel synthesis methods have allowed for significant improvements in the preparation of targeted compounds for drug discovery programs.[1] A major challenge in parallel synthesis design is the development of useful, general routes toward desired compounds without compromising the initial targets because of limitations of library production techniques. An understanding of the scope of the reaction is critical for successful implementation of a parallel synthesis library. The compounds chosen from the virtual library for actual preparation in the production run are included to pose specific questions in a biological or physical property screen. Invariably, the production of compounds will result in a particular synthetic success rate, in which some compounds may be eliminated or removed because of low yields or higher than expected impurity profiles. A loss of the targeted compounds can severely impact the information content of the set. For our efforts, we have coupled development of synthesis conditions with evaluation of pilot libraries to establish the scope of a particular protocol. This allows the preparation of libraries of compounds with the greatest structural variation, at least within the limits of the synthetic method and specific conditions employed. LCMS and flow ^{1}H NMR analysis allow us to establish the structural integrity of the library and obtain meaningful results from biological or physical property evaluation.

For our discovery efforts, we were interested in the preparation of substituted pyrimidin-4(6)-one-5-carboxylic acids and their derivatives.[2] These compounds are differentiated from the more common pyrimidin-2-ones, which are typically the product of Biginelli multicomponent reactions from urea, aldehydes, and dicarbonyl compounds.[3] The regioisomeric pyrimidin-4-ones and pyrimidin-6-ones, prepared from amidines and 1,3-dicarbonyl compounds, are also of great interest because of their ease of synthesis and known biological activity.[4] The pyrimidin-4(6)-one-5-carboxylic acids are less well-known, but examples have been reported as mitotic kinesin KSP inhibitors for the treatment of proliferative diseases,[5] inhibitors of $\alpha 4\beta 1$ integrin binding,[6] endothelin receptor antagonists,[7] as having antiallergic activity,[8] and as plant growth regulators.[9] Pyrimidinone-5-carboxylate esters have been targeted as inhibitors of human leukocyte elastase inhibitors[10] and utilized as intermediates for the preparation of 2-arylpyrimidine herbicides,[11] targeted as agrochemical fungicides,[12] and angiotensin II receptor antagonists.[13] Pyrimidin-4(6)-one-5-carboxylic acid derivatives have been prepared by cyclocondensation of methylene malonic acid derivatives and amidines,[10,11,14−16] by the addition of acyl isothiocyanates to enamines[17,18] and by the addition of β-aminocrotonates to ketene.[19] The 1,2,4-trisubstituted pyrimidin-6-one-5-carboxylic acids **12**

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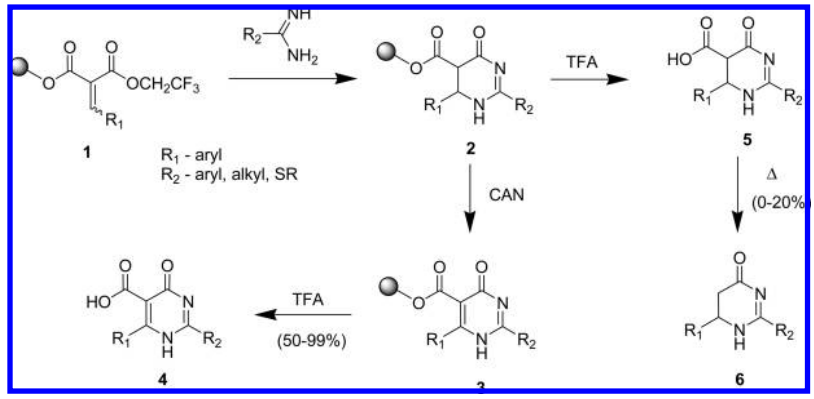
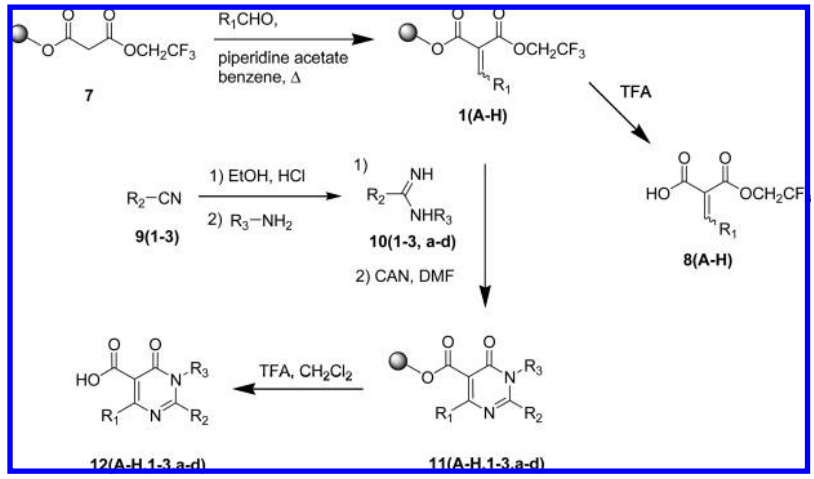
Scheme 1. Solid-Phase Synthesis of 2,6-Disubstituted Pyrimidin-6-one-5-carboxylic Acids



Scheme 2. Solid-Phase Synthesis of 2,3,6-Trisubstituted Pyrimidin-6-one-5-carboxylic Acids



and 4-one regioisomers **16** described herein are novel compounds that have not to our knowledge been previously prepared or investigated for biological activty.

Method Development

We recently reported the preparation of 2,4-disubstituted-pyrimidin-6-one-5-carboxylic acids **4** by solid-phase synthesis from the cyclocondensation of resin bound malonate esters and amidines (Scheme 1).[2] An expansion of this method using N-substituted amidines as precursors allows the preparation of novel N-substituted pyrimidinones **12** (Scheme 2). The solid phase sequence for preparation of disubstituted pyrimidinone-5-carboxylic acids **4** was accomplished in four synthetic steps (Scheme 1): (1) preparation of the substituted methylenemalonate resin **1**, (2) cyclocondensation with amidine to give the dihydropyrimidinone **2**, (3) oxidation to pyrimidinone **3**, and (4) cleavage from the resin to provide the final product **4**. In our previous studies, we had found that TFA cleavage of the resin bound dihydropyrimidinone **2** led to carboxylic acid **5,** which on prolonged treatment with TFA, would decarboxylate to give dihydropyrimidinone **6** in low yield.[2] Taylor, et al.[11] also observed decarboxylation of a dihydropyrimidinone upon saponification of an analogous methyl ester derivative. For the preparation of the trisubstituted pyrimidinone-5-carboxylic acids **12** (Scheme 2), we carried out the cyclocondensation of resin **1** with N-substituted amidines **10** followed by ceric ammonium nitrate (CAN) oxidation to give pyrimidinones **11**. The N-substituted amidines **10** were prepared by Pinner synthesis from the readily available nitriles **9** via the intermediate imidate hydrochlorides.[20] Cleavage of **11** with TFA afforded the trisubstituted pyrimidin-4-one-5-carboxylic acids **12**.

The unsymmetrical malonate ester resin **7** was prepared by treatment of Wang's resin with Meldrum's acid followed by esterification with trifluoroethanol as previously described.[21] Knoevenagel condensation of **7** with the appropriate aldehyde afforded substituted methylene malonates **1**. Aromatic and branched aliphatic aldehydes, which give good conversions to the alkylidene malonate resins **1(A-H)**, were chosen for the library starting resins. In each case, resin **7** was treated with a 10-fold excess of the aldehyde and 0.5 mol equiv of piperidine acetate in refluxing benzene. For large-scale preparation of **1**(**A**−**H**), use of a Dean−Stark trap was advantageous for removal of water and in most cases afforded reaction times of less than 1 h. By comparison, the reaction time for the conversion in the presence of activated molecular sieves without a Dean−Stark trap required at least 8 h. Loading of the resins was determined by direct cleavage ^{1}H NMR. Cleavage of a representative amount of resin (typically 100 mg) with a solution of hexamethyldisiloxane (HMDS) in TFA:$CDCl_3$ (1:1) washed with a minimum amount of $CDCl_3$ afforded an NMR compatible filtrate containing a known amount of HMDS and product **8** from a known

Table 1. Preparation of Alkylidene Malonate Resins **1**(**A**−**H**)[a]

resin	R_1CHO	loading (mequiv/g)	yield (%)
A	Ph	0.72	94
B	2-furyl	0.72	93
C	4-(F)Ph	0.73	95
D	(2-F-4-Cl-5-OMe)Ph	0.60	83
E	4-(NO_2)Ph	0.68	92
F	3-(CF_3)Ph	0.70	95
G	4-(OMe)Ph	0.74	98
H	*iso*-propyl	0.74	98

[a] Loading and yield were determined by direct cleavage ^{1}H NMR with 10 mM HMDS as an internal standard. Yields indicate the ratio of the observed loading to the theoretical loading for each resin.

amount of resin. Integration of the relative amounts of HMDS and **8** by ^{1}H NMR allowed determination of the yield of cleaved product **8** and the corresponding loading of resins **1**(**A**−**H**) (Table 1). Preparation of each resin **1**(**A**−**H**) was monitored individually to ensure complete conversion to the desired product and the highest loading possible. The yield of cleaved monoacid **8**(**A**−**H**) ranged from 83−98% with complete disappearance (<5%) of the unsubstituted malonic acid.

In the model study for the reaction scheme, benzylidene malonate resin **1**(**A**) was treated with a freshly prepared solution of N-(*n*-butyl)benzamidine **10**(**1**,**a**) in DMA at 70 °C for 6 h. It was important to obtain a basic solution of the amidine **10**(**1**,**a**) that was free of any excess amine that might react with the methylene malonate resin. Excess amine was avoided by treatment of a solution of the imidate hydrochloride with an equimolar amount of *n*-butylamine to afford the amidine hydrochloride salt, which was neutralized with aqueous NaOH to give the free amidine **10**(**1**,**a**). To avoid decomposition, solutions of the free amidines were prepared fresh and used immediately. A sample of the resin was analyzed by direct cleavage ^{1}H NMR and showed complete conversion to the tetrahydropyrimidine carboxylate **13**(**A**,**1**,**a**) evident by loss of the methylene ester resonance of **1A** (4.69 ppm) and the presence of two methine resonances (4.55 and 5.66 ppm) attributed to the unsaturated pyrimidine ring. Attempts to isolate this product led to decarboxylation as had been observed previously in the disubstituted pyrimidine series. Oxidation of the resin with ceric ammonium nitrate (CAN)[22] gave the resin bound pyrimidinone carboxylate **11**(**A**,**1**,**a**). Cleavage of the resin with TFA afforded quantitative recovery of the desired **12**(**A**,**1**,**a**) as determined by direct cleavage ^{1}H NMR and gravimetric analysis. Regiochemical assignment of the major product by 2D NMR (vide supra) was in agreement with the observations of regioselectivity in the analogous solution-phase reaction as reported by Veale et al.[10] Careful analysis of the LC-MS chromatogram showed a minor product (<5%) having an identical molecular ion by positive electospray MS to the major product peak. Purification by silica chromatography removed this minor impurity. However, we were concerned that the cyclocondensation might give mixtures of pyrimidinone isomers with less hindered amidines and that this would negatively impact the purity of some members of a pyrimidinone carboxylic acid library.

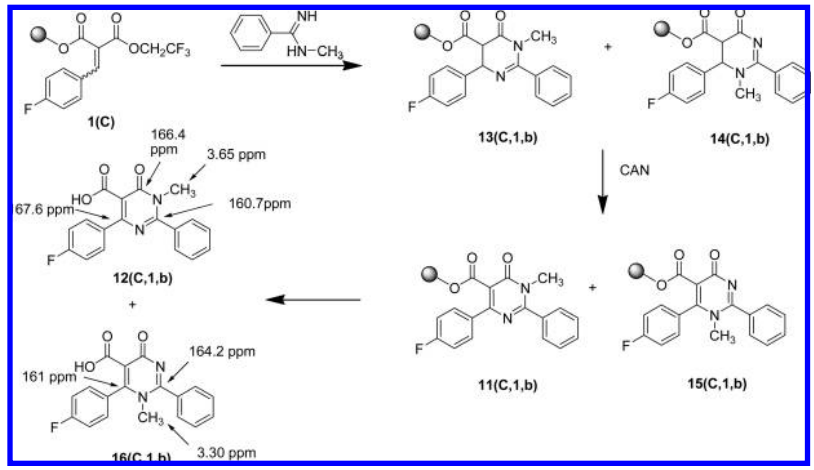
To investigate the regioselectivity of the cyclization in greater detail, *p*-fluorobenzylidene malonate resin **1**(**C**) was treated with the less-hindered *N*-methylbenzamidine **10**(**1**,**b**) using the standard conditions (Scheme 3). The *p*-fluoro substituent was chosen to allow facile monitoring of the resin bound intermediates by gel-phase ^{19}F NMR.[23,24] Gel-phase ^{19}F NMR of a suspension of **1**(**C**) in ^{7}*d*-DMF gave a signal for the CF_3 group at −73.4 and −73.9 ppm (corresponding to a 1:1 mixture of the *E* and *Z* isomers) and for the *p*-fluoro group at −109.0 ppm (Figure 1a). Treatment of **1**(**C**) with *N*-methylbenzamidine **10**(**1**,**b**) using the standard conditions afforded a resin consisting of a mixture of regioisomer dihydropyrimidinones **13** and **14**(**C**,**1**,**b**), as evidenced by ^{19}F NMR loss of the CF_3 group and chemical shift of the aromatic F to −114.2 and −115.7 ppm (Figure 1b). Direct cleavage ^{1}H NMR also supports the presence of regioisomeric products and shows a complex mixture of four diastereomeric carboxylic acid cleavage products. Oxidation with CAN led to the resin bound pyrimidinones **11** and **15**(**C**,**1**,**b**) and showed a shift in the 19F NMR of the aromatic fluorine to −110.6 and −111.2 ppm (Figure 1c) in what appears to be a nearly 1:1 mixture of regioisomers. Cleavage with TFA/CH_2Cl_2 afforded a 47:53 mixture of the two regioisomeric pyrimidinone carboxylic acids **12**(**C**,**1**,**b**) and **16**(**C**,**1**,**b**), which were separated by reverse phase chromatography.

Regioisomeric assignment of **12** and **16** were confirmed by ROESY1D and gHMBC NMR experiments.[25] Irradiation of the methyl protons at 3.3 ppm of **16**(**C**,**1**,**b**) show NOE responses from the protons of both aromatic rings suggesting that the methyl group is on the nitrogen between the two aromatic rings. Independent gHMBC experiments show a cross peak between the methyl proton at 3.3 ppm and the C2 (164.2 ppm) and the para-fluorophenyl bearing C6 (161 ppm) carbons of the pyrimidine ring, which would only be expected for the pyrimidin-4-one isomer **16** (3 bond proton-carbon long-range couplings). Irradiation of the methyl protons at 3.65 ppm of isomer **12**(**C**,**1**,**b**) shows NOE responses at the ortho and meta protons of the unsubstituted phenyl ring, but no response from the protons of the 4-fluorophenyl ring. Furthermore, the gHMBC experiment of **12** shows cross peaks between the methyl protons (3.65 ppm) and the C2 (160.7 ppm) and carbonyl C6 (166.4 ppm) carbons (3 bond proton-carbon long-range couplings), but not from parafluorophenyl bearing C4 (167.6 ppm). These observations confirm that the methyl group of **12** is on the nitrogen between the unsubstituted phenyl ring and the carbonyl at C6.

Library Production and Analysis

To investigate the potential scope of the solid phase route, a pilot library of 12 compounds was prepared in which the substitution of the amidine component **10**(**1**−**3**,**a**−**d**) was varied and the malonate resin **1**(**A**) was held constant (Table 2). Each of the 12 reactions were carried out in parallel using the three step protocol from malonate resin **1**(**A**). The cleavage filtrate was analyzed to determine the product ratios and the pyrimidin-6-one

Scheme 3. Synthesis of Regioisomeric Pyrimidin-6-one **12** and Pyrimidin-4-one **16**



carboxylic acids **12**(**A**,**1**−**3**,**a**−**d**) purified and isolated by silica chromatography. In each case, the desired 6-oxo isomer was observed as the major product of desired mass and the first eluted peak by normal phase silica chromatography. However, the isolated yields of **12** ranged from 9% to nearly quantitative. For the benzamidine (R_2 = Ph) and pentanamidines (R_2 = *n*-butyl), the 6-oxo isomer is obtained in good to excellent yield. The three *N*-methylamidines (R_3 = Me, entries 1b, 2b, 3b) gave mixtures of the two isomers in an approximate ratio of 2 to 1 for the 6-oxo and 4-oxo isomers, respectively. In the case of meta-methoxybenzamidines (entries 3,c and3,d), low yields of the desired trisubstituted pyrimidinones **12**(**A**,**3**,**c**−**d**) were obtained and an unexpected disubstituted pyrimidinone **4**(**A**,**3**) was obtained as the major product. The N−H pyrimidinone can be formed, as we have reported previ-

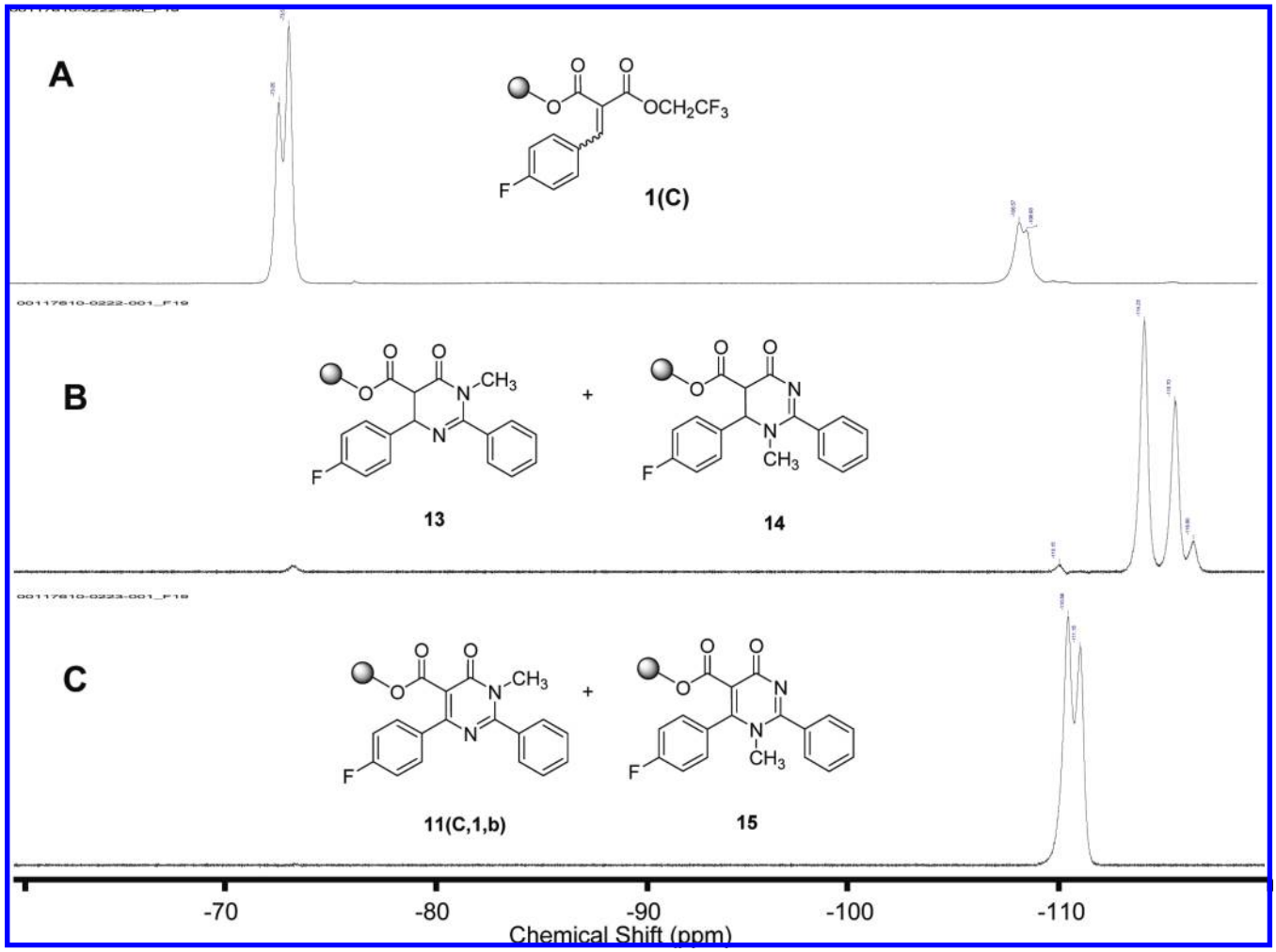
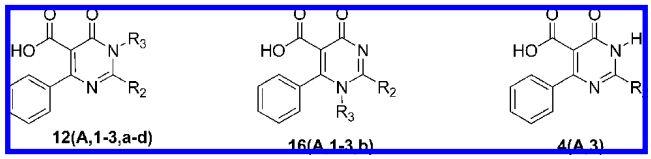


Figure 1. Gel-phase ^{19}FNMR of resin bound pyrimidinones and intermediates: (A) mixture of E and Z isomers of **1**(**C**) exhibiting CF_3 and *para*-F resonances, (B) mixture of dihydropyrimidinone regioisomers **13** and **14**, and (C) oxidized resin showing a mixture of regioisomeric pyrimidinones **11**(**C**,**1**,**b**) and **15**.

Table 2. Product Ratios and Yields from Test Library of Pyrimidinones **12**[a]



			product ratios and yields		
entry	R_2	R_3	**12**	**16**	**4**
1,a	Ph	*n*-butyl	94 (64)		
1,b		Me	65 (35)	35	
1,c		benzyl	93 (58)		
1,d		*iso*-propyl	99 (99)		
2,a	*n*-butyl	*n*-butyl	94 (70)		
2,b		Me	57 (65)	43	
2,c		benzyl	99 (28)		
2,d		*iso*-propyl	75 (20)		
3,a	3-(OMe)Ph	*n*-butyl	98 (37)		
3,b		Me	63 (53)	37	
3,c		benzyl	7 (9)		93
3,d		*iso*-propyl	44 (30)		55

[a] Product ratios were determined by LCMS analysis using the ELS detector signal for determination of relative amounts. Isolated yields after chromatographic purification are given in parenthesis.

ously,[2] from cyclocondensation of resin **1** with primary amidines. This is likely to occur by disproportionation of the N-substituted amidine to a disubstituted amidine and the free NH amidine, followed by cyclocondensation with the less hindered amidine. Taylor et al. have previously observed this disproportionation in an analogous solution phase reaction of a hindered N-substituted amidine and a benzylidene malonate derivative.[11] All twelve compounds **12**(**A**,**1**−**3**,**a**,**d**) have been confirmed by 1D and 2D NMR. In each case the observation of NOE responses of the R_3 protons with the only protons on R_2 is consistent with a 6-oxo isomer **12**. Independent gHMBC experiments further confirm the assignment by observation of the cross peaks between the R_3 protons and the C2/C6 ring carbons.

Using the optimized conditions established in the pilot library for the three-step solid phase cyclization, oxidation and cleavage, a library of 96 compounds was prepared from a set of 8 aldehydes (**A**−**H**) and twelve disubstituted amidines (Figure 2). The amidines **10** were prepared from three nitriles or imidates (R_2, **1**−**3**) and four amines (R_3, **a**−**d**), which were used in all possible combinations to give the twelve amidines for the full library. All eight resins **1**(**A**−**H**) had been prepared in bulk and were ready for the library production. For ease in the production, a set of 96 vials were arranged in an 8 × 12 array and mapped with the appropriate reagents. Following the initial cyclocondensation, the intermediate resins were washed using a STAR apparatus, which allows simultaneous washing of 96 individual resins.[20,26] The entire washing protocol for three solvents, three times each is less than one hour. The room temperature treatment of the reactions with CAN was also carried out on the STAR apparatus and followed with the usual resin washing sequence. Replacement of the washing rack with a collection rack of vessels allowed treatment of the resins with TFA and, after the cleavage reaction was complete, collection of the filtrate in the appropriate tared vial. The products were

	1,a	1,b	1,c	1,d	2,a	2,b	2,c	2,d	3,a	3,b	3,c	3,d
A	94	65	93	99	94	57	100	75	98	63	7	44
B	99	99	98	98	99	99	99	52	98	99	28	17
C	94	64	93	97	100	76	98	94	95	56	91	91
D	92	59	92	94	100	95	97	94	99	99	94	91
E	77	58	87	97	84	55	89	91	88	53	88	98
F	92	61	91	91	100	77	99	95	87	60	85	79
G	92	60	90	87	99	76	96	86	95	68	75	70
H	100	99	99	95	100	100	99	56	100	98	63	66

Figure 2. Plate view of the LCMS data for pyrimidinones **12**{**A**−**H**,**1**−**3**,**a**−**d**}. The aldehyde resins **1**(**A**−**H**) correspond to rows A−H. Amidines **10** are represented in each of the columns **1**,**a** through **3**,**d**. Each sample was analyzed by LCMS using ELS detection. The number in each cell represents the percent integration of the major peak compared to the total integration of all peaks in the chromatogram. Cells shaded in gray indicate reaction mixtures in which the major component is less than 80% by LCMS.

analyzed by LCMS to provide confirmation of molecular ion and initial indication of purity by ELS and UV detection (Figure 2). Analysis of the library was carried out by LCMS using a criteria of >85% purity by ELS detection and confirmation of the molecular ion by positive electrospray MS. Results were very similar to the observations of the pilot library, with 66 compounds have a purity of >85% without purification giving a library success rate of 70%. The *N*-methyl amidines (columns 2, 6, and 10) showed the lowest purity due to the expected mixture of regioisomeric products. Amidines **10**(**3**,**c**) and **10**(**3**,**d**) gave lower yields for some of the products (columns 11 and 12) but were acceptable in 7 out of 16 cases.

Analysis of the library by a "plate view" is very useful for making decisions concerning the purity of the library and the trends observed in the reaction sequence. From our initial run, we surmised that the *N*-methyl amidines, **10**(**1**,**b**), **10**(**2**,**b**), and **10**(**3**,**b**), could give rise to mixtures of the isomeric cyclization products, and this was confirmed in the production run of 96 members. These compounds could be separated to provide each isomer or kept in a library as a mixture to allow testing of both isomers. The decision to separate regioisomers depends on the intended objectives of the library of compounds. For our needs, we decided to leave the mixtures in unpurified form provided the total amount of the two isomers was greater than 85%. Even allowing for regioisomers (columns 1b, 2b, and 3b) there were thirteen compounds from the library that were below the 85% threshold level for purity. These compounds were purified by preparative LCMS and added in the appropriate positions to the set of compounds to provide 96 pyrimidines **12** for analysis by high-throughput flow ^{1}H NMR (Figure 3).

^{1}H NMR spectra were obtained for each of the samples prepared as a 30 mM solution in protonated acetonitrile. Samples were transferred to a 96 well plate for introduction into the spectrometer using a flow probe interfaced with a sample injector. Comparison of the observed spectra

	1,a	1,b	1,c	1,d	2,a	2,b	2,c	2,d	3,a	3,b	3,c	3,d
A	0.68	0.78	0.77	0.66	0.77	0.79	0.69	0	0.66	0.66	0.65	0.68
B	0.52	0.48	0	0.48	0	0	0.59	0.49	0.56	0.54	0	0
C	0.72	0.66	0.66	0.67	0.73	0	0.68	0.73	0.73	0.66	0.71	0.53
D	0	0.69	0.70	0.76	0.49	0.50	0.83	0.50	0.72	0.73	0.70	0.65
E	0.66	0.67	0.65	0.60	0.51	0.49	0.65	0	0.62	0.49	0.68	0.52
F	0.56	0.56	0.55	0.54	0.56	0.56	0.58	0.59	0.58	0.51	0.56	0.56
G	0.71	0.73	0.63	0.69	0.59	0.51	0.51	0.52	0.63	0.52	0.67	0.55
H	0.83	0.87	0.65	0.50	0.77	0.53	0.57	0	0.55	0	0.65	0.68

Figure 3. Plate view of the ^{1}H NMR data for pyrimidinones **12**{**A**−**H**,**1**−**3**,**a**−**d**}. The number in each cell represents the match of the experimental ^{1}H NMR compared to the predicted spectra with a value of zero to one. Values of unity represent complete correspondence of the predicted and observed resonances.

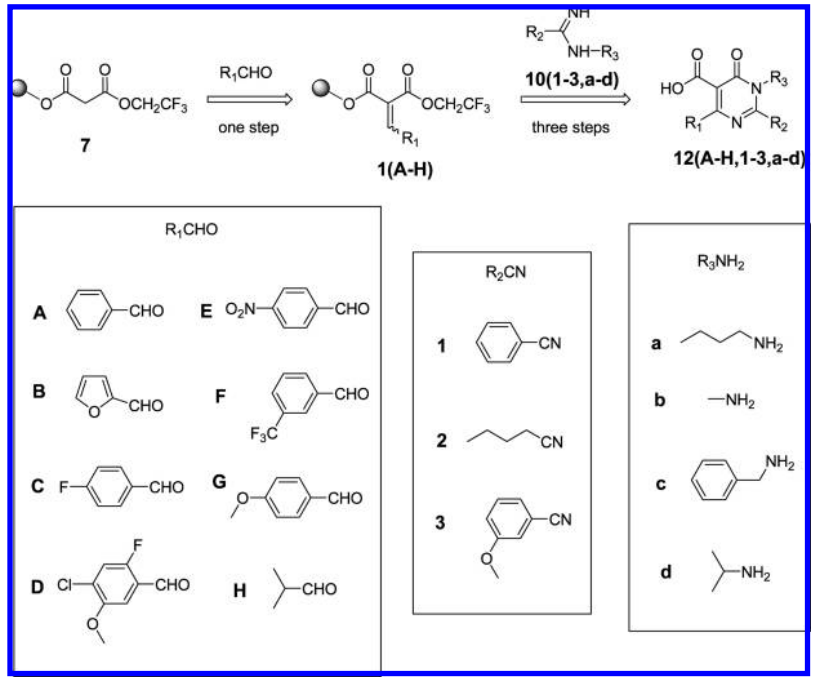
with predicted spectra was achieved using ACD software[27] and provided a value of agreement from 0 to 1. Values close to unity represented the best fit with the predicted spectra, whereas a value of zero shows no agreement. Using this package with default values, we obtained agreement with the predicted spectra in the range of 0.48 to 0.87. In eleven examples, we observed values of zero and inspection of the experimental spectra showed that these samples were of insufficient concentration to obtain sufficient signal-to-noise for the automated ACD software. Five of the library members (A2d, B3c, B3d, C2a, H2d) exhibited low yield in both the LCMS and NMR analysis. The remaining "null" examples from the NMR analysis all showed greater than 90% purity by LCMS, which indicated high purity for the sample, but insufficient concentration for the NMR experiment. The combination of LCMS and NMR analysis allows analysis of the library for confirmation of molecular weight, confirmation of structure by presence of predicted NMR resonances, and evaluation of yield by sufficient signal in the NMR spectra. The addition of an internal standard in the NMR samples would allow direct determination of sample concentrations and yields by comparative integration of the sample and internal standard resonances. In the final analysis, 85 compounds from the library were structurally confirmed by LCMS and flow probe ^{1}H NMR providing an overall success rate of 88%. This was achieved by intial analysis of the 96 samples by LCMS, purification of a selected subset of 13 samples by preparative LC to bring the set of 96 to greater that 85% by LCMS and final analysis of the set by high-throughput flow ^{1}H NMR.

In conclusion, we have developed a fully integrated approach for preparation of targeted compounds comprising of detailed development of a synthetic method, library production and structural confirmation of final products by LCMS and high-throughput flow ^{1}H NMR. This approach allows us to capture the greatest structural diversity in the set of compounds within the limits of the synthetic method and has been applied to the preparation of a 96 member library of pyrimidin-6-one-5-carboxylic acids **12**. Final compounds, consisting of the combined set of thirteen purified compounds and those obtained directly from the production run, were further analyzed by LCMS and ^{1}H NMR using a high-throughput flow system. Spectra analysis of the ^{1}H NMR data was achieved using an automated software package (ACD), which allowed a visual representation of the correspondence between experimental and predicted data. A total of 85 compounds were confirmed by chromatographic purity, mass spectral, and ^{1}H NMR analysis to provide a synthetic success rate of 88% for the 96 member library.

Experimental Section

General Procedures. Preparative scale polymer-supported reactions were carried out in standard glass vessels with overhead paddle stirrers and the resins subsequently washed using flasks fitted with a glass frit at the bottom and a sidearm connected to a valve (cat. #Z28,330-4, Aldrich Chemical Co., Milwaukee, WI or similar larger vessel). Prior to carrying out reactions, polymeric resins were dried in a vacuum desiccator and subsequently allowed to swell in anhydrous reaction solvent for 15−30 min in an inert atmosphere. Parallel and small-scale reactions (50−500 mg resin) were carried out using capped vessels or vials in a thermocouple controlled heating block placed on an orbital shaker (J-KEM, St. Louis, MO). Resins from parallel reactions were washed using a previously described custom designed SynThesis Array Reactor (STAR), which allows convenient washing and drying of resins either manually or using a Tecan programmed for solvent additions.[21,26]Wang or *p*-alkoxybenzyl alcohol resin (cat. #01927; 1.12 mequiv/g) was obtained from Chem-Impex International (Wood Dale, IL). Wang malonic acid resin (loading, 0.83 mequiv/g) was prepared as previously described.[21] Amidines were prepared by standard methods directly from ethyl benzimidate hydrochloride or by a two step Pinner sequence from nitriles 3-methoxybenzonitrile and valeronitrile.[20] Preparative normal phase chromatography was achieved using prepacked silica columns (75 g silica, Biotage). Preparative and analytical reverse phase liquid chromatographic separations were obtained using aqueous 0.1% TFA/acetonitrile mixtures as the mobile phase. Analytical chromatography was carried out using a 4.6 mm i.d. × 50 mm C18 stationary phase column, flow rate of 1.4 mL/min, and a 5 min gradient from 5% to 95% acetonitrile in 0.1% aqueous TFA followed by a 2 min hold at 95% acetonitrile for a 7 min total run time. Autoprep preparative chromatography was carried out using a 21.2 mm i.d. × 5.0 cm C18 column on a Sciex LCMS system as recently described.[28] Detection was obtained using total ion current (TIC), UV detection (210 and 254 nm), or evaporative light scattering detection (ELSD). FT-IR spectra of resins were obtained using KBr pellets prepared from resin ground with anhydrous KBr. Analysis of polymer loading was determined by direct cleavage ^{1}H NMR using hexamethyldisiloxane (HMDS) as an internal standard.[29,30] An aliquot of resin (50−100 mg) was weighed into a fritted syringe barrel vessel and treated with 10 mM HMDS in TFA/$CDCl_3$ (1:1) for 30 min. The resin was washed 3 times with $CDCl_3$, and the combined

Scheme 4. Solid-Phase Synthesis of the 96-Member Pyrimidinone Library



filtrates used directly for NMR analysis. Resin loading was determined by ^{1}H NMR spectroscopy by integrating characteristic and resolved protons of the products versus the CH_3 protons in HMDS. NMR parameters (acquisition time, pulse width, number of points) were optimized to obtain integrals accurate to within 1%. Gel-phase ^{19}F NMR samples were prepared by placing approximately 75 mg of resin in a 5 mm NMR tube and adding sufficient ^7d-DMF to provide a slurry.[23]

2,2,2-Trifluoroethyl Malonate Resin (7). Using the previously described method,[21] 53.0 g of Wang malonic acid resin was converted to 57.7 g of orange resin. ^{1}H NMR loading: calcd 0.848, found 0.827 (98%).

General Procedure for the Preparation of 2,2,2-Trifluoroethyl-2-methylene-substituted Malonate Resins (1A−H). To an oven-dried flask equipped with an overhead stirrer, Dean−Stark trap and N_2 line was added 2,2,2-trifluoroethyl malonate resin and anhydrous benzene (15 mL/mmol). The stirred suspension was treated with 10 equivalents of aldehyde and 0.5 equiv each of piperidine and acetic acid. The stirred suspension was heated to reflux for 1 h and continued heating until the distillate was clear. After allowing the mixture to cool to room temperature, the suspension was transferred to a solid-phase reaction flask and washed three times each with DMF, MeOH, and CH_2Cl_2. The reaction was filtered, and the solid swept with N_2 overnight to afford the dry resin. A 100 mg sample of dry resin was analyzed by direct cleavage ^{1}H NMR to provide loading and purity information.

2,2,2-Trifluoroethyl-2-benzylidenemalonate Resin (1A). The general procedure provided an orange resin which on cleavage gave two isomers (44% A/56% B): direct cleavage ^{1}H NMR ($CDCl_3$/TFA) δ 4.69(A and B, m, 2H), 7.26 − 7.56(A and B, m, 5H), 8.11(A, s, 1H), 8.16(B, s, 1H). ^{1}H NMR loading: calcd 0.771, found 0.722 (93.7% yield).

2,2,2-Trifluoroethyl-2-furylidenemalonate Resin (1B). The general procedure provided a dark brown resin which on cleavage gave two isomers (46% A/54% B): direct cleavage ^{1}H NMR ($CDCl_3$/TFA) δ 4.73(A and B, m, 2H), 6.62 (B, dd, 1H, J = 3.6 Hz, J = 1.7 Hz), 6.72 (A, dd, 1H, J = 3.6 Hz, J = 1.7 Hz), 7.05 (B, d, 1H, J = 3.5 Hz), 7.63 (B, s, 1H), 7.79 (A and B, m, 3H), 8.10 (A, s, 1H). ^{1}H NMR loading: calcd 0.777, found, 0.724 (93.1% yield).

2,2,2-Trifluoroethyl-2-(4-fluoro)benzylidenemalonate Resin (1C). The general procedure provided a bright orange resin which on cleavage gave two isomers (46% A/54% B): direct cleavage ^{1}H NMR ($CDCl_3$/TFA) δ 4.73(A and B, m, 2H), 6.62 (B, dd, 1H, J = 3.6 Hz, J = 1.7 Hz), 6.72 (A, dd, 1H, J = 3.6 Hz, J = 1.7 Hz), 7.05 (B, d, 1H, J = 3.5 Hz), 7.63 (B, s, 1H), 7.79 (A and B, m, 3H), 8.10 (A, s, 1H). ^{1}H NMR loading: calcd 0.777, found, 0.724 (93.1% yield). Gel-phase ^{19}FNMR (^7d-DMF) δ −73.0 and −73.5 (CF_3), −108.6 and −108.9 (1F).

2,2,2-Trifluoroethyl-2-(2-fluoro-4-chloro-5-methoxy)benzylidenemalonate Resin (1D). The general procedure provided an orange resin which on cleavage gave two isomers (48% A/52% B): direct cleavage ^{1}H NMR ($CDCl_3$/TFA) δ 3.91 (A and B, m, 3H), 4.66 (A and B, m, 2H), 7.00 (B, d, 1H, J = 6.3 Hz), 7.15 (A, d, 1H, J = 6.3 Hz), 7.23 (A, d, 1H, J = 0.9 Hz), 7.26 (B, s, 1H), 8.14 (A, s, 1H), 8.16 (B, s, 1H). ^{1}H NMR loading: calcd 0.725, found, 0.603 (83.1% yield).

2,2,2-Trifluoroethyl-2-(4-nitro)benzylidenemalonate Resin (1E). The general procedure provided an orange-brown resin which on cleavage gave two isomers (31% A/69% B): direct cleavage ^{1}H NMR ($CDCl_3$/TFA) δ 4.66 (A and B, m, 2H), 7.65 (B, d, 2H, J = 8.8 Hz), 7.72 (A, d, 2H, J = 8.8 Hz), 8.14 (A, s, 1H), 8.20 (B, s, 1H), 8.32 (B, d, 2H, J = 8.8 Hz), 8.32 (A, d, 2H, J = 8.9 Hz). ^{1}H NMR loading: calcd 0.745, found, 0.682 (91.5% yield).

2,2,2-Trifluoroethyl-2-(3-trifluoromethyl)benzylidenemalonate Resin (1F). The general procedure provided an orange resin which on cleavage gave two isomers (30% A/70% B): direct cleavage ^{1}H NMR ($CDCl_3$/TFA) δ 4.68 (A and B, m, 2H), 7.60 − 7.81 (A and B, m, 4H), 8.13 (A, s, 1H), 8.19 (B, s, 1H). ^{1}H NMR loading: calcd 0.732, found, 0.695 (94.9% yield).

2,2,2-Trifluoroethyl-2-(4-methoxy)benzylidenemalonate Resin (1G). The general procedure provided an orange resin which on cleavage gave two isomers (28% A/72% B): direct cleavage ^{1}H NMR ($CDCl_3$/TFA) δ 3.93 (A and B, s, 3H), 4.71 (A and B, m, 2H), 7.01 (A and B, m, 2H), 7.47 (B, d, 2H, J = 8.9), 7.65 (A, d, 2H, J = 8.9), 8.10 (A and B, s, 1H). ^{1}H NMR loading: calcd 0.753, found, 0.740 (98.2% yield).

2,2,2-Trifluoroethyl-2-isopropylidenemalonate Resin (1H). The general procedure provided an orange resin which on cleavage gave two isomers (49% A/51% B): direct cleavage ^{1}H NMR ($CDCl_3$/TFA) δ 1.15 (A and B, m, 6H), 2.97 (B, m, 1H), 3.43 (A, m, 1H), 4.68 (A and B, m, 2H), 7.48 (B, d, 1H, J = 3.5 Hz), 7.51 (A, d, 1H, J = 3.5 Hz). ^{1}H NMR loading: calcd 0.792, found, 0.776 (98% yield).

1-Butyl-6-oxo-2,4-diphenyl-1,4,5,6-tetrahydropyrimidine-5-carboxylate Resin (13{A,1,a}). To 0.21 g (0.66 meq/g; 0.14 mmol) of resin **1A** was added a solution of 0.24 g (1.38 mmol) of *N*-(*n*-butyl)benzamidine[31] in 4 mL of dimethylacetamide. The reaction vessel was capped, heated to 70 °C and agitated by rocking for 6 h. After the vial was allowed to cool, the contents were transferred to a solid-phase reaction flask and the resin washed three times each with DMF, MeOH, and CH_2Cl_2. The resin was filtered in the flask and dried with a stream of N_2 overnight to afford an orange resin which was used directly in the next step: FTIR (KBr) 3022, 2919, 1646, 1700, 1731 cm^{-1}; direct cleavage ^{1}H NMR ($CDCl_3$/TFA) δ 0.74 (t, 3H, J = 7.3 Hz), 1.08 (m, 2H), 1.50 (m, 2H), 3.90 (m, 2H), 4.55 (m, 1H), 5.66 (m, 1H), 7.38 (m, 2H), 7.50 (m, 3H), 7.64 (m, 4H), 7.81 (t, 1H, J = 6.8 Hz). ^{1}H NMR loading: calcd 0.627, found 0.518 (83% yield).

1-Butyl-6-oxo-2,4-diphenyl-1,6-dihydropyrimidine-5-carboxylate Resin (11{A,1,a}). To 0.22 g (0.11 mmol) of 1-butyl-6-oxo-2,4-diphenyl-1,4,5,6-tetrahydropyrimidine-5-carboxylate resin **13**{**A**,**1**,**a**} was added a solution of 620 mg (1.13 mmol) ceric ammonium nitrate in 3 mL of dimethylacetamide. The reaction vessel was capped and allowed to agitate by rocking for 2 h at rt. The contents of the vessel were transferred to a solid-phase resin washing flask and washed three times each with DMF, MeOH, and CH_2Cl_2. The resin was filtered in the flask and dried with a stream of N_2 overnight to afford an orange resin: FTIR (KBr) 3022, 2914, 1731, 1655 cm^{-1}; direct cleavage ^{1}H NMR ($CDCl_3$/TFA) δ 0.83 (t, 3H, J = 7.3 Hz), 1.27 (m, 2H), 1.75 (m, 2H), 4.17 (t, 2H, J = 8.0 Hz), 7.51 (m, 4H), 7.67 (m, 5H), 7.82 (m, 1H). ^{1}H NMR loading: calcd 0.520, found 0.520 (100% yield).

1-Butyl-6-oxo-2,4-diphenyl-1,6-dihydropyrimidine-5-carboxylic Acid 12{A,1,a}. To 0.22 g (0.11 mmol) of resin **11**{**A**,**1**,**a**} was added 2 mL of a mixture of TFA in CH_2Cl_2 (1:1). The cleavage reaction was allowed to agitate at rt for 30 min; the filtrate was collected, and the resin was washed three times with CH_2Cl_2. Collected filtrates were concentrated to afford a crude yellow oil. Analysis by LCMS showed two products in a 10:1 ratio both having the correct molecular ion (M + 1, 349). Purification by silica chromatography using CH_2Cl_2:acetic acid (98:2) as the eluant afforded a single product which was concd in vacuo to afford 40 mg (quant.) of an off-white solid: ^{1}H NMR ($CDCl_3$) δ 0.80 (t, 3H, J = 7.3 Hz), 1.21 (sextet, 2H, J = 7.5 Hz), 1.67 (pentet, 2H, J = 7.6 Hz), 4.12 (t, J = 7.8 Hz), 7.40 − 7.65 (m, 10H); ^{13} CNMR (CDCl3) δ 13.3, 19.8, 30.4, 47.3, 109.3 (C5), 127.9, 128.2, 128.9, 129.4, 130.6, 131.2, 133.5, 137.6, 160.6, 164.1, 165.9, 168.6; MS (ES+) *m*/z 349 (M+1, 100). HRMS (ES+) *m*/*z* calcd for (M + H $C_{21}H_{21}N_2O_3$) 349.1547, found 349.1535.

1-Methyl-6-oxo-2-phenyl-4-(4-fluorophenyl)-1,4,5,6-tetrahydropyrimidine-5-carboxylate (13{C,1,b}) and 1-Methyl-4-oxo-2-phenyl-6-(4-fluorophenyl)-1,4,5,6-tetrahydropyrimidine-5-carboxylate Resin (14). To 1.38 g (0.657 meq/g; 0.91 mmol) of 2,2,2-trifluoroethyl-2-(4-fluoro)benzylidenemalonate resin (**3C**) was added a solution of 1.24 g (9.25 mmol) of *N*-methylbenzamidine[32] in 30 mL of dimethylacetamide. The slurry was stirred with an overhead paddle stirrer and heated to 70 °C for 6 h. After the mixture was allowed to cool, the contents were transferred to a solid-phase reaction flask, and the resin was washed three times each with DMF, MeOH, and CH_2Cl_2. The resin was filtered in the flask and dried with a stream of N_2 overnight to afford an orange resin: FTIR (KBr) 3025, 2922, 1739, 1681, 1603 cm^{-1}; direct cleavage ^{1}H NMR ($CDCl_3$/TFA) shows a mixture of four isomers. The resin was used directly in the next step: ^{1}H NMR loading: calcd 0.643, found 0.703 (100% yield). Gel-phase ^{19}F NMR (^{7}*d*-DMF) δ −114.2 and −115.7 (1F).

1-Methyl-6-oxo-2-phenyl-4-(4-fluorophenyl)-1,6-dihydropyrimidine-5-carboxylate (11{C,1,b}) and 1-Methyl-4-oxo-2-phenyl-6-(4-fluorophenyl)-1,4-dihydropyrimidine-5-carboxylate Resin (15). To 1.28 g (0.90 mmol) of resin mixture **13** and **14** was added a solution of 5.0 g (9.12 mmol) of ammonium cerium (IV) nitrate in 25 mL of dimethylacetamide. The slurry was stirred with an overhead paddle stirrer for 2 h, filtered, and subsequently washed three times each with DMF, MeOH, and CH_2Cl_2. The resin was filtered in the flask and dried with a stream of N_2 overnight to afford 1.19 g of an orange resin: FTIR (KBr) 3025, 2921, 1733, 1654, 1601 cm^{-1}; a mixture of isomers observed (A, 53%, 4-oxo-isomer; B, 47%, 6-oxo-isomer) by direct cleavage ^{1}H NMR ($CDCl_3$/TFA) δ 3.12 (B, 53%, s, 3H) and 3.34 (A, 47%, s, 3H), 6.78 and 6.91 (A and B, t, 2H), 7.06 and 7.14 (A and B, m, 2H), 7.24−7.47 (m, 5H). ^{1}H NMR loading: calcd 0.643, found 0.622 (97% yield). Gel phase ^{19}F NMR (*^{7}d-DMF*) δ −110.6 and −111.2 (1F).

1-Methyl-4-oxo-2-phenyl-6-(4-fluorophenyl)-1,4-dihydropyrimidine-5-carboxylic Acid (16{C,1,b}). To 1.19 g (0.62 mequiv/g; 0.74 mmol) of resin mixture **11**{**C**,**1**,**b**} and **15** was added 5 mL of TFA in CH_2Cl_2 (1:1) and the mixture allowed to agitate for 30 min. The filtrate was collected and the resin treated a second time with 5 mL of TFA in CH_2Cl_2 (1:1). The resin was washed three times with a minimum amount of CH_2Cl_2. Combined filtrates were concd in vacuo

to afford a yellow oil which is a mixture of isomers (LCMS: first isomer at 2.26 min (A, 62%) and second isomer at 2.67 min (B, 38%). Purification by reverse phase chromatography afforded 137 mg (42%) of the first eluted isomer major product as 1-methyl-4-oxo-2-phenyl-6-(4-fluorophenyl)-1,6-dihydropyrimidine-5-carboxylic acid, TFA salt (1:1): TLC (5% acetic acid/CH_2Cl_2) R_f = 0.07; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.24 (s, 3 H) 7.12 (t, J = 8.50 Hz, 2 H) 7.28 (dd, J = 8.30, J = 4.98 Hz, 2 H) 7.47 (t, J = 7.52 Hz, 2 H) 7.52 − 7.61 (m, 3 H) 13.37 (br. s., 2 H); ^{19} FNMR (376 MHz, $CDCl_3$) δ ppm −108.16 (br. s., 1 F) −76.02 (s, 3 F, TFA); ^{13} CNMR (101 MHz, $CDCl_3$) δ ppm 42.4, 111.5 (C5), 116.7 (d, J = 22 Hz), 127.0 (d, J = 3 Hz), 128.6, 129.1, 129.6 (d, J = 9 Hz), 131.0, 132.5, 161.0, 163.8 (d, J = 253.5 Hz), 164.2, 164.3, 170.0. HRMS (ES+) m/z calcd for (M + H $C_{18}H_{14}FN_2O_3$) 325.0983, found 325.0982.

1-Methyl-6-oxo-2-phenyl-4-(4-fluorophenyl)-1,6-dihydropyrimidine-5-carboxylic acid (12{C,1,b}). The second eluted peak from cleavage of resin mixture **11**{**C**,**1**,**b**} and **15** was collected and concd in vacuo to afford 86 mg of (36%) a yellow solid as 1-methyl-6-oxo-2-phenyl-4-(4-fluorophenyl)-1,4-dihydropyrimidine-5-carboxylic acid: TLC (5% acetic acid/CH_2Cl_2) R_f = 0.25; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.46 − 3.72 (m, 3 H) 6.86 − 7.16 (m, 2 H) 7.38 − 7.74 (m, 7 H) 12.93 (br. s., 1 H); ^{19} FNMR (376 MHz, $CDCl_3$) δ ppm −109.07 (br. s., 1 F); ^{13} CNMR (101 MHz, $CDCl_3$) δ 35.6, 108.1 (C5), 115.0 (d, J = 22.2 Hz), 128.3, 129.0, 131.8 (d, J = 9 Hz), 131.9, 132.7, 133.3 (d, J = 3 Hz), 160.6, 164.3 (d, J = 251.8 Hz), 165.0, 166.3, 167.6. HRMS (ES+) m/z calcd for (M + H $C_{18}H_{14}FN_2O_3$) 325.0983, found 325.0981.

Pilot Library: Preparation of 1,2-Disubstituted-6-oxo-4-phenyl-1,6-dihydropyrimidine-5-carboxylic Acids. (12{A,1−3,a−d}). Polymer reaction vessels were assembled for 12 parallel reactions. To each vessel was added 277 mg (0.20 mmol) of resin 3A and 3 mL of anhydrous DMA. The resins were agitated for 1 h and subsequently filtered. The vessels were treated with 5 mL of a 0.35 M solution of the appropriate amidine in DMA (see table for list of amidines 1−12), agitated by gentle stirring and heated to 70 °C for 6 h. After the reaction mixtures were allowed to cool, each resin was washed three times with 3 mL of DMA. The filtered resins were treated with a 5 mL solution of 0.4 M ceric ammonium nitrate in DMA for 2 h at rt. After draining the vessels, the resins were transferred to a parallel washing apparatus (STAR block) and sequentially washed three times each with 5 mL aliquots of DMF, MeOH and CH_2Cl_2. Cleavage of products from the resins was carried out by treatment with 1 mL of TFA/CH_2Cl_2 (1:1) for 30 min, followed by three 1 mL washes with CH_2Cl_2. Combined filtrates were concd under a stream of N_2 to afford the crude products. Each sample was purified by silica chromatography (95% CH_2Cl_2, 5% acetic acid) and the fractions containing the product concd in vacuo.

1-*n*-Butyl-2,4-diphenyl-6-oxo-1,6-dihydropyrimidine-5-carboxylic Acid (12{A,1,a}). LCMS analysis of the crude product showed a single major product of the desired mass (rt = 4.38 min, 94% by ELSD). Purification by silica chromatography afforded 44.6 mg (64%) of a solid, which was spectroscopically identical to the previously obtained material.

1-Methyl-2,4-diphenyl-6-oxo-1,6-dihydropyrimidine-5-carboxylic Acid (12{A,1,b}). LCMS analysis of the crude product showed two major products of the desired mass; major isomer (rt = 3.68 min, 65% by ELSD) and minor isomer (rt = 3.27 min, 35% by ELSD). Collection of the first eluted compound (major isomer) by silica chromatography afforded 21.1 mg (35%) of the desired product: ^{1}H NMR ($CDCl_3$) δ 3.65 (s, 3H), 7.42 (m, 3H), 7.54−7.64 (m, 7H); ^{13} CNMR (CDCl3) δ 35.6, 108.7 (C5), 127.9, 128.8, 129.0, 129.4, 130.6, 131.8, 133.1, 137.6, 160.3, 164.0, 166.4, 168.9; MS (ES+) 307 (M+1, 100), 289 (30), 263 (38), 118 (23). HRMS (ES+) m/z calcd for (M+H: $C_{18}H_{15}N_2O_3$) 307.1083, found 307.1063.

1-Benzyl-2,4-diphenyl-6-oxo-1,6-dihydropyrimidine-5-carboxylic Acid (12{A,1,c}). LCMS analysis of the crude product showed a single major product of the desired mass (rt = 4.42 min, 93% by ELSD). Purification by silica chromatography afforded 43.9 mg (58%) of a solid: ^{1}H NMR ($CDCl_3$) δ 5.37 (s, 2H), 6.99 (m, 2H), 7.27 (m, 3H), 7.38−7.55 (m, 8H), 7.66 (d, 2H, J = 8.0 Hz); ^{13} CNMR ($CDCl_3$) δ 50.2, 109.4 (C5), 127.1, 127.9, 128.3, 128.5, 128.9, 128.9, 129.5, 130.8, 131.4, 133.3, 134.7, 137.4, 160.7, 164.0, 166.0, 168.8; MS (ES+) 383 (M+1), 275 (18). HRMS (ES+) m/z calcd for (M + H $C_{24}H_{19}N_2O_3$) 383.1396, found 383.1383.

1-iso-Propyl-2,4-diphenyl-6-oxo-1,6-dihydropyrimidine-5-carboxylic Acid (12{A,1,d}). LCMS analysis of the crude product showed a single major product of the desired mass (rt = 4.21 min, 99% by ELSD). Purification by silica chromatography afforded 66.5 mg (99%) of a solid: ^{1}H NMR ($CDCl_3$) δ 1.65 (d, 6H, J = 6.8 Hz), 4.54 (septet, 1H, J = 6.8 Hz), 7.37−7.45 (m, 3H), 7.53−7.63 (m, 7H); ^{13} CNMR ($CDCl_3$) δ 19.6, 56.4, 109.9, 127.8, 127.9, 129.0, 129.4, 130.6, 131.2, 134.2, 137.5, 160.7, 164.3, 166.8, 168.1; MS (ES+) 335 (M+1, 66), 293 (73), 275 (100). HRMS (ES+) m/z calcd for (M + H $C_{20}H_{19}N_2O_3$) 335.1396, found 335.1360.

1,2-Di-*n*-butyl-4-phenyl-6-oxo-1,6-dihydropyrimidine-5-carboxylic Acid (12{A,2,a}). LCMS analysis of the crude product showed a single major product of the desired mass (rt = 4.79 min, 94% by ELSD). Purification by silica chromatography afforded 45.6 mg (70%) of a solid: ^{1}H NMR ($CDCl_3$) δ 0.99 (t, 3H, J = 7.2 Hz), 1.03 (t, 3H, J = 7.2 Hz), 1.48 (m, 4H), 1.79 (m, 4H), 2.86 (t, 2H, J = 7.7 Hz), 4.12 (t, 2H, J = 7.9 Hz), 7.45 (m, 3H), 7.58 (dd, 2H, J = 7.4 Hz, J = 1.4 Hz); ^{13} CNMR ($CDCl_3$) δ 13.6, 13.8, 20.2, 22.4, 28.9, 30.4, 34.7, 44.9, 108.5(C5), 127.8, 129.2, 130.5, 137.9, 162.7, 164.1, 165.8, 168.9; MS (ES+) 329 (M + 1, 100). HRMS (ES+) m/z calcd for (M + H $C_{19}H_{25}N_2O_3$) 329.1865, found 329.1857.

1-Methyl-2-*n*-butyl-4-phenyl-6-oxo-1,6-dihydropyrimidine-5-carboxylic Acid (12{A,2,b}). LCMS analysis of the crude product showed two major products of the desired mass; major isomer (rt = 3.90 min, 57% by ELSD) and minor isomer (rt = 3.30 min, 43% by ELSD). Collection of the first eluted compound (major isomer) by silica chroma-

tography afforded 37.3 mg (65%) of the desired product: ^{1}H NMR ($CDCl_3$) δ 0.99 (t, 3H, J = 7.3 Hz), 1.48 (sextet, 2H, J = 7.6 Hz), 1.83 (pentet, 2H, J = 7.6 Hz), 2.88 (t, 2H, J = 7.9 Hz), 3.69 (s, 3H), 7.44 (m, 3H), 7.57 (dd, 2H, J = 7.7 Hz, J = 1.4 Hz); ^{13} CNMR ($CDCl_3$) δ 13.8, 22.4, 28.2, 31.5, 35.4, 108.4, 127.8, 129.2, 130.5, 137.9, 162.9, 163.9, 166.0, 169.1; MS (ES+) 287 (M + 1, 100), 269 (26), 243 (32). HRMS (ES+) *m*/*z* calcd for (M + H $C_{16}H_{19}N_2O_3$) 287.1396, found 287.1381.

1-Benzyl-2-*n*-butyl-4-phenyl-6-oxo-1,6-dihydropyrimidine-5-carboxylic Acid (12{A,2,c}). LCMS analysis of the crude product showed a single major product of the desired mass (rt = 4.76 min, 100% by ELSD). Purification by silica chromatography afforded 20.4 mg (28%) of a solid: ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 3H, J = 7.4 Hz), 1.37 (sextet, 2H, J = 7.7 Hz), 1.74 (pentet, 2H, J = 7.7 Hz), 2.81 (t, 2H, J = 7.7 Hz), 5.42 (s, 2H), 7.21 (d, 2H, J = 6.4 Hz), 7.43 (m, 6H), 7.62 (dd, 2H, J = 7.7 Hz, J = 1.4 Hz); ^{13} CNMR ($CDCl_3$) δ 13.7, 22.3, 28.5, 34.9, 47.6, 108.7 (C5), 126.6, 127.8, 128.5, 129.3, 129.4, 130.7, 134.0, 137.7, 163.3, 164.0, 166.0, 169.1; MS (ES+) 363 (M + 1). HRMS (ES+) *m*/*z* calcd for (M + H $C_{22}H_{23}N_2O_3$) 363.1709, found 363.1704.

1-iso-Propyl-2-*n*-butyl-4-phenyl-6-oxo-1,6-dihydropyrimidine-5-carboxylic Acid (12{A,2,d}). LCMS analysis of the crude product showed a single major product of the desired mass (rt = 4.49 min, 75% by ELSD). Purification by silica chromatography afforded 12.6 mg (20%) of a solid: ^{1}H NMR ($CDCl_3$) δ 0.99 (t, 3H, J = 7.5 Hz), 1.48 (sextet, 2H, J = 7.5 Hz), 1.71 (d, 6H, J = 6.8 Hz), 1.80 (m, 2H), 2.90 (t, 2H, J = 7.8 Hz), 4.69 (m, 1H), 7.44 (m, 3H), 7.57 (dd, 2H, J = 7.7 Hz, J = 1.4 Hz); ^{13} CNMR ($CDCl_3$) δ 13.8, 19.5, 22.3, 29.3, 36.0, 53.2, 109.4, 126.6, 127.8, 129.2, 137.8, 162.5, 164.2, 166.7, 168.5; MS (ES+) 315 (M + 1, 66), 273 (86), 255 (100). HRMS (ES+) *m*/*z* calcd for (M + H $C_{18}H_{23}N_2O_3$) 315.1709, found 315.1690.

1-*n*-Butyl-2-(3-methoxy)phenyl-4-phenyl-6-oxo-1,6-dihydropyrimidine-5-carboxylic Acid (12{A,3,a}). LCMS analysis of the crude product showed a single major product of the desired mass (rt = 4.47 min, 98% by ELSD). Purification by silica chromatography afforded 28.0 mg (37%) of a solid: ^{1}H NMR ($CDCl_3$) δ 0.83 (t, 3H, J = 7.4 Hz), 1.25 (sextet, 2H, J = 7.2 Hz), 1.70 (pentet, 2H, J = 7.6 Hz), 3.87 (s, 3H), 4.09 (t, 2H, J = 7.8 Hz), 7.08 (m, 3H), 7.43 (m, 4H), 7.61 (m, 2H); ^{13} CNMR ($CDCl_3$) δ 13.4, 19.9, 30.5, 47.4, 55.6, 109.4, 113.9, 116.8, 120.1, 127.9, 129.4, 130.2, 130.6, 134.6, 137.6, 159.8, 160.4, 164.1, 165.8, 168.7; MS (ES+) 379 (M + 1, 100). HRMS (ES+) *m*/*z* calcd for (M + H $C_{22}H_{23}N_2O_4$) 379.1658, found 379.1649.

1-Methyl-2-(3-methoxy)phenyl-4-phenyl-6-oxo-1,6-dihydropyrimidine-5-carboxylic Acid (12{A,3,b}). LCMS analysis of the crude product showed two major products of the desired mass; major isomer (rt = 3.78 min, 63% by ELSD) and minor isomer (rt = 3.46 min, 37% by ELSD). Collection of the first eluted compound (major isomer) by silica chromatography afforded 35.5 mg (53%) of the desired product: ^{1}H NMR ($CDCl_3$) δ 3.62 (s, 3H), 3.85 (s, 3H), 7.13 (m, 3H), 7.42 (m, 4H), 7.62 (d, 2H, J = 6.6 Hz); ^{13} CNMR ($CDCl_3$) δ 35.6, 55.6, 109.1, 114.4, 117.3, 120.7, 127.9, 129.4, 130.2, 130.6, 134.3, 137.6, 159.9, 160.2, 164.3, 166.2, 168.6; MS (ES+) 337 (M + 1, 100), 293 (21). HRMS (ES+) *m*/*z* calcd for (M + H $C_{19}H_{17}N_2O_4$) 337.1188, found 337.1168.

1-Benzyl-2-(3-methoxy)phenyl-4-phenyl-6-oxo-1,6-dihydropyrimidine-5-carboxylic Acid (12{A,3,c}). LCMS analysis of the crude product showed a single product of the desired mass (rt = 4.44 min, 7% by ELSD) and a second product of lower mass (rt = 3.64 min, 93% by ELS, MS (ES+) 323), which was identified as **4**(**A**,**3**). Purification by silica chromatography of the desired product (first eluted compound) afforded 7.4 mg (9%) of a solid: ^{1}H NMR ($CDCl_3$) δ 3.65 (s, 3H), 5.36 (s, 2H), 6.88 (t, 1H, J = 1.5 Hz), 7.06 (m, 4H), 7.30−7.48 (m, 7H), 7.66 (dd, 2H, J = 8.1 Hz, J = 1.4 Hz); ^{13} CNMR ($CDCl_3$) δ 50.4, 55.3, 109.4, 113.4, 117.7, 120.5, 127.0, 127.9, 128.3, 129.0, 129.6, 130.1, 130.9, 134.3, 134.9, 137.4, 159.6, 160.6, 163.8, 166.0, 169.1; MS (ES+) 413 (M + 1). HRMS (ES+) *m*/*z* calcd for (M + H $C_{25}H_{21}N_2O_4$) 413.1500, found 413.1500.

1-iso-Propyl-2-(3-methoxy)phenyl-4-phenyl-6-oxo-1,6-dihydropyrimidine-5-carboxylic Acid (12{A,3,d}). LCMS analysis of the crude product showed a single product of the desired mass (rt = 4.27 min, 44% by ELSD) and a second product of lower mass (rt = 3.64 min, 55% by ELS, MS (ES+) 323), which was identified as **4**(**A**,**3**). Purification by silica chromatography of the desired product (first eluted compound) afforded 22.0 mg (30%) of a solid: ^{1}H NMR ($CDCl_3$) δ 1.65 (d, 6H, J = 6.6 Hz), 3.86 (s, 3H), 4.54 (septet, 1H, J = 6.6 Hz), 7.08 (m, 3H), 7.43 (m, 4H), 7.61 (m, 2H); ^{13} CNMR ($CDCl_3$) δ 19.6, 55.5, 56.4, 110.1, 113.5, 116.7, 119.7, 127.9, 129.4, 130.3, 130.6, 135.4, 137.5, 159.9, 160.4, 164.4, 166.7, 168.1; MS (ES+) 365 (M + 1, 100), 323 (85), 305 (68). HRMS (ES+) *m*/*z* calcd for (M + H $C_{21}H_{21}N_2O_4$) 365.1501, found 365.1509.

2-(3-Methoxy)Phenyl-4-phenyl-6-oxo-1,6-dihydropyrimidine-5-carboxylic Acid (4{A,3}). Collection of the second eluted compound from silica chromatography purification of pyrimidinone **12**{**A**,**3**,**c**} afforded a white solid corresponding to the primary amidine product **4**{**A**,**3**}: ^{1}H NMR (DMSO-d_6) δ 3.83 (s, 3H), 7.16 (dd, 1H, J = 8.2 Hz, J = 1.4 Hz), 7.50 (m, 4H), 7.77 (m, 4H), 13.3 (brs, 1H); ^{13} CNMR (DMSO-d_6) δ 55.4, 112.9, 117.5, 118.1, 120.5, 128.2, 128.4, 129.9, 130.1, 133.6, 137.3, 156.6, 159.1, 159.4, 162.0, 167.0; MS (ES+) 323 (M + 1, 100), 305 (59).

Library Synthesis. Preparation of 1,2,4-Trisubstituted-6-oxo-1,6-dihydropyrimidine-5-carboxylic Acids (12{A−H,1−3,a−d}). A parallel synthesis of 96 compounds was carried out from eight polymer bound methylene-substituted malonate esters **1**{**A**−**H**} and twelve amidines **10**{**1**−**12**}. A set of 12 reaction flasks was prepared containing 0.138 g (0.100 mmol) each of resin **3**{**A**}. Similar sets of 12 reaction flasks were prepared for resins **3**{B−H} such that each flask contained 0.100 mmole of the appropriate resin to give a total set of 96 reaction flasks. These reactions vessels were arranged in an 8 × 12 array for ease in reagent mapping with the resins in the appropriate row **A**−**H**. The vessels in each column **1**−**12** were treated with the appropriate amidine. For example, each vessel in column 1 was treated with 3 mL of a 0.33 M solution of *N*-(*n*-butyl)benzamidine **4**{**1**} in DMA (prepared from 2.12 g (12 mmol)

of **4**{**1**} in 24 mL of DMA). Vessels in columns 2 through 12 were each treated with 3 mL of a 0.33 M solution of the appropriate amindines **4**{**2**−**12**} in DMA, respectively. The vessels were capped, agitated and heated to 70 °C for 6 h. Using the STAR apparatus for resin washing, each resin was washed three times with DMF and subsequently treated with 3 mL of 0.4 M ceric ammonium nitrate in DMA for 2 h at rt. The resins were washed three times each with DMF, MeOH and CH_2Cl_2. The washing apparatus of the STAR block was replaced with a collection rack containing 96 tared vessels. Cleavage of the resins was achieved by treatment of each vessel with 1 mL of TFA/CH_2Cl_2 (1:1) for 30 min followed by two 1 mL washes with CH_2Cl_2. The combined filtrates were concd initially under a stream of N_2 and subsequently in vacuo to afford 96 vessels containing the final products.

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Supporting Information Available. Preparation of amidines **10**(**1**−**3**,**a**−**d**), calculation of theoretical loadings for resins, full characterization of pilot library **12**(**A**, **1**−**3**,**a**−**d**), and full 1D and 2D spectra of **12**(**C**,**1**,**b**) and **16**(**C**,**1**,**b**). This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) (a) Edwards, P. J. *IDrugs* **2006**, *9* (5), 347–355. (b) Marsh, I. *Nat. Rev. Drug Discovery* **2002**, *1* (11), 925.
(2) Hamper, B. C.; Gan, K. Z.; Owen, T. J. *Tetrahedron Lett.* **1999**, *40* (27), 4973–4976.
(3) For a general review, see (a) Kappe, C. O *Acc. Chem. Res.* **2000**, *33*, 879–888. For recent examples using solid phase synthesis, see (b) Matloobi, M.; Kappe, C. O. *J. Comb. Chem.* **2007**, *9*, 275. (c) Gross, G. A.; Wurziger, H.; Schober, A. *J. Comb. Chem.* **2006**, *8*, 153. (d) Lusch, M. J.; Tallarico, J. A. *Org, Lett.* **2004**, *6*, 3237. (e) Zhang, L.; Rana, T. M. *J. Comb. Chem.* **2004**, *6*, 457. (f) Perez, R.; Beryozkina, T.; Zbruyev, O. I.; Haas, W.; Kappe, C. O. *J. Comb. Chem.* **2002**, *4*, 501–510. (g) Valverde, M. G.; Dallinger, D.; Kappe, C. O. *SynLett* **2001**, *6*, 741–744. (h) Kappe, C. O. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 49–51. (I) Marzinzik, A. L.; Felder, E. R. *J. Org. Chem.* **1998**, *63*, 723–727. (j) Robinett, L. D.; Yager, K. M.; Phelan, J. C. *Book of Abstracts*, 211th ACS National Meeting, New Orleans, LA, March 24−28, 1996; American Chemical Society: Washington, DC, 1996;ORGN-122. (k) Wipf, P.; Cunningham, A. *Tetrahedron Lett.* **1995**, *36* (43), 7819–7822.
(4) (a) Brown, D. J.; Evans, R. F.; Cowden, W. B.; Fenn, M. D. *The Pyrimidines*; Taylor, E. C., Ed.; Wiley: New York, 1994. (b) Katritzky, A. R.; Rees, C. W., Eds. *Comprehensive Heterocyclic Chemistry*; Pergamon: 1984; Vol. 1. (c) Hobbs, J. B. Purine and Pyrimidine Targets. In *Comprehensive Medicinal Chemistry, Vol. 2*; Sammes, P. G., Ed; Pergamon: 1990; pp 299−332. (d) Ellingboe, J.; Alessi, T.; Millen, J.; Sredy, J.; King, A.; Prusiewicz, C.; Guzzo, F.; VanEngen, D.; Bagli, J. *J. Med. Chem.* **1990**, *33*, 2892–2899. (e) Hussain, S. M.; El-Barbary, A. A.; Mansour, S. A. J. *Heterocycl. Chem.* **1985**, *22*, 169–171.
(5) Morgans, D. J. C., Jr.; Knight, S. D.; Newlander, K. A.; Dhanak, D.; Zhou, H.-J.; Adams, N. D. *Chem. Abstr.* **2003**, *139*, 395942; PCT Int. Appl. WO 2003094839, 2003.
(6) Biediger, R. J.; Chen, Q.; Holland, G. W.; Kassir, J. M.; Li, W.; Market, R. V.; Scott, I. L.; Wu, C.; Decker, R. E.; Li, J. *Chem. Abstr.* **2002**, *136*, 369608; Eur. Pat. Appl. EP 1203766, 2002.
(7) (a) Osswald, M.; Dorsch, D.; Mederski, W.; Amendt, C.; Grell, M. *Chem. Abstr.* **2003**, *138*, 379204; PCT Int. Appl. WO 2003039539, 2003. (b) Osswald, M.; Mederski, W.; Dorsch, D.; Schmitges, C.; Wilm, C.; Christadler, M. *Chem. Abstr.* **1997**, *127*, 318978; Ger. Offen. DE 19612101, 1997.
(8) Hermecz, I.; Breining, T.; Vasvari-Debreczy, L.; Horvath, A.; Meszaros, Z.; Bitter, I.; DeVos, C.; Rodriguez, L. *J. Med. Chem.* **1983**, *26* (10), 1494–1499.
(9) McNulty, P. J.; Warner, H. L. *Chem. Abstr.* **1979**, *91*, 34092; U.S. Patent US 4147528, 1979.
(10) Veale, C. A.; Steelman, G. B.; Chow, M. M. *J. Org. Chem.* **1993**, *58* (16), 4490–4493.
(11) Taylor, E. C.; Zhou, P.; Tice, C. M.; Lidert, Z.; Roemmele, R. C. *Tetrahedron Lett.* **1997**, *38* (25), 4339–4342. Taylor, E. C.; Zhou, P.; Tice, C. M. *Tetrahedron Lett.* **1997**, *38* (25), 4343–4346.
(12) Ono, R.; Nagaoka, M. *Chem. Abstr.* **2006**, *145*, 249219; Jpn. Kokai Tokkyo Koho JP 2006213623, 2006.
(13) (a) Kuroita, T.; Sakamoto, H.; Igawa, H.; Sasaki, M.; Asano, K.; Maekawa, T. *Chem. Abstr.* **2008**, *149*, 10031; PCT Int. Appl. WO 2008062905, 2008. (b) Atwal, K. S.; Ahmed, S. Z.; Bird, J. E.; Delaney, C. L.; Dickinson, K. E. J.; Ferrara, F. N.; Hedberg, A.; Miller, A. V.; Moreland, S.; O'Reilly, B. C.; Schaeffer, T. R.; Waldron, T. L.; Weller, H. N. *J. Med. Chem.* **1992**, *35* (25), 4751–4763.
(14) Cho, H.; Ueda, M.; Ohnaka, Y.; Hayashimatsu, M. *Heterocycles* **1984**, *22* (9), 1959–1963.
(15) Lorente, A.; Garcia, N. J. L.; Fuentes, L.; Soto, J. L. *Synthesis* **1985**, (1), 86–89.
(16) (a) Sitte, A.; Paul, H. *Chem. Ber* **1969**, *102* (2), 615–22. (b) Ye, F.; Chen, B.; Huang, X. *Synthesis* **1989**, (4), 317–320. (c) Jeanneau-Nicolle, E.; Benoit-Guyod, M.; Leclerc, G. *Synth. Commun.* **1991**, *21* (14), 1443–1454.
(17) (a) Assy, M. G.; El-Bahaie, S.; Ibrahim, M. R.; Ibrahim, Y. A. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **1996**, *35B* (6), 598–601. (b) El-Bahaie, S.; Assy, M. G.; Kadry, A. *Collect. Czech. Chem. Commun.* **1990**, *55* (4), 1049–1054.
(18) De-Stevens, G.; Smolinsky, B.; Dorfman, L. *J. Org. Chem.* **1964**, *29* (5), 1115–1119.
(19) Kato, T.; Yamanaka, H.; Kawamata, J.; Shimomura, H. *Chem. Pharm. Bull.* **1969**, *17* (9), 1889–1895.
(20) (a) Roger, R.; Nelson, D. G. *Chem. Rev.* **1961**, *61*, 179. (b) Pinner, A.; Klein, *Chem. Ber.* **1877**, *10*, 1889. (c) Boyd, G. V. Recent Advances in the Synthesis of Amidines. In *The Chemistry of Amidines and Imidates*; Vol. 2; Patai, S., Rappoport, Z., Eds.; Wiley: New York, 1991; pp 339−366.
(21) Hamper, B. C.; Snyderman, D. M.; Owen, T. J.; Scates, A. M.; Owsley, D. C.; Kesselring, A. S.; Chott, R. C. *J. Comb. Chem* **1999**, *1* (2), 140–150.
(22) For the use of CAN as an oxidant for solid phase oxidation of dihydropyridines, see Gordeev, M. F.; Patel, D. V.; Wu, J.; Gordon, E. M. *Tetrahedron Lett.* **1996**, *37* (27), 4643–4646.
(23) Hamper, B. C.; Kolodziej, S. A.; Scates, A. M. *Tetrahedron Lett.* **1998**, *39* (15), 2047–2050.
(24) For recent examples of gel-phase ^{19}F NMR of solid-phase resins, see (a) Waller, F. K.; Spjut, S.; Bostroem, D.; Elofsson, M. *Org. Biomol. Chem.* **2007**, *5* (15), 2464–2471. (b) Svensson, A.; Fex, T.; Kihlberg, J. *Tetrahedron Lett.* **1996**, *37*, 7649–7652. (c) Shapiro, M. J.; Kumaravel, G.; Petter, R. C.; Beveridge, R. *Tetrahedron Lett.* **1996**, *37*, 4671–4674.
(25) Crouch, R.; Boyer, R. D.; Johnson, R.; Krishnamurthy, K. *Magn. Reson. Chem.* **2004**, *42* (3), 301–307.
(26) Hamper, B. C. *Chem. Abstr* **1998**, *128*, 142450; U.S. Patent 5792430, August 11, 1998.
(27) ACD software is available from Advanced Chemical Development: www.acdlabs.com.

(28) Hamper, B. C.; Jerome, K. D.; Yalamanchili, G.; Walker, D. M.; Chott, R. C.; Mischke, D. A. *Biotechnol. Bioeng. (Comb. Chem.)* **2000**, *71* (1), 28–37.
(29) Hamper, B. C.; Kolodziej, S. A.; Scates, A. M.; Smith, R. G.; Cortez, E. *J. Org. Chem.* **1998**, *63*, 708–718.
(30) Hamper, B. C.; Kesselring, A. S. , Solid Phase Synthesis of Di-102-peptoids from Acrylate Resin: *N*-Acetyl-*N*-benzyl-β-alaninyl-*N*-benzyl-β-alanine. In *Solid-Phase Organic Synthesis*, Vol. 1; Czarnik, A. W., Ed.; John Wiley & Sons: New York, 2001; pp 55−72.
(31) Shilcrat, S. C.; Mokhallalati, M. K.; Fortunak, J. M. D.; Pridgen, L. N. *J. Org. Chem.* **1997**, *62* (24), 8449–8454.
(32) Ferroni, R.; Simoni, D.; Binato, G.; Nastruzzi, C.; Manfredini, S.; Orlandini, P.; Feriotto, G.; Gambari, R. *Farmaco* **1991**, *46* (11), 1311–1322.

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