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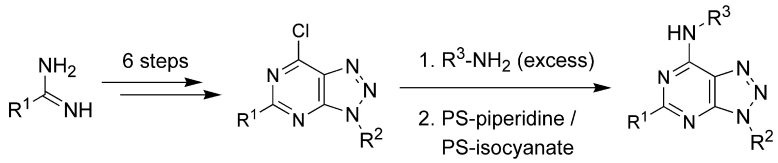

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Solution-Phase Synthesis of a Library of 3,5,7-Trisubstituted 3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidines

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An efficient solution-phase parallel synthesis of a library of 3,5,7-trisubstituted [1,2,3]triazolo[4,5-*d*]-pyrimidines is described. Monosubstituted amidines may be converted to 2-substituted 5-amino-4,6-dihydroxypyrimidines in four steps. Treatment with a primary amine followed by cyclization yields the 7-chloro-3,5-disubstituted [1,2,3]triazolo[4,5-*d*]pyrimidines as penultimate intermediates. Final nucleophilic substitution of the 7-chloro group with an excess of a primary or secondary amine, a hydrazine or a *O*-alkylhydroxylamine proceeds efficiently. Scavenging of the excess amine with a resin-bound isocyanate in the presence of resin-bound piperidine as a base affords the desired 3,5,7-trisubstituted [1,2,3]triazolo-[4,5-*d*]pyrimidines in good yields and purities.

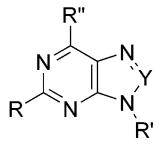
Introduction

In recent years, combinatorial chemistry has emerged as a major tool for accelerating drug discovery through its impact on both lead generation and lead optimization strategies,[1] and both solid- and solution-phase parallel synthetic approaches have been adopted for this purpose.[1,2] In particular, solution-phase strategies have become increasingly popular, since traditional analytical techniques such as TLC, HPLC (ELSD), and NMR can be readily utilized to monitor reactions.[2] Moreover, reactions can sometimes be carried out in a wider variety of solvents and under more stringent conditions.[2]

Owing to the important role played by naturally occurring purines in several biochemical and physiological pathways, purine derivatives and their various isosteric analogues have been of interest over the years for a variety of biological targets and therapeutic indications. More recently, purine derivatives, such as olomoucine, purvalanol, roscovitine, and related analogues, have been identified as potent inhibitors of kinases, while other purine derivatives, such as myoseverin, have been identified as potent inhibitors of microtubule assembly processes.[3] In view of these findings, purines and related structural classes may be privileged scaffolds for drug discovery and high throughput screening. 3,5,7-Trisubstituted [1,2,3]triazolo[4,5-*d*]pyrimidines, which can be considered as 8-aza analogues of similarly substituted purines (Scheme 1), are one such example.[4] We have developed a facile and rapid solution-phase parallel approach for a diverse library of these compounds.

[1,2,3]Triazolo[4,5-*d*]pyrimidines can in principle be synthesized (Scheme 2) by either a triazole-first approach (assembly of a suitably substituted triazole followed by cyclization) or the pyrimidine-first approach (assembly of a suitable substituted pyrimidine followed by cyclization). Both approaches have been described in the literature, with the triazole-first approach particularly described in the published literature[5] and the pyrimidine-first approach described in the patent literature.[6] However, there has not been any published or patented approach to readily generate libraries of compounds in this series using either of the two approaches described above. We therefore set out to develop a general method to prepare a library of compounds using the pyrimidine-first approach.

Scheme 1



Y = CH; Purines

Y = N; [1,2,3]Triazolo[4,5*d*]pyrimidines

Results and Discussion

The synthetic scheme for the pyrimidine-first approach is depicted in Scheme 3. The first point of diversity (R^1) is introduced using an amidine. A N-unsubstituted amidine **(1)** is condensed with diethylmalonate **(2)** in the presence of sodium ethoxide to obtain the 2-substituted 4,6-dihydroxypyrimidine **(3)**. Controlled nitration of **(3)** with fuming nitric acid gives the corresponding 5-nitro analogue **(4)**. Chlorination with phosphorus oxychloride results in complete conversion of the dihydroxypyrimidines to the corresponding dichloropyrimidines **(5)** in good yields. The dichloronitropyrimidines are then reduced to the corresponding dichloroaminopyrimidines **(6)** with iron and acetic acid. The mild conditions for this reduction are necessary to prevent reductive dechlorination of one or both of the chlorines on the pyrimidine ring. At this stage, the second point of diversity (R^2) is introduced into the molecule. Thus, 2-substituted 5-amino-4,6-dichloro-pyrimidines are alkylated by

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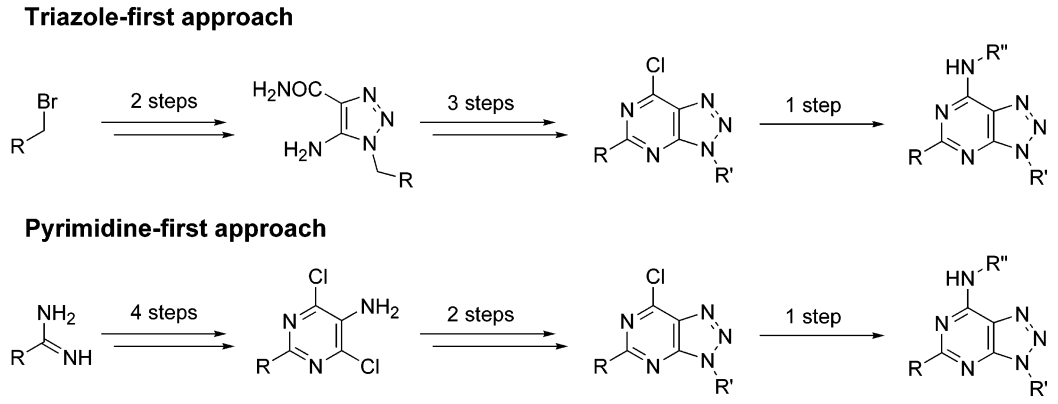
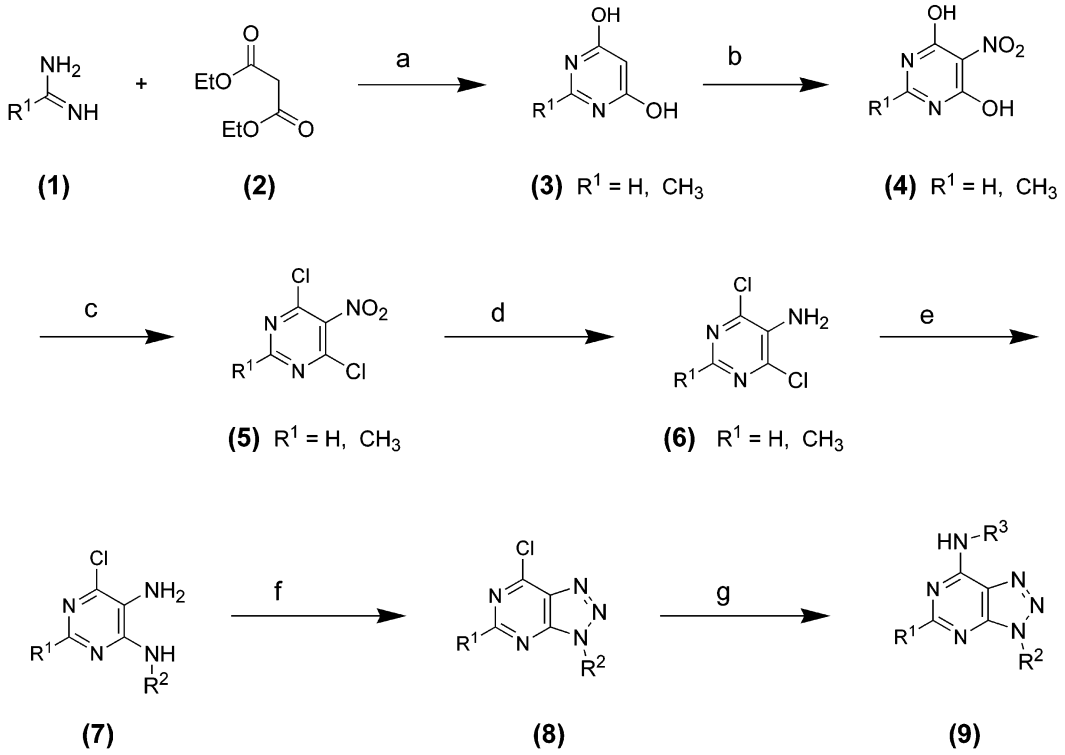
Scheme 2



Scheme 3[a]

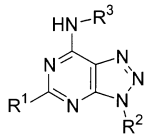


[a] (a) EtONa/EtOH; (b) HNO_3; (c) $POCl_3$, $PhN(Et)_2$; (d) Fe/AcOH; (e) R^2-NH_2; (f) $NaNO_2$/AcOH/DCM; (g) R^3-NH_2(excess); PS-piperidine/PS-isocyanate.

heating with substituted primary amines, including aromatic (substituted anilines) and aliphatic amines (benzylamine) for 24−48 h at high temperature. This predominantly results in monoalkylation of the symmetric molecules **(7)**. Some dialkylated product formation occurs as well, but chromatographic purification at this stage is rarely required. The monoalkylated product is then readily cyclized with sodium nitrite using mild acidic conditions to generate the triazolopyrimidines **(8)** in good yields. Purification by flash chromatography is necessary at this stage because it is the penultimate stage in the synthesis. The cyclized products are relatively nonpolar and are readily separated from the more polar impurities using parallel silica gel flash chromatography. Once all the intermediates **(8**) are obtained, the final point of diversity (R^3) is introduced in the molecules via the nucleophilic displacement of the last remaining chlorine with a variety of amines (primary and secondary amines, aromatic amines, hydrazines, and hydroxylamines) to yield the desired 3,5,7-trisubstituted triazolopyrimidines **(9)**. This step can also be considered as a "diversity explosion" step, because each intermediate **(8)** can be treated with a diverse set of amines, hydrazines, or *O*-alkylhydroxylamines at this stage to generate a fairly large library of diverse compounds. Purification of the final compounds is unnecessary, because the reactions are driven to completion by use of an excess of the amines followed by scavenging of the excess amine with a suitable solid-phase scavenger (PS-isocyanate) in the presence of a polymer-bound base (PS-piperidine). Parallel filtration and washing of the resins followed by parallel concentration of the filtrates gives the desired 3,5,7-trisubstituted 3*H*-[1,2,3]-triazolo[4,5-*d*]pyrimidines in good yields and purities (Table 1).

In general, both primary amines and secondary aliphatic amines appear to give good yields (57−100%) and purities (63−100%). However, a less nucleophilic aromatic amine, such as aniline, under the same conditions does not always

Table 1. MS and HPLC (ELSD) Purities of Library Compounds Synthesized



entry no.	cmpd no.	R^1	R^2	R^3 amine used	MW	mass found	purity (%)
1		H	benzyl	benzyl	316	317	94.6
2		H	benzyl	ethanolamine	270	271	98.5
3		H	benzyl	aniline	302	303	93.2
4		H	benzyl	cyclohexylamine	308	309	99.6
5		H	benzyl	phenylhydrazine	317	318	95
6		H	benzyl	benzyloxyamine	332	333	99.4
7		H	benzyl	Boc-piperazine	395	396	98.9
8		H	benzyl	homoveratrylamine	390	391	87.1
9		H	phenyl	benzyl	302	303	98.7
10		H	phenyl	ethanolamine	256	257	85.9
11		H	phenyl	aniline	288	289	94.5
12		H	phenyl	cyclohexylamine	294	295	99.2
13		H	phenyl	phenylhydrazine	303	304	64
14		H	phenyl	benzyloxyamine	318	319	99.6
15		H	phenyl	Boc-piperazine	381	382	98.6
16		H	phenyl	homoveratrylamine	376	377	98.8
17		H	*p*-methoxyphenyl	benzyl	332	333	96
18		H	*p*-methoxyphenyl	ethanolamine	286	287	97
19		H	*p*-methoxyphenyl	aniline	318	319	85.8
20		H	*p*-methoxyphenyl	cyclohexylamine	324	325	97.3
21		H	*p*-methoxyphenyl	phenylhydrazine	333	334	68
22		H	*p*-methoxyphenyl	benzyloxyamine	348	349	93.1
23		H	*p*-methoxyphenyl	Boc-piperazine	411	412	96.1
24		H	*p*-methoxyphenyl	homoveratrylamine	406	407	95
25		H	*p*-chlorophenyl	benzyl	337	338	95
26		H	*p*-chlorophenyl	ethanolamine	291	292	96.1
27		H	*p*-chlorophenyl	aniline	323	324	87
28		H	*p*-chlorophenyl	cyclohexylamine	329	330	98.8
29		H	*p*-chlorophenyl	phenylhydrazine	338	339	90.9
30		H	*p*-chlorophenyl	benzyloxyamine	353	354	95.7
31		H	*p*-chlorophenyl	Boc-piperazine	416	417	95.5
32		H	*p*-chlorophenyl	homoveratrylamine	411	412	98.5
33	**9i**	H	*p*-tolyl	benzyl	316	317	100
34	**9j**	H	*p*-tolyl	ethanolamine	270	271	99.1
35	**9k**	H	*p*-tolyl	aniline	302	303	99.2
36	**9l**	H	*p*-tolyl	cyclohexylamine	308	309	100
37	**9m**	H	*p*-tolyl	phenylhydrazine	317	318	92.8
38	**9n**	H	*p*-tolyl	benzyloxyamine	332	333	100
39	**9o**	H	*p*-tolyl	Boc-piperazine	395	396	100
40	**9p**	H	*p*-tolyl	homoveratrylamine	390	391	99.8
41		methyl	benzyl	benzyl	330	331	94
42	**9q**	methyl	benzyl	ethanolamine	284	285	96.8
43		methyl	benzyl	aniline	316	317	89.9
44		methyl	benzyl	cyclohexylamine	322	323	99.5
45		methyl	benzyl	phenylhydrazine	331	332	69
46		methyl	benzyl	benzyloxyamine	346	347	99
47		methyl	benzyl	Boc-piperazine	409	410	98.4
48		methyl	benzyl	homoveratrylamine	404	405	90
49		methyl	*p*-chlorophenyl	benzyl	351	352	100
50		methyl	*p*-chlorophenyl	ethanolamine	305	306	99
51	**9t**	methyl	*p*-chlorophenyl	aniline	336	337	99.6
52		methyl	*p*-chlorophenyl	cyclohexylamine	343	344	100
53		methyl	*p*-chlorophenyl	phenylhydrazine	352	353	93
54		methyl	*p*-chlorophenyl	benzyloxyamine	367	368	100
55		methyl	*p*-chlorophenyl	Boc-piperazine	430	431	100
56		methyl	*p*-chlorophenyl	homoveratrylamine	425	426	100
57		methyl	*p*-methoxyphenyl	benzyl	346	347	96.1
58		methyl	*p*-methoxyphenyl	ethanolamine	300	301	76
59		methyl	*p*-methoxyphenyl	aniline	332	333	86
60		methyl	*p*-methoxyphenyl	cyclohexylamine	338	339	99.5
61		methyl	*p*-methoxyphenyl	phenylhydrazine	347	348	78
62		methyl	*p*-methoxyphenyl	benzyloxyamine	362	363	98.4
63		methyl	*p*-methoxyphenyl	Boc-piperazine	425	426	97.4
64		methyl	*p*-methoxyphenyl	homoveratrylamine	420	421	93.7

Table 1. (Continued)

entry no.	cmpd no.	R^1	R^2	R^3 amine used	MW	mass found	purity (%)
65	**9a**	methyl	phenyl	benzyl	316	317	100
66	**9b**	methyl	phenyl	ethanolamine	270	271	87.6
67	**9c**	methyl	phenyl	aniline	302	303	98.9
68	**9d**	methyl	phenyl	cyclohexylamine	308	309	100
69	**9e**	methyl	phenyl	phenylhydrazine	317	318	89.9
70	**9f**	methyl	phenyl	benzyloxyamine	332	333	100
71	**9g**	methyl	phenyl	Boc-piperazine	395	396	100
72	**9h**	methyl	phenyl	homoveratrylamine	390	391	96.4
73	**9r**	methyl	*p*-tolyl	benzyl	330	331	100
74		methyl	*p*-tolyl	ethanolamine	284	285	66
75		methyl	*p*-tolyl	aniline	316	317	94.6
76		methyl	*p*-tolyl	cyclohexylamine	322	323	96.6
77	**9s**	methyl	*p*-tolyl	phenylhydrazine	331	332	87.2
78		methyl	*p*-tolyl	benzyloxyamine	346	347	94.5
79		methyl	*p*-tolyl	Boc-piperazine	409	410	100
80		methyl	*p*-tolyl	homoveratrylamine	404	405	95.3

yield as high a purity (see, for example, entries 19, 27, 43, and 59 in Table 1, which show <90% purities whereas entries 3, 11, 35, 51, 67, and 75 show >90% purities). The same is true of a hydrazine, such as phenylhydrazine which tends to give less than desirable purities in several cases (see, for example, entries 13, 21, 45, 61, 69, and 77 which show <90% purities). The lower purity observed from phenylhydrazine is probably a result of the lower stabilities of the products, since phenylhydrazine itself, as expected, appears to be a strong nucleophile, and product formation is quite rapid (reactions were monitored by TLC). This lower purity is particularly evident from the ^{1}H NMR spectra of the products (entries 37, 69, and 77). An *O*-alkylhydroxylamine, such as benzyloxyamine, on the other hand, appears to be quite reactive and gives excellent purities and yields (for example, entries 6, 14, 22, 30, 38, 46, 54, 62, 70, and 78 show substantially >90% purities). Finally, the scope of this methodology extends to amines containing an unprotected hydroxyl group, as well, although the purities may be somewhat less than desired. Thus, ethanolamine with an unprotected hydroxyl group gives only moderately good purities in several instances (for example, entries 10, 58, 66, and 74 show <90 % purities), probably owing to undesired side-reactions at the unprotected hydroxyl group. In general, the yields and purities of the products appear to be quite independent of the structure of the intermediates (**8**). Thus, the nature of the R^1 substituent does not appear to significantly influence the course of the final nucleophilic substitutions of intermediates **(8)** with the various amines (for example, entries 1−40 for R^1 = H versus entries 41−80 for R^1 = CH_3; the purities for these two sets of compounds are all quite similar). The same appears to be true where the nature of the R^2 substituent is concerned (for example, entries 1, 9, 17, 25, and 33 for R^1 = H and R^3 = benzyl and entries 41, 49, 57, 65, and 73 for R^1 = CH_3 and R^3 = benzyl, in which again the purities for these two sets of compounds are all quite similar).

Conclusion

In conclusion, we have successfully attempted the generation of a small library of 2 × 5 × 8 = 80 [1,2,3]triazolo-[4,5-*d*]pyrimidines from a set of commercially available amidines (2), primary amines (5), and primary and secondary amines, hydrazines, and *O*-alkylhydroxylamines (8) in good yields and purities. Our present results illustrate the feasibility of this method to generate a considerably larger and more diverse library of 3,5,7-trisubstituted 3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidines from such sets of commercially available "building blocks".

Experimental Section

All starting materials and solvents were purchased from Aldrich Chemical Co. (Milwaukee, WI) and were used as such without any further purification. Resins (PS-isocyanate and PS-piperidine) were purchased from Calbiochem (Novabiochem, San Diego, CA). ^{1}H NMR data was obtained using a 300-MHz Varian VXR-300S NMR spectrometer with TMS as the internal standard. Mass spectra and HPLC (ELSD) data were recorded on a Finnigan AQA HPLC (ELSD) instrument (ThermoQuest Corporation, CA) with SEDEX 75 ELS detection using a PrincetonSPHER HTS C18, 5-μm, 60-Å, 3 × 50 mm column (Princeton Chromatography, Inc.). Each HPLC (ELSD) run was carried out using a linear gradient of 25−100% CH_3CN/H_2O (0.1% TFA) in 2.4 min, and the retention time (R_t) for the expected (major) product was recorded. 4,6-Dihydroxypyrimidine **(3a)** and 4,6-dihydroxy-2-methylpyrimidine **(3b)** were prepared according to published methods from formamidine and acetamidine, respectively.[7] 4,6-Dihydroxy-5-nitropyrimidine **(4a)** was also prepared according to a published method from 4,6-dihydroxypyrimidine **(3a)**.[7]

4,6-Dihydroxy-2-methyl-5-nitropyrimidine (4b). 4,6-Dihydroxy-2-methylpyrimidine (10 g, 79.2 mmol) was added slowly in portions to 20 mL of 90% nitric acid while stirring at 0 °C. The mixture was stirred at 0 °C for 1 h and then at r.t. for 1 h. It was poured onto crushed ice, and the resulting precipitate was collected by filtration, washed thoroughly with water, and dried in vacuo to yield 12.1 g of a light-pink solid (89%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.3 (s, 3H). MS: 195 (M + 1 + Na). HPLC (ELSD) purity: 100%.

4,6-Dichloro-5-nitropyrimidine (5a). 4,6-Dihydroxy-5-nitropyrimidine (1.57 g, 10 mmol) and diethylaniline (2 mL, 20 mmol) were mixed in $POCl_3$ (10 mL), and the mixture was stirred under reflux for 2.5 h. The suspension immediately went into solution when refluxing started. The

mixture was poured on ice and allowed to stand with occasional vigorous shaking. The tan precipitate was collected by filtration, washed well with water, and dried in vacuo to yield 1.31 g (70%) of the product as a tan solid. TLC showed a major product with minor impurities but complete absence of the starting material. The crude product was used as such for the next step. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.85 (s, 1H). MS: 195 (M + 1).

4,6-Dichloro-2-methyl-5-nitropyrimidine (5b). This was prepared by a procedure similar to that for **5a**. Yield: 8.1 g (56%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.7 (s, 3H). MS: 209 (M + 1). HPLC (ELSD) purity: 97%.

5-Amino-4,6-dichloropyrimidine (6a). 4,6-Dichloro-5-nitropyrimidine (1.31 g, 7 mmol) was dissolved in a mixture of glacial acetic acid (26 mL) and methanol (12 mL). Iron powder (1.4 g) was added to it in portions. The mixture was then stirred at 60−65°C for 2 h, cooled to r.t., and filtered. The filtrate was concentrated in vacuo. The residue was extracted with DCM, and the organic extract was washed with 1 N NaOH, water, and brine and dried over anhydrous $MgSO_4$. It was then filtered and concentrated in vacuo to a tan solid. Purification by flash chromatography (eluting with 1% MeOH in DCM) yielded the pure product as a off-white solid, 0.7 g (64%). MS: 164 (M + 1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.2 (s, 1H).

5-Amino-4,6-dichloro-2-methylpyrimidine (6b). This was prepared by a procedure similar to that for **6a**. Yield: 4.5 g (65%). MS: 178 (M + 1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.6 (s, 1H).

General Procedure for the Preparation of 6-Chloro-N^4-pyrimidinyl-4,5-diamines (7). 5-Amino-4,6-dichloropyrimidine (4.92 or 5.5 mmols) and the appropriate amine (4.92 or 5.5 mmol; 1 equiv) were dissolved in ethoxyethanol (10 mL), and the mixture was stirred under reflux for 24−48 h. TLC showed complete consumption of starting material. The mixture was concentrated in vacuo, diluted with water, and extracted with DCM. The DCM layer was washed with water and brine and dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to a dark oil. Purification by flash chromatography (elution with DCM followed by 0.5−1% MeOH in DCM) yielded the pure products.

6-Chloro-N^4-benzylpyrimidinyl-4,5-diamine (7a). Yield: 0.870 g (68%). MS: 235 (M + 1). HPLC (ELSD): 99%.

6-Chloro-N^4-phenylpyrimidinyl-4,5-diamine (7b). Yield: 0.76 g (64%). MS: 221 (M + 1). HPLC (ELSD): 88%.

6-Chloro-N^4-(*p*-methoxyphenyl)pyrimidinyl-4,5-diamine (7c). Yield: 0.91 g (66%). MS: 251 (M + 1). HPLC (ELSD): 99%.

6-Chloro-N^4-(*p*-chlorophenyl)-pyrimidinyl-4,5-diamine (7d). Yield: 0.5 g (36%). MS: 255 (M + 1). HPLC (ELSD): 92%.

6-Chloro-N^4-*p*-tolylpyrimidinyl-4,5-diamine (7e). Yield: 0.8 g (85%). MS: 235 (M + 1). HPLC (ELSD): 97%.

6-Chloro-2-methyl-N^4-benzylpyrimidinyl-4,5-diamine (7f). Yield: 0.93 g (76%). MS: 249 (M + 1). HPLC (ELSD): 94%.

6-Chloro-2-methyl-N^4-phenylpyrimidinyl-4,5-diamine (7 g). Yield: 0.66 g (57%). MS: 235 (M + 1). HPLC (ELSD): 97%.

6-Chloro-2-methyl-N^4-(*p*-methoxyphenyl)-pyrimidinyl-4,5-diamine (7h). Yield: 1.0 g (77%). MS: 265 (M + 1). HPLC (ELSD): 85%.

6-Chloro-2-methyl-N^4-(*p*-chlorophenyl)-pyrimidinyl-4,5-diamine (7i). Yield: 0.63 g (48%). MS: 270 (M + 1). HPLC (ELSD): 84%.

6-Chloro-2-methyl-N^4-*p*-tolylpyrimidinyl-4,5-diamine (7j). Yield: 0.81 g (66%). MS: 249 (M + 1). HPLC (ELSD): 81%.

General Procedure for the Preparation of 7-Chloro-3-substituted 3*H*-[1,2,3]Triazolo[4,5-*d*]pyrimidines (8). 6-Chloro-N^4-substituted pyrimidinyl-4,5-diamine (1.95−3.78 mmol; 1 equiv) was dissolved in a mixture of DCM (12.5 mL) and 50% aqueous acetic acid (12.5 mL). Sodium nitrite (1.1 equiv) was added to the above stirred solution at r.t. The mixture was stirred at r.t. for 30 min. It was then separated, and the DCM layer was drawn off, washed with water and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to a brown solid. Purification by flash chromatography (eluting with DCM) yielded the pure products as yellow solids.

7-Chloro-3-benzyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine (8a). Yield: 0.9 g (70%). MS: 246 (M + 1). HPLC (ELSD): 100%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.1 (s, 1H), 7.6 (m, 5H), 6.0 (s, 2H).

7-Chloro-3-phenyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine (8b). Yield: 0.89 g (54%). MS: 232 (M + 1). HPLC (ELSD): 100%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.2 (s, 1H), 8.15 (d, 2H), 7.7 (t, 2H), 7.6 (t, 1H).

7-Chloro-3-(*p*-methoxyphenyl)-3*H*-[1,2,3]triazolo[4,5-*d*]-pyrimidine (8c). Yield: 0.92 g (98%). MS: 262 (M + 1). HPLC (ELSD): 98%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.15 (s, 1H), 8.0 (d, 2H), 7.25 (d, 2H), 3.85 (s, 3H).

7-Chloro-3-(*p*-chlorophenyl)-3*H*-[1,2,3]triazolo[4,5-*d*]-pyrimidine (8d). Yield: 0.6 g (39%). MS: 266 (M + 1). HPLC (ELSD): 100%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.2 (s, 1H), 8.2 (d, 2H), 7.8 (d, 2H).

7-Chloro-3-*p*-tolyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine (8e). Yield: 0.54 g (74%). MS: 246 (M + 1). HPLC (ELSD): 99%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.0 (s, 1H), 8.05 (d, 2H), 7.4 (t, 2H), 2.45 (s, 3H).

7-Chloro-5-methyl-3-benzyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine (8f). Yield: 0.63 g (65%). MS: 260 (M + 1). HPLC (ELSD): 100%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45 (m, 2H), 7.35 (m, 3H), 5.8 (s, 2H), 2.85 (s, 3H).

7-Chloro-5-methyl-3-phenyl-3*H*-[1,2,3]triazolo[4,5-*d*]-pyrimidine (8 g). Yield: 0.13 g (75%). MS: 246 (M + 1). HPLC (ELSD): 100% purity. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.2 (d, 2H), 7.6 (m, 2H), 7.5 (m, 1H), 2.9 (s, 3H).

7-Chloro-5-methyl-3-(*p*-methoxyphenyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine (8h). Yield: 0.51 g (49%). MS: 276 (M + 1). HPLC (ELSD): 100%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.05 (d, 2H), 7.1 (d, 2H), 3.9 (s, 3H), 2.9 (s, 3H).

7-Chloro-5-methyl-3-(*p*-chlorophenyl)-3*H*-[1,2,3]triazolo-[4,5-*d*]pyrimidine (8i). Yield: 0.49 g (72%). MS: 280 (M + 1). HPLC (ELSD): 95%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.2 (d, 2H), 7.8 (d, 2H), 2.8 (s, 3H).

7-Chloro-5-methyl-3-*p*-tolyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine (8j). Yield: 0.42 g (50%). MS: 260 (M + 1). HPLC

(ELSD): 100%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.05 (d, 2H), 7.4 (d, 2H), 2.9 (s, 3H), 2.45 (s, 3H).

General Procedure for the Preparation of 3,5,7-Trisubstituted 3*H*-[1,2,3]Triazolo[4,5-*d*]pyrimidines (9). 7-Chloro-3-substituted 3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine (0.05 mmol) was dissolved in anhydrous THF (3 mL) in a 2-dram glass vial. A solution of the appropriate amine (0.15 mmol; 3 equiv) in anhydrous THF (1 mL) was added. The mixture was stirred and heated at 60° C for 3 h, then cooled to r.t., and polystyrene−piperidine (0.2 mmol) and polystyrene−isocyanate (0.2 mmol) were added. The mixture was then stirred at r.t. overnight filtered using a fritted polypropylene tube, and the filtrate was collected. The resin in the fritted polypropylene tube was washed with THF and DCM, and the combined filtrate and washings were concentrated in vacuo to yield the product. A library of 80 compounds was run in parallel in this fashion. The products were analytically characterized by HPLC (ELSD) with ELS detection. The purities of all 80 compounds are listed in Table 1. In addition, the yields of at least 20 randomly selected compounds were determined by measuring their accurate weights after high-vacuum drying, and these 20 compounds were also additionally characterized by ^{1}H NMR. The yields of these 20 compounds are listed below, together with their MS, HPLC (ELSD), and ^{1}H NMR data.

Benzyl-(5-methyl-3-phenyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7-yl)-amine (9a). Yield: 88%. MS: 317 (M + 1). HPLC (ELSD): 100% (R_t = 1.57 min). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.1 (d, 2H), 7.5 (m, 2H), 7.4−7.2 (m, 6H), 4.85 (d, 2H), 2.6 (s, 3H).

2-(5-Methyl-3-phenyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7-ylamino)-ethanol (9b). Yield: 76%. MS: 271 (M + 1). HPLC (ELSD): 87.6% (R_t = 0.73 min). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.1 (d, 2H), 7.35−7.6 (m, 3H), 3.8−4.0 (m, 4H), 2.6 (s, 3H).

(5-Methyl-3-phenyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7-yl)-phenyl-amine (9c). Yield: 97%, MS: 303 (M + 1), HPLC (ELSD): 98.9% (R_t = 1.73 min), ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.15 (d, 2H), 7.8 (d, 2H), 7.5 (d, 2H), 7.4 (m, 4H), 2.7 (s, 3H).

Cyclohexyl-(5-methyl-3-phenyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7-yl)-amine (9d). Yield: 67%. MS: 309 (M + 1). HPLC (ELSD): 100% (R_t = 1.55 min). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.2 (m, 2H), 7.4−7.6 (m, 3H), 2.6 (s, 3H), 2.2 (m, 2H), 1.3−1.9 (m, 9H).

***N*-(5-Methyl-3-phenyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7-yl)-*N*-phenylhydrazine (9e).** Yield: 100%. MS: 318 (M + 1). HPLC (ELSD): 89.9% (R_t = 1.25 min). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.1 (m, 1H), 7.65−7.4 (m, 3H), 7.3−7.2 (m, 4H), 6.95−7.05 (m, 2H), 2.7 (s, 2H).

***O*-Benzyl-*N*-(5-methyl-3-phenyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7-yl)-hydroxylamine (9f).** Yield 100%. MS: 333 (M + 1). HPLC (ELSD): 100% (R_t = 1.51 min). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.0 (d, 2H), 7.3−7.6 (m, 8H), 5.2 (s, 2H), 2.4 (s, 3H).

4-(5-Methyl-3-phenyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7-yl)-piperazine-1-carboxylic Acid *tert*-Butyl Ester (9 g). Yield: 100%. MS: 396 (M + 1). HPLC (ELSD): 100% (R_t = 2.02 min). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.2 (d, 2H), 7.6 (t, 2H), 7.45 (m, 1H), 4.65 (m, 2H), 4.1 (m, 2H), 3.6 (m, 4H), 2.6 (s, 3H), 1.5 (s, 9H).

[2-(3,4-Dimethoxyphenyl)-ethyl]-(5-methyl-3-phenyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7-yl)amine (9h). Yield: 100%. MS: 391 (M + 1). HPLC (ELSD): 96.4% (R_t = 1.40 min). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.2 (m, 2H), 7.6 (m, 2H), 7.4 (m, 1H), 6.9−6.7 (m, 3H), 3.95 (m, 2H), 3.85 (2s, 6H), 2.9−3.1 (m, 2H), 2.6 (s, 3H).

Benzyl-(3-*p*-tolyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7-yl)amine (9i). Yield: 100%. MS: 317 (M + 1). HPLC (ELSD): 100% purity (R_t = 1.66 min). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.6 (s, 1H), 8.0 (d, 2H), 7.3−7.5 (m, 7H), 4.95 (d, 2H), 2.4 (s, 3H).

2-(3-*p*-tolyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7-ylamino)ethanol (9j). Yield: 100%. MS: 271 (M + 1). HPLC (ELSD): 99.1% (R_t = 0.83 min). ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.0 (s, 1H), 8.5 (s, 1H), 8.0 (d, 2H), 7.45 (d, 2H), 4.85 (s, 1H), 3.65 (m, 4H), 2.4 (s, 3H).

(3-*p*-Tolyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7-yl)-phenylamine (9k). Yield: 100%. MS: 303 (M + 1). HPLC (ELSD): 99.2% (R_t = 1.71 min). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.7 (s, 1H), 8.05 (d, 2H), 7.85 (d, 2H), 7.4−7.5 (m, 4H), 7.2 (m, 1H), 2.45 (s, 3H).

Cyclohexyl-(3-*p*-tolyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7-yl)amine (9l). Yield: 100%. MS: 309 (M + 1). HPLC (ELSD): 100% (R_t = 1.67 min). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.5 (s, 1H), 8.0 (m, 2H), 7.4 (d, 2H), 2.45 (s, 3H), 2.2 (m, 2H), 1.3−1.9 (m, 9H).

***N*-(3-*p*-tolyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7-yl)-*N*-phenylhydrazine (9m).** Yield: 100%. MS: 318 (M + 1). HPLC (ELSD): 92.8% (R_t = 1.34 min). ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.5 (s, 1H), 8.0 (m, 2H), 7.6−7.4 (m, 3H), 7.2 (t, 2H), 6.8 (d, 2H), 2.4 (s, 3H).

***O*-Benzyl-*N*-(3-*p*-tolyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7-yl)hydroxylamine (9n).** Yield: 100%. MS: 333 (M + 1); HPLC (ELSD): 100% (R_t = 1.52 min); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.8 (t, 3H), 7.3−7.5 (m, 7H), 5.15 (s, 2H), 2.4 (s, 3H).

4-(3-*p*-tolyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7-yl)-piperazine-1-carboxylic Acid *tert*-Butyl Ester (9o). Yield: 57%. MS: 396 (M + 1). HPLC (ELSD): 100% (R_t = 1.98 min). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.5 (s, 1H), 8.0 (d, 2H), 7.4 (d, 2H), 4.7 (m, 2H), 4.1 (m, 2H), 3.6 (m, 4H), 2.4 (s, 3H), 1.5 (s, 9H).

[2-(3,4-Dimethoxy-phenyl)-ethyl]-(3-*p*-tolyl-3*H*-[1,2,3]-triazolo[4,5-*d*]pyrimidin-7-yl)amine (9p). Yield: 97%. MS: 391 (M + 1). HPLC (ELSD): 99.8% (R_t = 1.54 min). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.55 (s, 1H), 8.0 (m, 2H), 7.4 (m, 2H), 6.7−6.9 (m, 3H), 4.0 (m, 2H), 3.85 (2s, 6H), 3.0 (m, 2H), 2.45 (s, 3H).

2-(3-Benzyl-5-methyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7-ylamino)ethanol (9q). Yield: 100%. MS: 285 (M + 1). HPLC (ELSD): 96.8% (R_t = 0.71 min). ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.7 (s, 1H), 7.2−7.4 (m, 5H), 5.7 (s, 2H), 4.8 (s, 1H), 3.6 (m, 4H), 2.5 (s, 3H).

Benzyl-(5-methyl-3-*p*-tolyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7-yl)amine (9r). Yield: 100%. MS: 331 (M + 1). HPLC (ELSD): 100% (R_t = 1.64 min). ^{1}H NMR (300 MHz,

$CDCl_3$): δ 8.0 (d, 2H), 7.3−7.5 (m, 7H), 4.9 (d, 2H), 2.65 (s, 3H), 2.4 (s, 3H).

***N*-(5-Methyl-3-*p*-tolyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7-yl)-*N*-phenylhydrazine (9s).** Yield: 100%. MS: 332 (M + 1). HPLC (ELSD): 87.2% (R_t = 1.35 min). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.0−7.8 (m, 2H), 7.4−7.2 (m, 3H), 7.2 (m, 2H), 7.0−6.8 (m, 3H), 2.6 (bs, 3H), 2.4 (s, 3H).

[3-(4-Chlorophenyl)-5-methyl-3*H*-[1,2,3]triazolo[4,5-*d*]-pyrimidin-7-yl)-*N*-phenylamine (9t). Yield: 100%. MS: 337 (M + 1). HPLC (ELSD): 99.6% (R_t = 1.90 min). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.2 (d, 2H), 7.85 (d, 2H), 7.55 (m, 2H), 7.45 (m, 2H), 7.2 (m, 1H), 2.75 (s, 3H).

Supporting Information Available. HPLC (ELSD) and ^{1}H NMR spectra of final compounds **(9a−t)** and intermediates **(8a−j)**. This material is available free of charge via the Internet at http://pubs.acs.org.

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