

Preparation of a 7-Arylthieno[3,2-d]pyrimidin-4-Amine Library

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A focused kinase library of 7-arylthieno[3,2-d]pyrimidin-4-amine analogues is readily prepared via solution-phase parallel synthesis. This strategy relies on a key cyclization of a 3-aminothiophene-2-carboxamide with a formamide to construct the thienopyrimidine core. Further elaborations of this core via substitution and Suzuki coupling reactions allow the introduction of other diversity points. This methodology is demonstrated through the preparation of a 72-membered library of 7-arylthieno[3,2-d]pyrimidin-4-amines in good yields and high purities.

Introduction

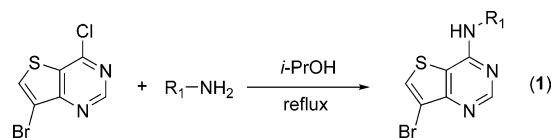
Combinatorial chemistry plays a key role both in the search for lead structures of pharmacologically active compounds and in lead optimization. The high incidence of heterocyclic frameworks in known pharmaceutical and agrochemical structures makes them an attractive target for combinatorial synthetic approaches.¹ In particular, heterocyclic compounds such as quinazolines, pyrimidopyrimidines, pyrazolopyrimidines, thienopyrimidines, and pyridopyrimidines are especially appealing because they exhibit a broad range of biological activities. For example, the thienopyrimidine nuclei are the key structure features of many types of biologically active compounds, such as kinase inhibitors,² LHCR agonists,³ phosphodiesterase inhibitors,⁴ antifolate and anti-malarial agents,⁵ blood platelet aggregation inhibitors,⁶ and reversible inhibitors of the gastric (H^+/K^+) ATPase.⁷ Consequently, thienopyrimidines have become a well-sought privileged class of compounds in drug discovery programs, and a practical strategy for the construction of a library of thienopyrimidines should aid both SAR studies and screenings for new leads. Although many methodologies have been developed for the synthesis of various substituted thienopyrimidines,^{2–7,8} the parallel solution-phase synthesis of a 7-arylthieno[3,2-d]pyrimidin-4-amine analog library has not been reported. We envision that an efficient strategy should lead to a library of 4,7-disubstituted thieno[3,2-d]pyrimidine analogues.

We focus our attention on 7-bromo-4-chlorothieno[3,2-d]pyrimidine, **4**, as the attractive core structure for the library production. Compound **4** contains two points of transformation (4-Cl and 7-Br) and presents multiple functionalities that can be exploited for the synthesis of a wide array of heterocycles. This approach should lead to a large number of diverse 4,7-functionalized analogues. Our synthetic strategy is to functionalize them at C-4 via the nucleophilic substitution reaction of the chlorothienopyrimidine with

amines and at C-7 via a Suzuki coupling reaction (Scheme 1). To avoid the potential selectivity issues of C–Br at C-7 versus activated C–Cl at C-4 in the Suzuki coupling step, we first chose to carry out the amination reaction of **4** at C-4 to obtain the intermediates **5**; then, we performed a palladium-catalyzed C-arylation reaction of **5** at C-7 to obtain product **6** (Scheme 1). Herein, we report on the preparation of a small demonstration library of this strategy, based on nucleophilic substitution at the 4-position, followed by a Suzuki-coupling reaction at the 7-position.

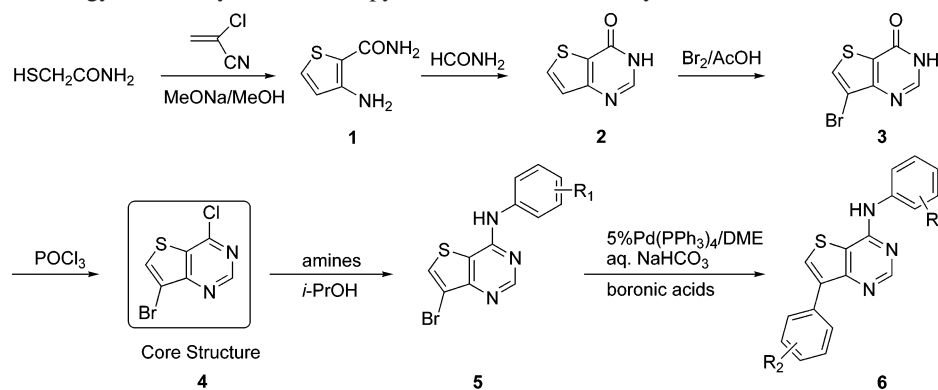
Results and Discussions

The starting material 3-aminothiophene-2-carboxamide (**1**) is synthesized according to literature procedures.⁹ Cyclization of compound **1** with formamide provides thieno[3,2-d]pyrimidin-4(3*H*)-one (**2**). The subsequent reaction of **2** with bromine, followed by phosphoryl trichloride, gives the key 7-bromo-4-chlorothieno[3,2-d]pyrimidine core structure (**4**). The first diversity point R^1 is introduced by the substitution of thieno[3,2-d]pyrimidine (**4**) with various aromatic amines to give compound **5**, as shown in eq 1.



The substitution reactions are carried out with aromatic amines in a solvent such as *i*-PrOH at 60 °C, and product **5** is purified by simple trituration with ethyl ether. A diverse set of aromatic amines, such as substituted anilines (entries 1–3, 5, 6, and 8–11, Table 1) and heteroaromatic amines (entries 4, 7, and 12, Table 1), generally give the desired compounds **5** in excellent yields and high purities, and the results are summarized in Table 1. We also examine the substitution reaction of compound **4** with aliphatic amines: the desired products are obtained in excellent yields and high purities under the same reaction condition (entries 13 and 14, Table 1).

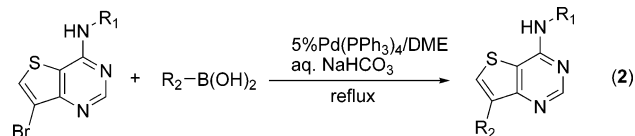
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Scheme 1. Synthetic Strategy of a 7-Arylthieno[3,2-d]pyrimidine-4-amine Library**Table 1.** Results of the Amino Substitution of 7-Bromo-4-chlorothieno[3,2-d]pyrimidines **5** Based on eq 1

entry	R ¹	solvent	product	MW	M + 1	yield ^a
1	3-chloro-4-[(3-fluorobenzyl)oxy]phenyl	<i>i</i> -PrOH	5.1	463	464	97
2	3-cyanophenyl	<i>i</i> -PrOH	5.2	330	331	96
3	3-(trifluoromethyl)phenyl	<i>i</i> -PrOH	5.3	373	374	98
4	2-[(3-fluorophenyl)methyl]-2H-indazol-5-yl	<i>i</i> -PrOH	5.4	453	454	98
5	4-chloro-3-(trifluoromethyl)phenyl	<i>i</i> -PrOH	5.5	407	408	97
6	3-chloro-4-fluorophenyl	<i>i</i> -PrOH	5.6	357	358	97
7	1-[(3-fluorophenyl)methyl]-1H-indazol-5-yl	<i>i</i> -PrOH	5.7	453	454	96.5
8	3,5-dichlorophenyl	<i>i</i> -PrOH	5.8	373	374	97
9	3-bromophenyl	<i>i</i> -PrOH	5.9	383	384	96
10	phenyl	<i>i</i> -PrOH	5.10	305	306	97
11	3-chlorophenyl	<i>i</i> -PrOH	5.11	339	340	97
12	1H-indol-5-yl	<i>i</i> -PrOH	5.12	344	345	93
13	4-(4-chlorophenylcarbamoyl)-piperazin-1-yl	<i>i</i> -PrOH	5.13	453	454	94
14	4-(4-fluorophenylcarbamoyl)-piperazin-1-yl	<i>i</i> -PrOH	5.14	436	437	90

^a Product purity is more than 95% by proton NMR, and the yield (%) is the isolated yield.

The second diversity point R² is introduced via a Suzuki coupling reaction¹⁰ (tetrakis(triphenylphosphine)palladium/dimethoxyethane/NaHCO₃) as shown in eq 2.



The results are summarized in Table 2. As evident from Table 2, all arylboronic acids, such as unsubstituted phenyl boronic acid (entries 1–12, Table 2), electron-donating substituted phenyl boronic acids (entries 13–24, 37–48, and 61–72, Table 2), and electron-withdrawing substituted phenyl boronic acids (entries 25–36 and 49–60, Table 2), proceed to give the desired products **6** as a 72-member library in high yields and high purities. However, for substrates **5.13** and **5.14** (entries 13 and 14, Table 1), the coupling reactions do not proceed well, and the desired products are not observed (entries 73 and 74, Table 2), perhaps because of the solubility of the substrates. The second diversity point can also be introduced via other cross-coupling reactions such as Heck, Sonogashira and Stille, etc., which have been extensively reported in the literature.¹⁰ Further studies and efforts to extend the scope of this transformation are currently underway.

In conclusion, a 72-member library of disubstituted thieno[3,2-d]pyrimidines is generated in solution phase from readily available anilines and aromatic boronic acids in good to high yields and high purities. This new strategy provides an

efficient way to access a large number of 7-arylthieno[3,2-d]pyrimidin-4-amines, which are of great interest for medicinal chemistry. The screening of the library for molecular targets is in progress.

Experimental Section

General Information. All solvents and reagents were obtained from commercial sources and were used without additional purification. The mass spectra were recorded on an 1100 LC/MS system (Agilent Technology Corporation) with Alltech ELSD 2000 using a YMC ODS-A, 5- μ m, 120 Å, 4.6 \times 50 mm (Waters, Inc.). The HPLC (ELSD) runs for the compounds were carried out using a linear gradient of 15–80% CH₃CN/H₂O (0.035% TFA) in 4–12 min. The retention time (*t*_R) for the expected product was recorded. ¹H NMR data was obtained using a 300 MHz Varian VXR-300S spectrometer with DMSO-*d*₆ or CDCl₃ as the internal standard and DMSO-*d*₆ or CDCl₃ as the solvent. Chemical shifts (δ) are reported in parts per million and coupling constants (*J*) are reported in hertz. Standard and peak multiplicities are indicated as follows: s, singlet; d, doublet; t, triplet; m, multiplet; dd, doublet of doubler; br, broad. Compound **1** was prepared according to the literature method.⁹

Procedure for the Preparation of 7-Bromo-4-chlorothieno[3,2-d]pyrimidine (4). 3-Aminothiophene-2-carboxamide (**1**) (1.42 g, 10.0 mmol) was dissolved in formamide (5 mL). The resulting solution was heated at 180 °C for 5 h, and then it was allowed to stand at room temperature for 2 h. The precipitate that formed was collected by vacuum

Table 2. 7-Arylthieno[3,2-d]pyrimidin-4-amine Analogs **6** Based on eq 2

entry	R ¹	R ²	product	MW	M + 1	yield ^a
1	3-chloro-4-[(3-fluorobenzyl)oxy]phenyl	phenyl	6.1	461	462	83
2	3-cyanophenyl	phenyl	6.2	328	329	87
3	3-(trifluoromethyl)phenyl	phenyl	6.3	371	372	86
4	2-[(3-fluorophenyl)methyl]-2H-indazol-5-yl	phenyl	6.4	451	452	85
5	4-chloro-3-(trifluoromethyl)phenyl	phenyl	6.5	405	406	88
6	3-chloro-4-fluorophenyl	phenyl	6.6	355	356	84
7	1-[(3-fluorophenyl)methyl]-1H-indazol-5-yl	phenyl	6.7	451	452	86
8	3,5-dichlorophenyl	phenyl	6.8	371	372	87
9	3-bromophenyl	phenyl	6.9	381	382	76
10	phenyl	phenyl	6.10	303	304	94
11	3-chlorophenyl	phenyl	6.11	337	338	86
12	1H-indol-5-yl	phenyl	6.12	342	343	71
13	3-chloro-4-[(3-fluorobenzyl)oxy]phenyl	3-ethoxyphenyl	6.13	505	506	87
14	3-cyanophenyl	3-ethoxyphenyl	6.14	372	373	91
15	3-(trifluoromethyl)phenyl	3-ethoxyphenyl	6.15	415	416	90
16	2-[(3-fluorophenyl)methyl]-2H-indazol-5-yl	3-ethoxyphenyl	6.16	495	496	87
17	4-chloro-3-(trifluoromethyl)phenyl	3-ethoxyphenyl	6.17	449	450	88
18	3-chloro-4-fluorophenyl	3-ethoxyphenyl	6.18	399	400	89
19	1-[(3-fluorophenyl)methyl]-1H-indazol-5-yl	3-ethoxyphenyl	6.19	495	496	87
20	3,5-dichlorophenyl	3-ethoxyphenyl	6.20	415	416	92
21	3-bromophenyl	3-ethoxyphenyl	6.21	425	426	83
22	phenyl	3-ethoxyphenyl	6.22	347	348	92
23	3-chlorophenyl	3-ethoxyphenyl	6.23	381	382	91
24	1H-indol-5-yl	3-ethoxyphenyl	6.24	386	387	82
25	3-chloro-4-[(3-fluorobenzyl)oxy]phenyl	4-fluorophenyl	6.25	479	480	85
26	3-cyanophenyl	4-fluorophenyl	6.26	346	347	81
27	3-(trifluoromethyl)phenyl	4-fluorophenyl	6.27	389	390	82
28	2-[(3-fluorophenyl)methyl]-2H-indazol-5-yl	4-fluorophenyl	6.28	469	470	84
29	4-chloro-3-(trifluoromethyl)phenyl	4-fluorophenyl	6.29	423	424	80
30	3-chloro-4-fluorophenyl	4-fluorophenyl	6.30	373	374	82
31	1-[(3-fluorophenyl)methyl]-1H-indazol-5-yl	4-fluorophenyl	6.31	469	470	88
32	3,5-dichlorophenyl	4-fluorophenyl	6.32	389	390	85
33	3-bromophenyl	4-fluorophenyl	6.33	399	400	78
34	phenyl	4-fluorophenyl	6.34	321	322	88
35	3-chlorophenyl	4-fluorophenyl	6.35	355	356	84
36	1H-indol-5-yl	4-fluorophenyl	6.36	360	361	74
37	3-chloro-4-[(3-fluorobenzyl)oxy]phenyl	4-methoxyphenyl	6.37	491	492	80
38	3-cyanophenyl	4-methoxyphenyl	6.38	358	359	84
39	3-(trifluoromethyl)phenyl	4-methoxyphenyl	6.39	401	402	86
40	2-[(3-fluorophenyl)methyl]-2H-indazol-5-yl	4-methoxyphenyl	6.40	481	482	86
41	4-chloro-3-(trifluoromethyl)phenyl	4-methoxyphenyl	6.41	435	436	83
42	3-chloro-4-fluorophenyl	4-methoxyphenyl	6.42	385	386	76
43	1-[(3-fluorophenyl)methyl]-1H-indazol-5-yl	4-methoxyphenyl	6.43	481	482	85
44	3,5-dichlorophenyl	4-methoxyphenyl	6.44	401	402	83
45	3-bromophenyl	4-methoxyphenyl	6.45	411	412	75
46	phenyl	4-methoxyphenyl	6.46	333	334	87
47	3-chlorophenyl	4-methoxyphenyl	6.47	367	368	89
48	1H-indol-5-yl	4-methoxyphenyl	6.48	372	373	80
49	3-chloro-4-[(3-fluorobenzyl)oxy]phenyl	3,4-difluorophenyl	6.49	497	498	86
50	3-cyanophenyl	3,4-difluorophenyl	6.50	364	365	82
51	3-(trifluoromethyl)phenyl	3,4-difluorophenyl	6.51	407	408	81
52	2-[(3-fluorophenyl)methyl]-2H-indazol-5-yl	3,4-difluorophenyl	6.52	487	488	87
53	4-chloro-3-(trifluoromethyl)phenyl	3,4-difluorophenyl	6.53	441	442	82
54	3-chloro-4-fluorophenyl	3,4-difluorophenyl	6.54	391	392	79
55	1-[(3-fluorophenyl)methyl]-1H-indazol-5-yl	3,4-difluorophenyl	6.55	487	488	86
56	3,5-dichlorophenyl	3,4-difluorophenyl	6.56	407	408	84
57	3-bromophenyl	3,4-difluorophenyl	6.57	417	418	72
58	Phenyl	3,4-difluorophenyl	6.58	339	340	86
59	3-chlorophenyl	3,4-difluorophenyl	6.59	373	374	85
60	1H-indol-5-yl	3,4-difluorophenyl	6.60	378	379	75
61	3-chloro-4-[(3-fluorobenzyl)oxy]phenyl	3-methoxyphenyl	6.61	491	492	85
62	3-cyanophenyl	3-methoxyphenyl	6.62	358	359	87
63	3-(trifluoromethyl)phenyl	3-methoxyphenyl	6.63	401	402	88
64	2-[(3-fluorophenyl)methyl]-2H-indazol-5-yl	3-methoxyphenyl	6.64	481	482	88
65	4-chloro-3-(trifluoromethyl)phenyl	3-methoxyphenyl	6.65	435	436	86
66	3-chloro-4-fluorophenyl	3-methoxyphenyl	6.66	385	386	84
67	1-[(3-fluorophenyl)methyl]-1H-indazol-5-yl	3-methoxyphenyl	6.67	481	482	87
68	3,5-dichlorophenyl	3-methoxyphenyl	6.68	401	402	89
69	3-bromophenyl	3-methoxyphenyl	6.69	411	412	82
70	phenyl	3-methoxyphenyl	6.70	333	334	90
71	3-chlorophenyl	3-methoxyphenyl	6.71	367	368	92
72	1H-indol-5-yl	3-methoxyphenyl	6.72	372	373	76
73	4-(4-chlorophenylcarbonyl)-piperazin-1-yl	phenyl	6.73	450		0
74	4-(4-fluorophenylcarbonyl)-piperazin-1-yl	phenyl	6.74	433		0

^a Product purity is more than 95% by proton NMR and yield is the isolated yield.

filtration to give 3*H*-thieno[3,2-*d*]pyrimidin-4-one (**2**) (1.52 g, 99% yield) as a white solid. A solution of bromine (1 mL) in acetic acid (3 mL) was added to a solution of 3*H*-thieno[3,2-*d*]pyrimidin-4-one (**2**) (0.98 g, 6.4 mmol) in acetic acid (4 mL). The reaction mixture was heated at reflux for 10 h. The resulting suspension was allowed to cool to room temperature and then was poured into a saturated aqueous solution of sodium bicarbonate to be neutralized. The solid product was collected by vacuum filtration to give 7-bromo-3*H*-thieno[3,2-*d*]pyrimidin-4-one (**3**) (1.18 g, 80% yield) as a pale yellow solid. A solution of 7-bromo-3*H*-thieno[3,2-*d*]pyrimidin-4-one (**3**) (1.18 g, 5.1 mmol) in phosphorus oxychloride (4 mL) under N₂ was heated at reflux for 4 h. The resulting solution was allowed to cool to room temperature and was poured into a saturated aqueous solution of sodium bicarbonate to be neutralized. The aqueous mixture was extracted with ethyl acetate. The organic layer was washed with water, followed by saturated aqueous sodium chloride, and dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure to yield 7-bromo-4-chlorothieno[3,2-*d*]pyrimidine (**4**) (1.04 g, 82%) as a yellow solid.

7-Bromo-4-chlorothieno[3,2-*d*]pyrimidine (4). Yellow solid. ¹H NMR (300 MHz, CDCl₃): δ 9.12 (s, 1H), 8.07 (s, 1H).

General Procedure for the Preparation of 7-Bromo-*N*-arylthieno[3,2-*d*]pyrimidine-4-amines (5). 7-Bromo-4-chlorothieno[3,2-*d*]pyrimidine (0.53 g, 2.1 mmol) and the appropriate aniline (2.1 mmol) were heated at 60 °C for 5 h in isopropanol (15 mL). The mixture was then cooled to room temperature and concentrated, and the resulting material was triturated with ethyl ether and collected by suction filtration to yield 7-bromo-*N*-arylthieno[3,2-*d*]pyrimidine-4-amine hydrochloride (**5**) as a white solid. The free base could be obtained by using saturated sodium bicarbonate in isopropanol for 3–12 h, followed by filtration of solids, which were then washed with water and dried under vacuum.

7-Bromo-*N*-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}-thieno[3,2-*d*]pyrimidin-4-amine (5.1). White solid. Yield: 97%. ES-MS: 464/466 [(M + 1)⁺]. ¹H NMR (300 MHz, DMSO-*d*₆): δ 9.89 (s, 1H), 8.66 (s, 1H), 8.41 (s, 1H), 7.96 (s, 1H), 7.58 (m, 1H), 7.47 (m, 1H), 7.15–7.33 (m, 4H), 5.25 (s, 2H).

7-Bromo-*N*-(3-cyanophenyl)thieno[3,2-*d*]pyrimidin-4-amine (5.2). White solid. Yield: 96%. ES-MS: 331/333 [(M + 1)⁺]. ¹H NMR (300 MHz, DMSO-*d*₆): δ 10.01 (s, 1H), 8.74 (s, 1H), 8.48 (s, 1H), 8.21 (s, 1H), 7.82–7.85 (m, 1H), 7.31–7.41 (m, 2H).

7-Bromo-*N*-[3-(trifluoromethyl)phenyl]thieno[3,2-*d*]pyrimidin-4-amine (5.3). White solid. Yield: 98%. ES-MS: 374/376 [(M + 1)⁺]. ¹H NMR (300 MHz, DMSO-*d*₆): δ 10.05 (s, 1H), 8.74 (s, 1H), 8.51 (s, 1H), 8.18 (s, 1H), 7.81–7.83 (m, 1H), 7.29–7.38 (m, 2H).

7-Bromo-*N*-{2-[(3-fluorophenyl)methyl]-2*H*-indazol-5-yl}thieno[3,2-*d*]pyrimidin-4-amine (5.4). White solid. Yield: 98%. ES-MS: 454/456 [(M + 1)⁺]. ¹H NMR (300 MHz, DMSO-*d*₆): δ 9.91 (s, 1H), 8.63 (s, 1H), 8.52 (s, 1H), 8.36 (s, 1H), 8.11 (s, 1H), 7.63 (d, *J* = 9 Hz, 1H), 7.40–7.47 (m, 2H), 7.13–7.18 (m, 3H), 5.67 (s, 2H).

7-Bromo-*N*-[4-chloro-3-(trifluoromethyl)phenyl]thieno[3,2-*d*]pyrimidin-4-amine (5.5). White solid. Yield: 97%. ES-MS: 408/410 [(M + 1)⁺]. ¹H NMR (300 MHz, DMSO-*d*₆): δ 10.04 (s, 1H), 8.72 (s, 1H), 8.52 (s, 1H), 8.19 (s, 1H), 7.78–7.80 (m, 2H).

7-Bromo-*N*-(3-chloro-4-fluorophenyl)thieno[3,2-*d*]pyrimidin-4-amine (5.6). White solid. Yield: 97%. ES-MS: 358/360 [(M + 1)⁺]. ¹H NMR (300 MHz, DMSO-*d*₆): δ 10.03 (s, 1H), 8.73 (s, 1H), 8.53 (s, 1H), 8.17 (s, 1H), 7.76–7.78 (m, 2H).

7-Bromo-*N*-{1-[(3-fluorophenyl)methyl]-1*H*-indazol-5-yl}thieno[3,2-*d*]pyrimidin-4-amine (5.7). White solid. Yield: 96.5%. ES-MS: 454/456 [(M + 1)⁺]. ¹H NMR (300 MHz, DMSO-*d*₆): δ 9.92 (s, 1H), 8.58 (s, 1H), 8.33 (s, 1H), 8.12 (s, 1H), 8.10 (s, 1H), 7.69–7.72 (d, *J* = 9 Hz, 1H), 7.55–7.58 (d, *J* = 9 Hz, 1H), 7.29–7.37 (m, 1H), 7.00–7.09 (m, 3H), 5.67 (s, 2H).

7-Bromo-*N*-(3,5-dichlorophenyl)thieno[3,2-*d*]pyrimidin-4-amine (5.8). White solid. Yield: 97%. ES-MS: 374 [(M + 1)⁺]. ¹H NMR (300 MHz, DMSO-*d*₆): δ 10.02 (s, 1H), 8.75 (s, 1H), 8.53 (s, 1H), 8.38 (s, 1H), 8.17 (s, 2H).

7-Bromo-*N*-(3-bromophenyl)thieno[3,2-*d*]pyrimidin-4-amine (5.9). White solid. Yield: 96%. ES-MS: 384 [(M + 1)⁺]. ¹H NMR (300 MHz, DMSO-*d*₆): δ 10.02 (s, 1H), 8.73 (s, 1H), 8.46 (s, 1H), 8.18 (s, 1H), 7.80–7.83 (m, 1H), 7.27–7.37 (m, 2H).

7-Bromo-*N*-phenylthieno[3,2-*d*]pyrimidin-4-amine (5.10). White solid. Yield: 97%. ES-MS: 306/308 [(M + 1)⁺]. ¹H NMR (300 MHz, DMSO-*d*₆): δ 9.88 (s, 1H), 8.71 (s, 1H), 8.44 (s, 1H), 8.18 (s, 1H), 7.41–7.46 (m, 2H), 7.27–7.30 (m, 1H), 7.13–7.18 (m, 2H).

7-Bromo-*N*-(3-chlorophenyl)thieno[3,2-*d*]pyrimidin-4-amine (5.11). White solid. Yield: 97%. ES-MS: 340/342 [(M + 1)⁺]. ¹H NMR (300 MHz, DMSO-*d*₆): δ 10.01 (s, 1H), 8.72 (s, 1H), 8.44 (s, 1H), 8.16 (s, 1H), 7.79–7.82 (m, 1H), 7.25–7.34 (m, 2H).

7-Bromo-*N*-(1*H*-indol-5-yl)thieno[3,2-*d*]pyrimidin-4-amine (5.12). White solid. Yield: 93%. ES-MS: 345/347 [(M + 1)⁺]. ¹H NMR (300 MHz, DMSO-*d*₆): δ 11.45 (s, 1H), 11.19 (s, 1H), 8.70 (s, 1H), 8.42 (s, 1H), 7.74 (s, 1H), 7.43–7.51 (m, 2H), 7.19–7.22 (d, *J* = 8.4 Hz, 1H), 6.49 (s, 1H).

4-(7-Bromo-thieno[3,2-*d*]pyrimidin-4-yl)-piperazine-1-carboxylic Acid (4-Chloro-phenyl)-amide (5.13). White solid. Yield: 94%. ES-MS: 454/456 [(M + 1)⁺]. ¹H NMR (300 MHz, acetone-*d*₆): δ 8.55 (s, 1H), 8.22 (s, 1H), 8.20 (br, 1H), 7.54–7.57 (d, *J* = 9 Hz, 2H), 7.22–7.25 (d, *J* = 9 Hz, 2H), 4.08–4.12 (t, *J* = 5.5 Hz, 2H), 3.74–3.78 (t, *J* = 5.5 Hz, 2H).

4-(7-Bromo-thieno[3,2-*d*]pyrimidin-4-yl)-piperazine-1-carboxylic Acid (4-Fluoro-phenyl)-amide (5.14). White solid. Yield: 90%. ES-MS: 437/439 [(M + 1)⁺]. ¹H NMR (300 MHz, DMSO-*d*₆): δ 8.67 (s, 1H), 8.60 (s, 1H), 8.49 (s, 1H), 7.45–7.50 (m, 2H), 7.06–7.12 (m, 2H), 4.00–4.04 (t, *J* = 5.5 Hz, 2H), 3.64–3.68 (t, *J* = 5.5 Hz, 2H).

General Procedure for the Preparation of 7-Phenyl-*N*-arylthieno[3,2-*d*]pyrimidine-4-amines (6). A suspension of 7-bromo-*N*-arylthieno[3,2-*d*]pyrimidin-4-amine (**5**) (0.25 mmol) and tetrakis(triphenylphosphine)palladium (0) (14.4

mg, 0.0125 mmol) in dimethoxyethane (3 mL) was stirred at room temperature for 10 min. Arylboronic acid (0.3 mmol, 1.2 equiv) as a solid was added to this suspension, followed by 2.0 mL of 1 M aqueous sodium bicarbonate. The reaction mixture was heated at reflux for 2 h, cooled to room temperature, and diluted with 15 mL of water. The aqueous mixture was extracted with ethyl acetate. The organic layer was washed with water, followed by saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure. The resulting residue was purified by flash chromatography (10–20% ethyl acetate in hexane) to yield the compound **6** as a white solid.

7-Phenyl-N-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}-thieno[3,2-d]pyrimidin-4-amine (6.1). White solid. Yield: 83%. ES-MS: 462 [(M + 1)⁺]. ¹H NMR (300 MHz, DMSO-*d*₆): δ 9.74 (s, 1H), 8.68 (s, 1H), 8.45 (s, 1H), 8.00–8.08 (m, 3H), 7.67 (m, 1H), 7.18–7.51 (m, 8H), 5.25 (s, 2H).

7-Phenyl-N-{2-[(3-fluorophenyl)methyl]-2H-indazol-5-yl}thieno[3,2-d]pyrimidin-4-amine (6.4). White solid. Yield: 85%. ES-MS: 452 [(M + 1)⁺]. ¹H NMR (300 MHz, DMSO-*d*₆): δ 9.75 (s, 1H), 8.65 (s, 1H), 8.51 (s, 1H), 8.40 (s, 1H), 8.15 (s, 1H), 8.05–8.07 (d, *J* = 7.5 Hz, 2H), 7.62–7.65 (d, *J* = 9 Hz, 1H), 7.35–7.51 (m, 5H), 7.13–7.18 (m, 3H), 5.67 (s, 2H).

7-Phenyl-N-{1-[(3-fluorophenyl)methyl]-1H-indazol-5-yl}thieno[3,2-d]pyrimidin-4-amine (6.7). White solid. Yield: 86%. ES-MS: 452 [(M + 1)⁺]. ¹H NMR (300 MHz, DMSO-*d*₆): δ 9.81 (s, 1H), 8.64 (s, 1H), 8.41 (s, 1H), 8.16–8.18 (d, *J* = 6 Hz, 2H), 8.05–8.07 (d, *J* = 6 Hz, 2H), 7.72–7.75 (d, *J* = 9 Hz, 1H), 7.63–7.66 (m, 1H), 7.45–7.50 (t, *J* = 7.5 Hz, 2H), 7.35–7.40 (t, *J* = 7.5 Hz, 2H), 7.04–7.10 (m, 1H), 5.71 (s, 2H).

7-(3-Ethoxyphenyl)-N-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}thieno[3,2-d]pyrimidin-4-amine (6.13). White solid. Yield: 87%. ES-MS: 506 [(M + 1)⁺]. ¹H NMR (300 MHz, DMSO-*d*₆): δ 9.74 (s, 1H), 8.68 (s, 1H), 8.48 (s, 1H), 8.00 (s, 1H), 7.62–7.66 (m, 3H), 7.19–7.48 (m, 6H), 6.96 (m, 1H), 5.25 (s, 2H), 4.09 (q, *J* = 7 Hz, 2H), 1.34–1.39 (t, *J* = 7 Hz, 3H).

7-(3-Ethoxyphenyl)-N-{2-[(3-fluorophenyl)methyl]-2H-indazol-5-yl}thieno[3,2-d]pyrimidin-4-amine (6.16). White solid. Yield: 87%. ES-MS: 496 [(M + 1)⁺]. ¹H NMR (300 MHz, DMSO-*d*₆): δ 9.73 (s, 1H), 8.65 (s, 1H), 8.50 (s, 1H), 8.43 (s, 1H), 8.14 (s, 1H), 7.69–7.70 (d, *J* = 1.8 Hz, 1H), 7.61–7.64 (m, 1H), 7.47–7.50 (m, 2H), 7.15–7.18 (m, 3H), 6.94–6.95 (d, *J* = 2.4 Hz, 1H), 5.67 (s, 2H), 4.05–4.11 (q, *J* = 7 Hz, 2H), 1.34–1.38 (t, *J* = 7 Hz, 3H).

7-(3-Ethoxyphenyl)-N-{1-[(3-fluorophenyl)methyl]-1H-indazol-5-yl}thieno[3,2-d]pyrimidin-4-amine (6.19). White solid. Yield: 87%. ES-MS: 496 [(M + 1)⁺]. ¹H NMR (300 MHz, DMSO-*d*₆): δ 9.77 (s, 1H), 8.61 (s, 1H), 8.41 (s, 1H), 8.14 (s, 1H), 8.12 (s, 1H), 7.67–7.72 (m, 4H), 7.58–7.63 (m, 2H), 7.31–7.36 (m, 3H), 7.00–7.07 (m, 1H), 5.67 (s, 2H), 4.01–4.08 (q, *J* = 7 Hz, 2H), 1.30–1.35 (t, *J* = 7 Hz, 3H).

7-(4-Fluorophenyl)-N-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}thieno[3,2-d]pyrimidin-4-amine (6.25). White solid. Yield: 85%. ES-MS: 480 [(M + 1)⁺]. ¹H NMR (300 MHz, DMSO-*d*₆): δ 9.76 (s, 1H), 8.68 (s, 1H), 8.46 (s, 1H), 8.11–

8.16 (m, 2H), 8.00 (s, 1H), 7.66–7.69 (m, 1H), 7.46–7.48 (m, 1H), 7.24–7.35 (m, 6H), 5.25 (s, 2H).

7-(4-Fluorophenyl)-N-{2-[(3-fluorophenyl)methyl]-2H-indazol-5-yl}thieno[3,2-d]pyrimidin-4-amine (6.28). White solid. Yield: 84%. ES-MS: 470 [(M + 1)⁺]. ¹H NMR (300 MHz, DMSO-*d*₆): δ 9.76 (s, 1H), 8.65 (s, 1H), 8.50 (s, 1H), 8.40 (s, 1H), 8.10–8.15 (m, 3H), 7.61–7.64 (d, *J* = 9 Hz, 1H), 7.47–7.50 (d, *J* = 9 Hz, 1H), 7.28–7.39 (m, 3H), 7.15–7.18 (m, 3H), 5.67 (s, 2H).

7-(4-Fluorophenyl)-N-{1-[(3-fluorophenyl)methyl]-1H-indazol-5-yl}thieno[3,2-d]pyrimidin-4-amine (6.31). White solid. Yield: 88%. ES-MS: 470 [(M + 1)⁺]. ¹H NMR (300 MHz, CDCl₃): δ 9.76 (s, 1H), 8.65 (s, 1H), 8.51 (s, 1H), 8.21–8.26 (m, 2H), 8.14 (s, 1H), 7.71–7.74 (d, *J* = 9 Hz, 2H), 7.61–7.64 (d, *J* = 9 Hz, 2H), 7.46–7.51 (m, 2H), 7.37–7.42 (m, 2H), 7.07–7.10 (d, *J* = 9 Hz, 1H), 5.70 (s, 2H).

7-(4-Methoxyphenyl)-N-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}thieno[3,2-d]pyrimidin-4-amine (6.37). White solid. Yield: 80%. ES-MS: 492 [(M + 1)⁺]. ¹H NMR (300 MHz, DMSO-*d*₆): δ 9.71 (s, 1H), 8.67 (s, 1H), 8.33 (s, 1H), 8.00–8.05 (m, 3H), 7.66–7.67 (m, 1H), 7.46–7.48 (m, 1H), 7.18–7.34 (m, 4H), 7.03–7.06 (m, 2H), 5.25 (s, 2H), 3.81 (s, 3H).

7-(4-Methoxyphenyl)-N-{2-[(3-fluorophenyl)methyl]-2H-indazol-5-yl}thieno[3,2-d]pyrimidin-4-amine (6.40). White solid. Yield: 86%. ES-MS: 482 [(M + 1)⁺]. ¹H NMR (300 MHz, DMSO-*d*₆): δ 9.71 (s, 1H), 8.64 (s, 1H), 8.50 (s, 1H), 8.29 (s, 1H), 8.14 (s, 1H), 8.01–8.04 (d, *J* = 9 Hz, 2H), 7.40–7.64 (m, 3H), 7.15–7.18 (m, 3H), 7.02–7.05 (d, *J* = 9 Hz, 2H), 5.67 (s, 2H), 3.80 (s, 3H).

7-(4-Methoxyphenyl)-N-{1-[(3-fluorophenyl)methyl]-1H-indazol-5-yl}thieno[3,2-d]pyrimidin-4-amine (6.43). White solid. Yield: 85%. ES-MS: 482 [(M + 1)⁺]. ¹H NMR (300 MHz, DMSO-*d*₆): δ 9.77 (s, 1H), 8.63 (s, 1H), 8.30 (s, 1H), 8.18 (s, 1H), 8.17 (s, 1H), 8.01–8.04 (d, *J* = 9 Hz, 2H), 7.72–7.74 (d, *J* = 6 Hz, 1H), 7.63–7.65 (d, *J* = 6 Hz, 1H), 7.36–7.38 (m, 1H), 7.02–7.10 (m, 5H), 5.70 (s, 2H), 3.80 (s, 3H).

7-(3,4-Difluorophenyl)-N-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}thieno[3,2-d]pyrimidin-4-amine (6.49). White solid. Yield: 86%. ES-MS: 498 [(M + 1)⁺]. ¹H NMR (300 MHz, DMSO-*d*₆): δ 9.77 (s, 1H), 8.68 (s, 1H), 8.47 (s, 1H), 8.27 (m, 1H), 7.97 (m, 1H), 7.51–7.54 (m, 1H), 7.38–7.39 (m, 1H), 7.18–7.35 (m, 6H), 5.25 (s, 2H).

7-(3,4-Difluorophenyl)-N-{2-[(3-fluorophenyl)methyl]-2H-indazol-5-yl}thieno[3,2-d]pyrimidin-4-amine (6.52). White solid. Yield: 87%. ES-MS: 488 [(M + 1)⁺]. ¹H NMR (300 MHz, DMSO-*d*₆): δ 9.80 (s, 1H), 8.66 (s, 1H), 8.53 (s, 1H), 8.51 (s, 1H), 8.28 (m, 1H), 8.13 (s, 1H), 7.98 (m, 1H), 7.61–7.64 (m, 1H), 7.40–7.56 (m, 3H), 7.12–7.18 (m, 3H), 5.67 (s, 2H).

7-(3,4-Difluorophenyl)-N-{1-[(3-fluorophenyl)methyl]-1H-indazol-5-yl}thieno[3,2-d]pyrimidin-4-amine (6.55). White solid. Yield: 86%. ES-MS: 488 [(M + 1)⁺]. ¹H NMR (300 MHz, DMSO-*d*₆): δ 9.86 (s, 1H), 8.65 (s, 1H), 8.52 (s, 1H), 8.27 (m, 1H), 8.17 (s, 1H), 8.16 (s, 1H), 7.97 (m, 1H), 7.72–7.75 (d, *J* = 9 Hz, 1H), 7.62–7.65 (m, 1H),

7.51–7.54 (m, 1H), 7.35–7.37 (m, 1H), 7.04–7.12 (m, 3H), 5.70 (s, 2H).

7-(3-Methoxyphenyl)-N-{3-chloro-4-[(3-fluorobenzyl)-oxy]phenyl}thieno[3,2-d]pyrimidin-4-amine (6.61). White solid. Yield: 85%. ES-MS: 492 [(M + 1)⁺]. ¹H NMR (300 MHz, DMSO-*d*₆): δ 9.74 (s, 1H), 8.68 (s, 1H), 8.47 (s, 1H), 8.00 (s, 1H), 7.62–7.66 (m, 3H), 7.19–7.48 (m, 6H), 6.96 (m, 1H), 5.25 (s, 2H), 3.82 (s, 3H).

7-(3-Methoxyphenyl)-N-{2-[(3-fluorophenyl)methyl]-2H-indazol-5-yl}thieno[3,2-d]pyrimidin-4-amine (6.64). White solid. Yield: 88%. ES-MS: 482 [(M + 1)⁺]. ¹H NMR (300 MHz, DMSO-*d*₆): δ 9.75 (s, 1H), 8.65 (s, 1H), 8.51 (s, 1H), 8.44 (s, 1H), 8.14 (s, 1H), 7.48–7.70 (m, 5H), 7.36–7.44 (m, 2H), 7.15–7.18 (d, *J* = 9 Hz, 2H), 6.95–6.97 (d, *J* = 6 Hz, 1H), 5.67 (s, 2H), 3.84 (s, 3H).

7-(3-Methoxyphenyl)-N-{1-[(3-fluorophenyl)methyl]-1H-indazol-5-yl}thieno[3,2-d]pyrimidin-4-amine (6.67). White solid. Yield: 87%. ES-MS: 482 [(M + 1)⁺]. ¹H NMR (300 MHz, DMSO-*d*₆): δ 9.80 (s, 1H), 8.63 (s, 1H), 8.44 (s, 1H), 8.17 (s, 1H), 8.16 (s, 1H), 7.63–7.72 (m, 4H), 7.35–7.41 (m, 2H), 7.10–7.25 (m, 3H), 7.04–7.06 (d, *J* = 6 Hz, 1H), 5.67 (s, 2H), 3.84 (s, 3H).

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Supporting Information Available. Experimental procedures and ¹H NMR spectra for all new compounds reported in the text. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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