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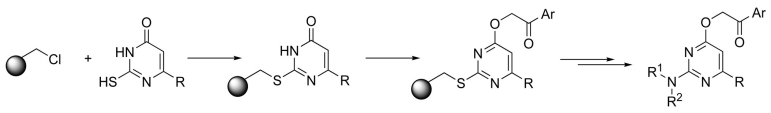

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Solution- and Solid-Phase Parallel Synthesis of 4-Alkoxy-Substituted Pyrimidines with High Molecular Diversity

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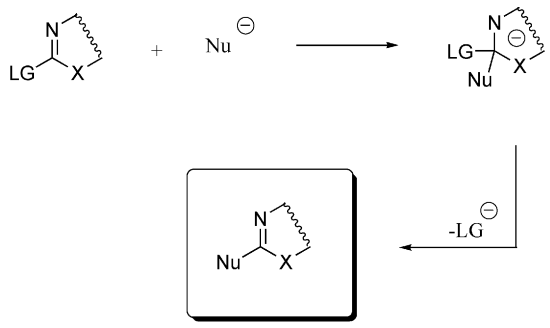
A simple and straightforward methodology toward the synthesis of novel 2,6-disubstituted-4-alkoxypyrimidine derivatives of type **16** and **19** has been developed. This methodology, initially developed in solution, can be perfectly adapted to the solid support under analogous conditions, taking full advantage of automated parallel synthesis systems. This successful methodology benefits from the key role played by the thioether linkage placed at the 2-position in **3**, **9**, or **13** in a double manner: on one side, the steric effect exerted by the thioether linkage is likely to be responsible for the very high observed selectivity toward the formation of the O-alkylation products. On the other side, this sulfur linkage can serve not only as a robust point of attachment for the heterocycle, stable to a number of reaction conditions, but also as a means of introducing a new element of diversity through activation to the corresponding sulfone (safety-catch linker concept) and subsequent ipso-substitution reaction with a variety of different *N*-nucleophiles.

Introduction

Heteroaromatic nucleophilic addition−elimination reactions are commonly recognized in many electron-deficient heterocycles.[1] Alkyl, arylsulfinyl, or sulfonyl substituents as leaving groups in electron-deficient heteroaromatic systems have been reported to have reactivity equivalent to or greater than that of a chloro group, and many examples concerning the reactivity of electron deficient azines bearing alkylsulfinyl and sulfonyl groups with simple nucleophiles have been reported[2,3] (Figure 1).

On the other hand, combinatorial chemistry and related multiple synthesis technologies toward the preparation of small-molecular-weight compound libraries are currently gaining wide acceptance as powerful tools for lead structure identification.[4] Thus, in the past few years, numerous protocols for the construction of several heterocyclic and other compound libraries have been disclosed.[5−7] In general, for most of these protocols, the use of solid-phase methods has been the technique of choice. From the several strategies developed, the construction of small heterocycles using solid-phase chemistry is usually done through the use of a polar functionality to attach the compounds to the resin. These polar groups invariably become part of the structure and eventually might limit the structure−activity relationships derived from these compounds. In an effort to overcome these limitations, the use of several traceless linkers has been reported. These include the use of activatable linkers,[8,9] photolabile linkers,[10] and silicon linkers.[11,12] In this respect, and on the basis of the known capability of sulfonyl groups to behave as efficient leaving groups in electron-deficient heterocycles, we identified and reported few years ago on the use of a sulfur-based linker that served not only as a point of attachment for an small heterocycle but also as a means to introduce further diversity into the molecule.[13,14] The linker remains inert through the entire synthetic sequence until "activated" by oxidation to the sulfone and then displaced by a wide variety of nucleophiles with concomitant release of the molecules from the solid support.



LG = Cl, Br, I, SOR, SO_2R

Figure 1.

With the aim of extending the scope of this methodology and in connection with our ongoing projects regarding the development of efficient methodologies that could be readily adapted for the combinatorial or parallel synthesis in solution or on solid supports of relevant core structures with a high degree of molecular diversity,[15−18] we decided to study the use of readily available 2-mercaptopyrimidinones of type **2** as potential versatile precursors toward the synthesis on solid support of libraries of different molecularly diverse pyrimidines in a parallel array. Pyrimidines represent an interesting pharmacophore widely distributed on natural and on synthetic products that display an ample variety of relevant biological properties.[19,20] For that reason, already several methodologies

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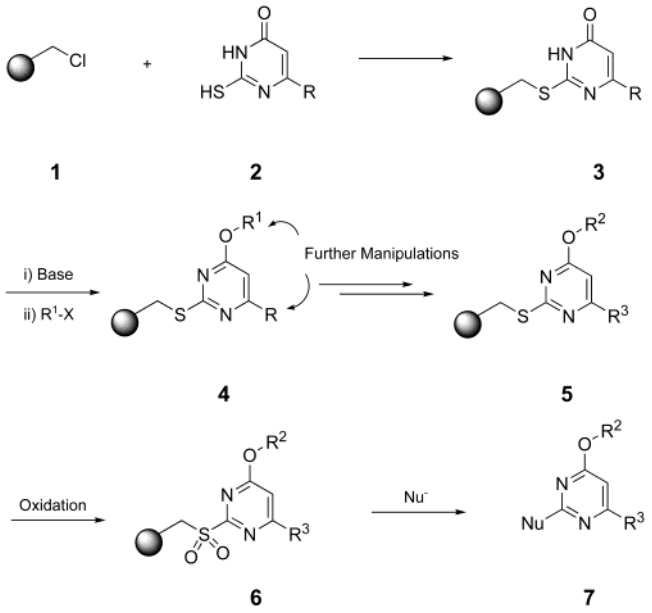


Figure 2.

based on known solution procedures toward the synthesis of pyrimidines with different substitution patterns have been successfully adapted to the solid phase.[21−26] A relatively little explored class of pyrimidines, however, are those bearing an alkoxy moiety at the 4-position. Recently, it has been shown that certain 4-alkoxypyrimidines are cyclin-dependent kinase inhibitors,[27] and other members of this class of pyrimidines have been identified as potential useful pesticides.[28,29]

4-Alkoxypyrimidines are usually prepared in a two-step sequence by first converting the corresponding pyrimidine-4-ones derivatives into 4-halopyrimidines, followed by nucleophilic displacement of the halide by an alkoxy group.[30,31] Alternatively, in a recent report the synthesis of 4-alkoxypyrimidines from esters and nitriles in the presence of trifluoromethanesulfonic anhydride has been described.[32] However, the most straightforward way to achieve this transformation would be the direct O-alkylation of the parent pyrimidin-4-ones derivatives with suitable alkylating agents in the presence of a base.[33−36] Because of its simplicity, this last approach would be especially suitable to be carried out on solid supports. Ideally, 2-mercaptopyrimidin-4-ones of type **2** would be attached onto a polymeric support of the halomethyl type **1** through the thiol group to give **3**. Subsequent O-alkylation reaction would result in the corresponding 4-alkoxypyrimidine derivatives **4**. Optionally, further suitable manipulations over the substituents at the 4- and 6-positions would enhance the introduction of additional diversity. Finally, oxidation of the thioether moiety to the corresponding sulfone **6** and nucleophilic displacement by different nucleophiles would produce the corresponding highly molecular diverse pyrimidines of type **7** with simultaneous release from the polymeric support (Figure 2).

Results and Discussion

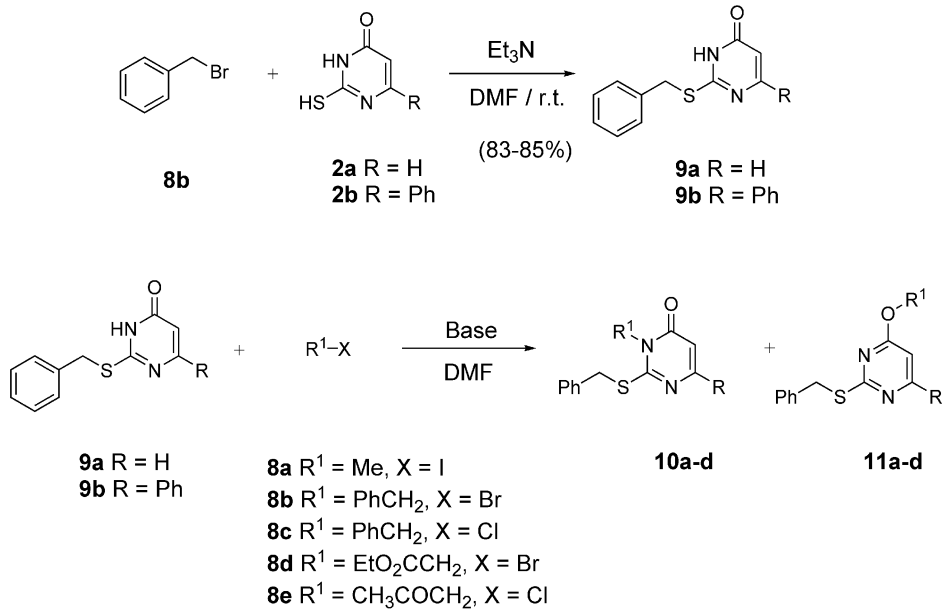
A known limitation against this simple approach is that this type of oxydiazines, although readily deprotonated under mild conditions, behave as ambident nucleophiles. In ambident systems, the principal factors controlling the site of alkylation are the structure of the alkylating agent, the nature of the solvent, the nature of the counterion, the nature of the leaving group, and the temperature.[37] Therefore, before embarking on a full program of new library synthesis, we first examined in solution the analogous strategy that should serve as a model case for a subsequent translation to the solid support.[34] Thus, reaction at 0 °C in DMF between benzyl bromide **8** and 2-mercapto-3*H*-pyrimidin-4-ones **2** smoothly resulted in the corresponding 2-thiobenzyl derivatives **9** in 83−85% yield. Next, to determine the best experimental conditions for a favorable O-alkylation vs. N-alkylation ratio, we studied the influence of the alkylating agent and the base using DMF as a solvent (Scheme 1).

We found that when methyl iodide **8a** was used as alkylating agent, independent of the base employed (either Cs_2CO_3, TMG or DBU), a mixture of both alkylated products **10** and **11** were obtained, with the alkylation reaction occurring at nitrogen predominantly in a ∼4:1 ratio. (Table 1, entries i−iii). However, when moving from methyl iodide **8a** to benzyl bromide **8b** or benzyl chloride **8c** as alkylating agents, again, a mixture of both alkylated products **10** and **11** was produced, but instead, the O-alkylated product **11b** was the major adduct obtained (Table 1, entries iv−vi). These last results showed that under these conditions, the steric effect exerted by the thiobenzyl group at the 2-position in **9** could be, at least in part, responsible for the observed predominant formation of the O- versus the N-alkylation products.[38] When this is effectively the case, the analogous tendency should be enhanced by using alkylating reagents with larger steric demand. Indeed, that was the observed effect when ethyl bromoacetate **8d** or chloro acetone **8e** were used as alkylating agents (Table 1, entries vii and viii).

Interestingly, by using phenacyl bromide **12a** as alkylating agent, the sole isolated products of these alkylations were the O-alkylated isomers **13a**−**b**, and only small amounts (<3%) of the corresponding N-alkylated derivatives were detected (Scheme 2).

Therefore, having established that under these conditions, alkylating reagents bearing large sterically demanding groups (e.g., phenacyl bromides) almost exclusively result in 4-alkoxypyrimidines of type **13** from **9** in good isolated yields, the next issue to be addressed before translating this methodology to the solid support was to check the robustness of the thioether moiety against different reaction conditions commonly used in a solid phase that could enhance the potential introduction of further molecular diversity and if this sulfur linkage could be activated through the corresponding sulfone and subsequently displaced by a variety of different nucleophiles. Thus, to begin our model studies, when compound **13a** was allowed to react with Grignard reagents in THF at room temperature, a smooth reaction leading to the corresponding tertiary alcohol derivatives **14a**−**b** took place in near-quantitative yields. Oxidation with 2.5 equiv of *m*-CPBA in CH_2Cl_2 at 0 °C resulted in the corresponding sulfones **15a**−**b**, also in good isolated yields. Finally, reaction at 60−80 °C in dioxane of activated **15a**−**b** with 1.2 equiv of a primary or a secondary amine (such as, for instance, those shown in Scheme 3) produced the

Scheme 1



Scheme 2

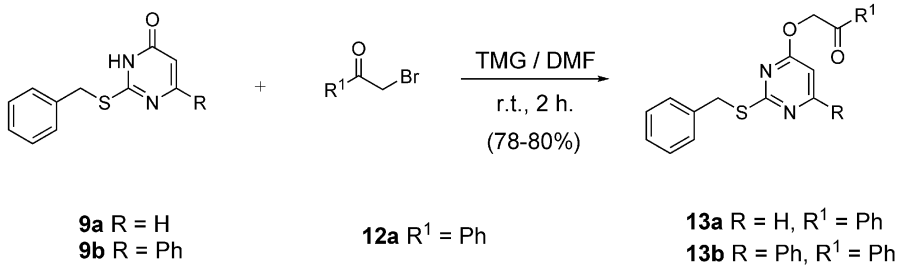


Table 1. O-Alkylation versus N-Alkylation Experiments

entry	R	R^1−X	base	compd/yield (%)	
i	H	Me−I	Cs_2CO_3	**10a**, 62	**11a**, 17
ii	H	Me−I	DBU	**10a**, 7	**11a**, 16
iii	H	Me−I	TMG	**10a**, 77	**11a**, 15
iv	H	BnBr	Cs_2CO_3	**10b**, 26	**11b**, 49
v	H	BnBr	TMG	**10b**, 33	**11b**, 51
vi	H	BnCl	TMG	**10b**, 33	**11b**, 49
vii	Ph	EtO_2CCH_2Br	TMG	**10c**, 11	**11c**, 68
viii	H	$MeCOCH_2Cl$	TMG	**10d**, 14	**11d**, 58

corresponding substitution products **16a**−**c** in very good yields (Scheme 3).

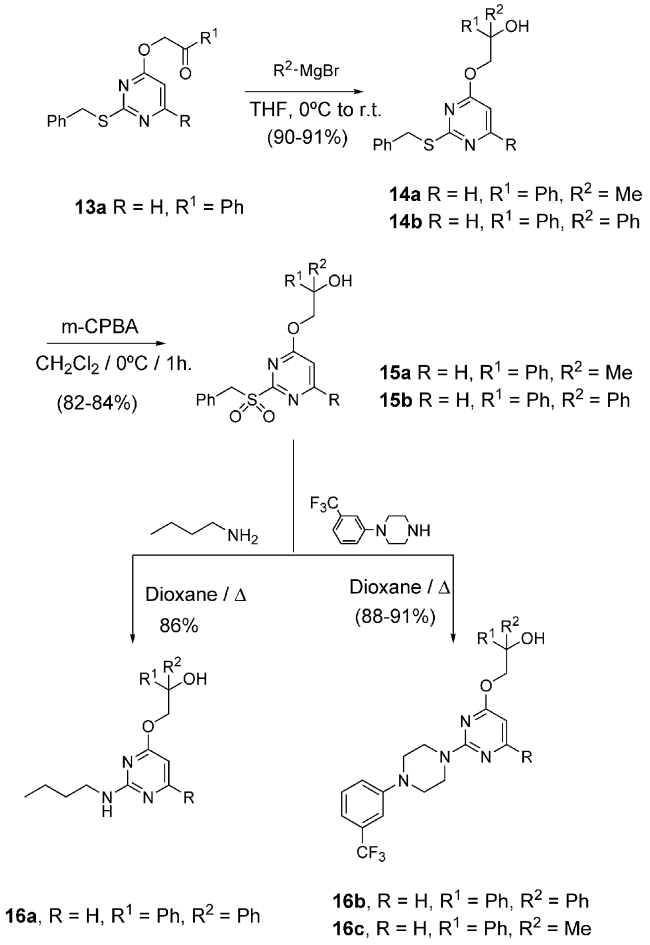
The data obtained from these experiments carried out in solution gave us a rather precise idea about the feasibility of translating this methodology to the solid support, taking full advantage of automated parallel synthesis systems toward the rapid preparation of collections of molecularly diverse 4-alkoxypyrimidines with different substitution patterns. To prove this hypothesis, we attached 2-mercaptopyrimidin-4-ones of type **2** to commercially available high-loaded Merrifield resin **1** (3.4 mmol/g) in DMF in the presence of Et_3N to give **3**. Partitioning of the resin beds **3** and alkylation reaction with different phenacyl bromides **12a**−**c** in the presence of a base such as TMG led to the corresponding 4-alkoxypyrimidine derivatives **17a**−**d**. The formation of these polymer-bound compounds was followed by FT-IR (see Experimental Section). Finally, oxidation of the thioether moiety in **17** by reaction with 3 equiv of *m*-CPBA led to the formation of the corresponding sulfones **18a**−**d**. These activated resin beds were then newly partitioned and allowed to react with a variety of N-nucleophiles in dioxane at 60−80 °C, leading to a collection of 2-amino-4-alkoxy pyrimidines of type **19**. Through this heteroaromatic ipso-substitution reaction, simultaneously to the introduction of a new element of diversity, compounds of type **19** were released from the resin (Scheme 4, Table 2).

These derivatives **19** were isolated in generally good overall yields (the only exception being the case of **19l**, as a result of the known poor nucleophilic character of anilines, entry xii, Table 2), and with good levels of purity (higher than 80%, HPLC analysis). A quick filtration through a small plug of silica afforded compounds **19** with purities >95% that were isolated and characterized by the usual spectroscopic techniques.

Conclusions

In summary, we have shown that easily available 2-mercaptopyrimidin-4-ones of type **2** can be used as versatile building blocks toward the preparation of different highly substituted 4-alkoxypyrimidine derivatives of types **16** and **19** in good overall yields through a simple O-alkylation reaction with appropriate alkylating agents. The methodology works equally well in solution or in solid phase, in this last case, taking full advantage of automated parallel synthesis systems for the rapid generation of collections of this type

Scheme 3



of compounds. In the solid-phase version of this methodology using high-loaded Merrifield resin (3.4 mmol/gr), we routinely used 150 mg of resin per compound and ended up with 75−90 mg of products in purities for the crude reaction mixtures generally higher than 80% (by HPLC analysis). This strategy benefits from the key role played by the thioether linkage placed at the 2-position in **3**, **9**, or **13** in a double sense: on one hand, the steric effect exerted by the thioether linkage is likely to be responsible for the very high observed selectivity toward the formation of the O-alkylation products. On the other hand, this sulfur linkage can serve not only as a robust point of attachment for the heterocycle, stable to a number of reaction conditions, but also as a mean of introducing a new element of diversity through activation to the corresponding sulfone (safety-catch linker concept) and subsequent ipso-substitution reaction with a variety of different N-nucleophiles. Because of the high combinatorial capacity of this methodology, further applications of this strategy toward different functionalized pyrimidines, as well as the extension for the final cleavage with different types of nucleophiles, are in progress and will be published on due course.

Experimental Section

General. All commercially available chemicals were used as purchased. DMF was dried over activated molecular sieves (4 Å). THF was dried over Na/benzophenone prior to use. All reactions were run under a positive pressure of dry N_2. Melting points (capillary tube) were measured with an electrothermal digital melting point apparatus IA 9100 and are uncorrected. IR spectra were recorded on a Mattson-Galaxy Satellite FT-IR. ^{1}H and ^{13}C NMR spectra were recorded at 200 and 50 MHz, respectively, on a Bruker DPX200 Advance instrument with TMS as internal standard. MS spectra were recorded on a VG Quattro instrument in the positive ionization FAB mode using 3-NBA or 1-thioglycerol as the matrix or in a Thermo Quest 2000 series apparatus for the EI (70 eV) mode. Elemental analyses were performed

Scheme 4

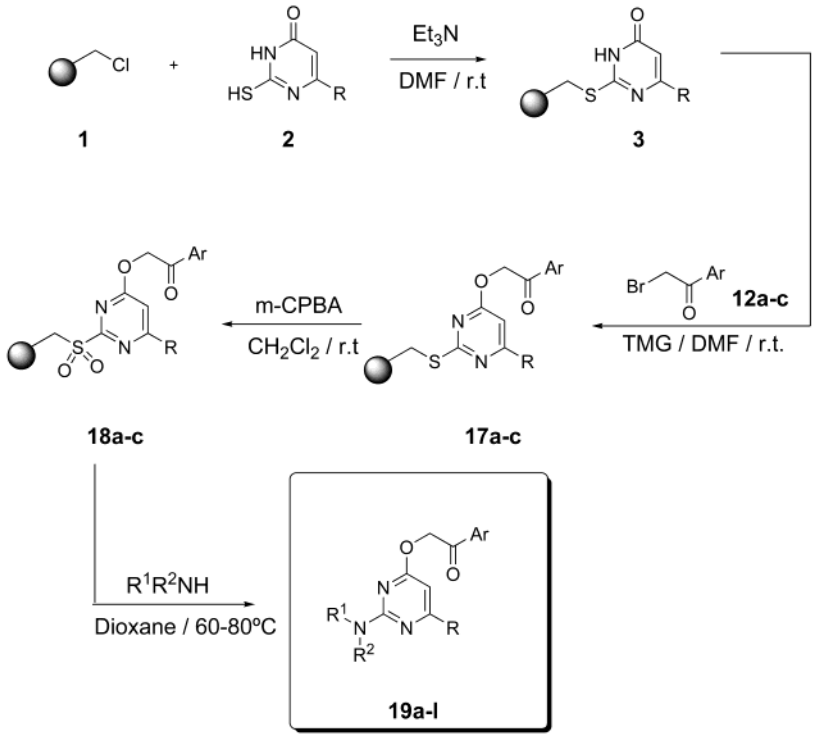
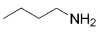
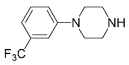
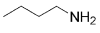
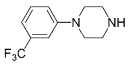
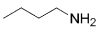
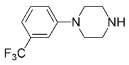
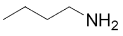
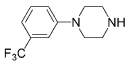
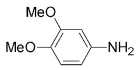


Table 2. Synthesized Derivatives **19a**−**l** through Parallel Solid-Phase Synthesis

Entry	R	Ar	R^1R^2NH	Compound	Yield
i	H	Ph		**19a**	58
ii	H	Ph		**19b**	54
iii	H	Ph		**19c**	55
iv	Ph	Ph		**19d**	68
v	Ph	Ph		**19e**	72
vi	H	3-O_2N-C_6H_4		**19f**	46
vii	H	3-O_2N-C_6H_4		**19g**	45
viii	H	3-O_2N-C_6H_4		**19h**	60
ix	H	4-Cl-C_6H_4		**19i**	41
x	H	4-Cl-C_6H_4		**19j**	63
xi	H	4-Cl-C_6H_4		**19k**	48
xii	H	4-Cl-C_6H_4		**19l**	32

on an apparatus from Thermo Instruments, model EA1110-CHNS. Analytical TLC was performed on precoated TLC plates, silica gel 60 F_{254} (Merck). Flash chromatography purifications were performed on silica gel 60 (230−400 mesh, Merck).

Synthesis of 2-Thiobenzylpyrimidin-4-ones 9a−b. General Procedure. To a cooled (0 °C) solution of the corresponding 2-mercapto-3*H*-pyrimidin-4-one **2a**−**b** (1 equiv) in DMF (3 mL/mmol), Et_3N (1.2 equiv) was added. To the mixture, benzyl bromide **8b** (1.2 equiv) was added dropwise. The reaction mixture was stirred from 0 °C to room temperature for 4 h. After this time, a white solid precipitates was collected by filtration and washed sequentially with small portions of H_2O, AcOEt, and Et_2O and then dried in high vacuum. Compounds **9a**−**b** were obtained with enough purity to be used in the next step without further purification.

2-Benzylsulfanyl-3*H*-pyrimidin-4-one (9a). According to the general procedure described above, reaction between **2a** (4.0 g, 30 mmol), **8b** (4.2 mL, 36 mmol), and Et_3N (5.01 mL) in DMF (90 mL) afforded 5.45 g (83%) of **9a** as a colorless solid. mp: 174−175 °C. IR (KBr): ν 3030w, 2790m, 2698m, 2620m, 1664s, 1557m, 1457m, 1275m, 1227s, 1177m, 976m, 930m, 822w, 707m. ^{1}H NMR (DMSO-d_6): δ 4.50 (s, 2H, PhCH_2) 6.23 (d, 1H, J = 5.8 Hz, H_{pyrim}), 7.35−7.50 (m, 5H_{arom}), 8.01 (d, 1H, J = 5.8 Hz, H_{pyrim}). ^{13}C NMR (DMSO-d_6): δ 33.7 (t, $PhCH_2$), 110.1 (d, CH_{pyrim}), 127.3, 128.5, 129.0 (3d, 5CH_{arom}), 137.1 (s, 2C_{arom}), 154.3 (d, CH_{pyrim}), 162.7 (s, CO). MS (FAB$^+$) *m*/*e*: 220 ([M + 2]$^+$, 14), 219 ([M + 1]$^+$, 100), 218 ([M]$^+$, 17), 217 (3), 185 (4), 168 (3), 167 (5), 165 (5). Anal. calcd. for $C_{11}H_{10}N_2OS$ (218.05): C, 60.53; H, 4.62; N, 12.83; S, 14.69. Found: C, 60.25; H, 4.80; N, 12.62; S, 14.99%.

2-Benzylsulfanyl-6-phenyl-3*H*-pyrimidin-4-one (9b). According to the general procedure described above, the reaction among **2b** (1.80 g-8.8 mmol), **8b** (1.30 mL-10.6 mmol), and Et_3N (1.47 mL) in DMF (27 mL) afforded 2.21 g (85%) of **9b** as a colorless solid. mp: 243−244 °C. IR (KBr): ν 2796w, 2738m, 2675m, 1660s, 1567s, 1461m, 1380m, 1238w, 1207w, 1060m, 987m, 930m, 840m, 780m, 700m. ^{1}H NMR ($CDCl_3$): δ 4.64 (s, 2H, PhCH_2) 6.70 (s, 1H, H_{pyrim}), 7.30−7.55 (m, 8H_{arom}), 8.00−8.05 (m, 2H_{arom}). ^{13}C NMR ($CDCl_3$): δ 33.8 (t, CH_2), 103.9 (d, CH_{pyrim}), 126.9, 127.3, 128.5, 128.7, 128.9, 130.6 (6d, 10CH_{arom}), 136.0, 137.4 (2s, 2C_{arom}), 160.3, 162.1 (2s, $C(2)_{pyrim}$, $C(6)_{pyrim}$), 163.9 (s, CO). MS (FAB)$^+$ *m*/*e*: 296 ([M + 2]$^+$, 11), 295 ([M + 1]$^+$, 37), 286 (13), 285 (95), 284 (14), 283 (100), 192 (40), 155 (19), 154 (81), 152 (10), 139 (11), 138 (27), 137 (50), 136

(80). Anal. calcd. for $C_{17}H_{14}N_2OS$ (294.08): C, 69.36; H, 4.79; N, 9.52; S, 10.89. Found: C, 69.62; H, 4.99; N, 9.35; S, 11.16%.

Alkylation Reaction of 9a−b. Synthesis of N-alkylated and O-alkylated Derivatives 10a−d and 11a−d. General Procedure. To a cooled (0 °C) solution of the corresponding 2-thiobenzyl pyrimidinone **9a−b** (1 equiv) in DMF (3 mL/mmol), 1.1 equiv of the corresponding base (Cs_2CO_3, DBU, or TMG) was added. The reaction mixture was stirred at 0 °C for 30 min, then the corresponding alkylating agent **8a−e** (1.1 equiv) was added dropwise. The reaction mixture was stirred from 0 °C to room temp until total disappearance of **9a−b** (TLC monitoring). The solvent was eliminated under reduced pressure, and the residue containing the mixture of **10a−d** and **11a−d** was separated by flash chromatography (*n*-hexane/AcOEt).

Alkylation with Methyl Iodide (8a). According to the general procedure described above, reaction between **9a** (250 mg, 1.15 mmol); methyl iodide **8a** (0.08 mL, 1.26 mmol); and Cs_2CO_3, DBU, or TMG (1.26 mmol) in DMF (3.5 mL) after 2 h resulted in **10a** (155 mg, 62%, Cs_2CO_3; 183 mg, 73%, DBU; 193 mg, 77%, TMG) and **11a** (42 mg, 17%, Cs_2CO_3; 40 mg, 16%, DBU; 37 mg, 15%, TMG), respectively.

Spectroscopic Data for 2-Benzylsulfanyl-3-methyl-3*H*-pyrimidin-4-one (10a). Isolated as a colorless solid. mp: 114−115 °C. IR (KBr): ν 3059w, 3025w, 2931w, 1665s, 1500s, 1453m, 1404m, 1331w, 1086m, 827m, 710m. ^{1}H NMR ($CDCl_3$): δ 3.52 (s, 3H, CH_3), 4.48 (s, 2H, CH_2), 6.26 (d, 1H, J = 6.4 Hz, CH_{pyrim}), 7.30−7.50 (m, $5H_{arom}$), 7.81 (d, 1H, J = 6.4 Hz, CH_{pyrim}). ^{13}CN NMR ($CDCl_3$): δ 30.1 (q, CH_3), 36.6 (t, CH_2), 110.0 (d, CH_{pyrim}), 127.7, 128.6, 129.2 (3d, $5CH_{arom}$), 135.6 (s, C_{arom}), 151.7 (d, CH_{pyrim}), 162.0 (s, C_{pyrim}), 162.8 (s, CO). MS (EI) *m*/*e*: 232 ($[M]^+$, 90), 199 (91), 187 (66), 186 (30), 141 (78), 122 (30), 121 (37), 112 (41), 111 (30), 110 (76), 104 (32), 91 (100), 82 (47). Anal. calcd. for $C_{12}H_{12}N_2OS$ (232.07): C, 62.04; H, 5.21; N, 12.06; S, 13.80. Found: C, 62.28; H, 4.96; N, 12.29; S, 14.09%.

Spectroscopic Data for 2-Benzylsulfanyl-4-methoxypyrimidine (11a). Isolated as a colorless oil. IR (film): ν 3058m, 3025m, 2953 m, 2855w, 1559s, 1464m, 1407m, 1322s, 1228m, 1180m, 1020s, 907m, 821m, 707m. ^{1}H NMR ($CDCl_3$): δ 3.98 (s, 3H, CH_3), 4.46 (s, 2H, CH_2), 6.44 (d, 1H, J = 5.8 Hz, CH_{pyrim}), 7.30−7.50 (m, $5H_{arom}$), 8.26 (d, 1H, J = 5.8 Hz, CH_{pyrim}). ^{13}C NMR ($CDCl_3$): δ 35.2 (t, CH_2), 53.8 (q, CH_3), 103.8 (d, CH_{pyrim}), 127.1, 128.4, 129.0 (3d, $5CH_{arom}$), 137.6 (s, C_{arom}), 157.1 (d, CH_{pyrim}), 168.9 (s, CO), 171.2 (s, C_{arom}). MS (EI) *m*/*e*: 233 ($[M + 1]^+$, 43), 232 ($[M]^+$, 88), 199 (100), 184 (62), 158 (58), 155 (49), 154 (55), 129 (58), 121 (56), 110 (88), 91 (93), 89 (46), 82 (48), 81 (43). Anal. calcd. for $C_{12}H_{12}N_2OS$ (232.07): C, 62.04; H, 5.21; N, 12.06; S, 13.80. Found: C, 62.29; H, 5.40; N, 11.84; S, 14.07%.

Alkylation with Benzyl Bromide 8b and Benzyl Chloride 8c. According to the general procedure described above, reaction between **9a** (250 mg, 1.15 mmol), benzyl bromide **8b** (0.15 mL, 1.26 mmol), and Cs_2CO_3 or TMG (1.26 mmol) in DMF (3.5 mL) after 2 h resulted in **10b** (100 mg, 26%, Cs_2CO_3; 128 mg, 33%, TMG) and **11b** (190 mg, 49%, Cs_2CO_3; 197 mg, 51%, TMG), respectively. Analogous reaction with benzyl chloride **8c** (1.26 mmol) and TMG (1.26 mmol) in DMF (3.5 mL) after 2 h resulted in **10b** (128 mg, 33%), and **11b** (190 mg, 49%).

Spectroscopic Data for 3-Benzyl-2-benzylsulfanyl-3*H*-pyrimidin-4-one (10b). Isolated as a colorless solid. mp: 86−87 °C. IR (KBr): ν 3059w, 3023w, 2930w, 1680s, 1579w, 1488s, 1414m, 1314m, 1153m, 990m, 859w, 815w, 732m, 702m. ^{1}H NMR ($CDCl_3$): 4.45 (s, 2H, PhCH_2S), 5.32 (s, 2H, PhCH_2N), 6.33 (d, 1H, J = 6.4 Hz, CH_{pyrim}), 7.30−7.40 (m, $10H_{arom}$), 7.84 (d, 1H, J = 6.4 Hz, CH_{pyrim}). ^{13}C NMR ($CDCl_3$): 36.9 (t, PhCH_2S), 47.2 (t, PhCH_2N), 110.6 (d, CH_{pyrim}), 127.6, 127.7, 128.5, 128.6, 129.2 (5d, $10CH_{arom}$), 134.6, 135.5 (2s, $2C_{arom}$), 151.8 (d, CH_{pyrim}), 162.1 (s, C_{pyrim}), 162.8 (s, CO). MS (EI) *m*/*e*: 308 ($[M]^+$, 29), 218 (42), 217 (93), 186 (33), 185 (72), 167 (54), 158 (84), 148 (83), 121 (39), 111 (74), 106 (72), 95 (26), 92 (28), 91(100). Anal. calcd. for $C_{18}H_{16}N_2OS$ (308.10): C, 70.10; H, 5.23; N, 9.08; S, 10.40. Found: C, 69.91; H, 5.36; N, 9.32; S, 10.66%.

Spectroscopic Data for 4-Benzyloxy-2-benzylsulfanylpyrimidine (11b). Isolated as a colorless oil. IR (film): ν 3033m, 2946m, 1559s, 1439s, 1317s, 1221s, 1074w, 994s, 910m, 821m, 746m, 705m. ^{1}H NMR ($CDCl_3$): δ 4.48 (s, 2H, PhCH_2S), 5.44 (s, 2H, PhCH_2O), 6.51 (d, 1H, J = 5.8 Hz, CH_{pyrim}), 7.35−7.50 (m, $10H_{arom}$), 8.31 (d,1H, J = 5.8 Hz, $CH_{pyrim.}$). ^{13}C NMR ($CDCl_3$): δ 35.2 (t, PhCH_2S), 68.1 (t, PhCH_2O), 104.1 (d, CH_{pyrim}), 127.1, 128.1, 128.2, 128.4, 128.5, 128.8 (6d, $10CH_{arom}$), 135.9, 137.4 (2s, $2C_{arom}$), 157.3 (d, CH_{pyrim}), 168.3 (s, CO), 171.1 (s, C_{arom}). MS (EI) *m*/*e*: 308 ($[M]^+$, 64), 217 (76), 185 (54), 167 (50), 158 (76), 148 (77), 121 (47), 112 (50), 106 (63), 95 (50), 92 (43), 91 (100). Anal. calcd. for $C_{18}H_{16}N_2OS$ (308.10): C, 70.10; H, 5.23; N, 9.08; S, 10.40. Found: C, 70.23; H, 5.08; N, 9.29; S, 10.60%.

Alkylation with Ethyl Bromoacetate (8d). According to the general procedure described above, reaction between **9b** (150 mg, 0.50 mmol), ethyl bromoacetate **8d** (0.07 mL, 0.55 mmol), and TMG (0.07 mL, 0.55 mmol) in dry DMF (1.5 mL) after 2 h resulted in 20 mg (11%) of **10c** and 131 mg (68%) of **11c**.

Spectroscopic Data for (2-Benzylsulfanyl-6-oxo-4-phenyl-6H-pyrimidin-1-yl) Acetic Acid Ethyl Ester (10c). Isolated as a colorless solid. mp: 105−106 °C. IR (KBr): 2955s, 2925s, 2855m, 1730s, 1663s, 1510s, 1489s, 1461m, 1380m, 1249m, 1194m, 1081m, 1025w, 853m, 775m. ^{1}H NMR ($CDCl_3$): 1.33 (t, 3H, J = 7.2 Hz, CH_3CH$_2$O), 4.28 (q, 2H, J = 7.2 Hz, CH$_3$CH_2O), 4.66 (s, 2H, PhCH_2S), 4.89 (s, 2H, PhCH_2N), 6.75 (s, 1H, CH_{pyrim}), 7.35−7.50 (m, $8H_{arom}$), 8.00−8.05 (m, $2H_{arom}$). ^{13}C NMR ($CDCl_3$): δ 14.1 (q, CH_3), 35.0 (t, PhCH_2S), 44.7 (t, PhCH_2N), 62.1 (t, CH_3-CH_2O), 104.5 (d, CH_{pyrim}), 127.0, 127.9, 128.7, 128.8, 129.1, 130.7 (6d, $10CH_{arom}$), 135.4, 136.1 (2s, $2C_{arom}$), 159.4, 161.2, 162.3, 166.5 (4s, 2CO, $2C_{pyrim}$). MS (EI) *m*/*e*: 380 ($[M]^+$, 34), 347 (40), 273 (29), 217 (40), 201 (26), 188 (25), 184 (32), 116 (19), 102 (27), 91 (100). Anal. calcd. for $C_{21}H_{20}N_2O_3S$ (380.12): C, 66.29; H, 5.30; N, 7.36; S, 8.43. Found: C, 66.01; H, 5.05; N, 7.64; S, 8.14%.

Spectroscopic Data for (2-Benzylsulfanyl-6-phenylpyrimidin-4-yloxy) Acetic Acid Ethyl Ester (11c). Isolated as a colorless solid. mp: 84−85 °C. IR (KBr): ν 3051w, 3025w, 2986m, 2940m, 1741s, 1576s, 1536s, 1443m, 1371s,

1313m, 1258s, 1197s, 1063m, 1025m, 687m. ^{1}H NMR ($CDCl_3$): δ 1.31 (t, 3H, J = 7 Hz, C*H*$_3$CH$_2$O), 4.28 (q, 2H, J = 7.2 Hz, CH$_3$C*H*$_2$O), 4.49 (s, 2H, PhC*H*$_2$S), 4.95 (s, 2H, EtOOCC*H*$_2$O), 6.98 (s, 1H, H$_{pyrim}$), 7.30−7.55 (m, 8H$_{arom}$), 8.04−8.10 (m, 2H$_{arom}$). ^{13}C NMR: 14.2 (q, CH$_3$) 35.3 (t, PhCH$_2$S), 61.3, 62.8 (2t, CH$_3$*C*H$_2$O, EtOOC*C*H$_2$O), 99.0 (d, CH$_{pyrim}$), 127.1, 128.4, 128.5, 128.7, 128.8, 130.8 (6d, 10CH$_{arom}$), 136.4, 137.7 (2s, 2C$_{arom}$), 165.4 (s, C$_{pyrim}$), 168.2, 168.8 (2s, 2CO), 170.8 (s, C$_{pyrim}$). MS (EI) *m*/*e*: 381 ([M + 1]$^+$, 33), 380 ([M]$^+$, 99), 293 (85), 261 (27), 260 (81), 156 (35), 128 (36), 91 (100), 77 (24), 65 (29). Anal. calcd. for $C_{21}H_{20}N_2O_3S$ (380.12): C, 66.29; H, 5.30; N, 7.36; S, 8.43. Found: C, 66.10; H, 5.45; N, 7.22; S, 8.55%.

Alkylation with Chloro Acetone. According to the general procedure described above, reaction between **9a** (500 mg, 2.29 mmol), chloro acetone (0.21 mL, 2.75 mmol), and TMG (0.35 mL, 2.75 mmol) in dry DMF (7 mL), after 5 h, resulted in 87 mg (14%) of **10d** and 339 mg (54%) of **11d**.

Spectroscopic Data for 2-Benzylsulfanyl-3-(2-oxopropyl)-3*H*-pyrimidin-4-one (10d). Isolated as a colorless oil. IR (film): ν 3063w, 3030w, 2963w, 2930w, 1732s, 1682s, 1406m, 1360s, 1171s, 1064m, 827m, 706m. ^{1}H NMR ($CDCl_3$): δ 2.24 (s, 3H, CH$_3$), 4.45 (s, 2H, PhCH$_2$S), 4.87 (s, 2H, CH$_3$COC*H*$_2$N), 6.25 (d, 1H, J = 6.4 Hz, CH$_{pyrim}$), 7.3−7.4 (m, 5H$_{arom}$), 7.82 (d, 1H, J = 6.4 Hz, CH$_{pyrim}$). ^{13}C NMR ($CDCl_3$): δ 27.1 (q, CH$_3$), 36.8 (t, PhCH$_2$S), 52.5 (t, CH$_3$COCH$_2$N), 110.2 (d, CH$_{pyrim}$), 127.7, 128.5, 129.1 (3d, 5CH$_{arom}$), 135.0 (s, C$_{arom}$), 152.1 (d, CH$_{pyrim}$), 161.2 (s, C$_{pyrim}$), 162.0, 198.8 (2s, 2CO). MS (EI) *m*/*e*: 274 ([M]$^+$, 29), 241 (55), 217 (19), 184 (17), 183 (33), 152 (23), 151 (99), 141 (30), 121 (16), 112 (76), 110 (62), 109 (29), 92 (23), 91 (100). Anal. calcd. for $C_{14}H_{14}N_2O_2S$ (274.08): C, 61.29; H, 5.14; N, 10.21; S, 11.69. Found: C, 61.50; H, 5.26; N, 9.98; S, 11.95%.

Spectroscopic Data for 1-(2-Benzylsulfanylpyrimidin-4-yloxy)-propan-2-one (11d). Isolated as a colorless solid. mp: 59−60 °C. IR (KBr): δ 3057m, 3031m, 2928m, 1734s, 1558s, 1446m, 1410m, 1320m, 1222m, 1058m, 921m, 817f, 708m. ^{1}H NMR ($CDCl_3$): δ 2.17 (s, 3H, CH$_3$), 4.37 (s, 2H, PhC*H*$_2$S), 4.90 (s, 2H, CH$_3$COC*H*$_2$O), 6.57 (d, 1H, J = 5.8 Hz, CH$_{pyrim}$), 7.3−7.5 (m, 5H$_{arom}$), 8.32 (d, 1H, J = 5.8 Hz, CH$_{pyrim}$). ^{13}C NMR ($CDCl_3$): δ 26.1 (q, CH$_3$) 35.1 (t, PhCH$_2$S), 69.8 (t, CH$_3$COCH$_2$O), 103.7 (d, CH$_{pyrim.}$), 127.1, 128.4, 128.7 (3d, 5CH$_{arom}$), 137.1 (s, C$_{arom}$), 157.8 (d, CH$_{pyrim}$), 167.5 (s, CO), 171.1 (s, C$_{pyrim}$), 202.4 (s, CO). MS (EI) *m*/*e*: 275 ([M + 1]$^+$, 27), 274 ([M]$^+$, 77), 241 (59), 218 (28), 217 (82), 185 (63), 184 (85), 158 (42), 152 (48), 121 (54), 110 (45), 95 (48), 92 (36), 91 (100). Anal. calcd. for $C_{14}H_{14}N_2O_2S$ (274.08): C, 61.29; H, 5.14; N, 10.21; S, 11.69. Found: C, 61.37; H, 4.98; N, 10.33; S, 11.90%.

Alkylation with Bromoacetophenone 12a. Synthesis of 13a and 13b. According to the general procedure described above, reaction between **9a** (1.50 g, 6.9 mmol), **12a** (1.68 g, 8.2 mmol), and TMG (1.0 mL, 8.2 mmol) in dry DMF (20 mL) after 2 h resulted in 1.83 g (80%) of **13a**. Analogously, reaction between **9b** (500 mg, 1.7 mmol), **12a** (415 mg, 2.0 mmol), and TMG (0.26 mL, 2.0 mmol) in dry DMF (5 mL). after 4 h resulted in 526 mg (78%) of **13b**.

Spectroscopic Data for 2-(2-Benzylsulfanylpyrimidin-4-yloxy)-1-phenylethanone (13a). Isolated as a colorless solid. mp: 85−86 °C. IR (KBr): 3064w, 3028m, 2970w, 2919w, 1697s, 1565s, 1449s, 1412m, 1320s, 1223s, 1078m, 977m, 758m, 692m. ^{1}H NMR ($CDCl_3$): δ 4.24 (s, 2H, PhC*H*$_2$S), 5.61 (s, 2H, PhCOC*H*$_2$O), 6.65 (d, J = 5.6 Hz, 1H, CH$_{pyrim}$), 7.2−7.6 (m, 8H$_{arom}$), 7.95 (d, J = 7.8 Hz, 2H$_{arom}$), 8.34 (d, J = 5.6 Hz, 1H, CH$_{pyrim}$). ^{13}C NMR ($CDCl_3$): δ 35.1 (t, PhCH$_2$S), 67.5 (t, PhCOCH$_2$O), 103.9 (d, CH$_{pyrim}$), 127.0, 127.7, 128.4, 128.6, 128.8, 133.8 (6d, 10CH$_{arom}$), 134.2, 137.1 (2s, 2C$_{arom}$), 157.8 (s, CH$_{pyrim}$), 167.7 (s, C−O), 171.0 (s, C$_{pyrim}$), 192.6 (s, CO). MS (EI) *m*/*e*: 337 ([M + 1]$^+$, 10), 336 ([M]$^+$, 45), 303 (13), 218 (17), 217 (97), 186 (10), 185 (25), 184 (91), 158 (34), 121 (14), 105 (95), 92 (12), 91 (100). Anal. calcd. for $C_{19}H_{16}N_2O_2S$ (336.09): C, 67.84; H, 4.79; N, 8.33; S, 9.53. Found: C, 67.57; H, 5.01; N, 8.09; S, 9.66%.

Spectroscopic Data for 2-(2-Benzylsulfanyl-6-phenylpyrimidin-4-yloxy)-1-phenyl-ethanone (13b). Isolated as a colorless solid. mp: 134−135 °C. IR (KBr): 3064d, 3021d, 2930m, 1706m, 1564f, 1440m, 1375m, 1306f, 1247m, 1193f, 1075m, 966m, 766m, 697m. ^{1}H NMR ($CDCl_3$): δ 4.39 (s, 2H, PhCH$_2$S), 5.67 (s, 2H, CH$_3$COC*H*$_2$O), 7.05 (s, 1H, CH$_{pyrim}$), 7.1−7.4 (m, 5H$_{arom}$), 7.5−7.6 (m, 6H$_{arom}$), 8.00−8.10 (m, 4H$_{arom}$). ^{13}C NMR: δ 35.2 (t, PhCH$_2$S), 67.7 (t, CH$_3$COCH$_2$O), 99.1 (d, CH$_{pyrim}$), 127.0, 127.1, 127.7, 128.4, 128.6, 128.7, 128.8, 130.7, 133.8 (9d, 15CH$_{arom}$), 134.3, 136.4, 137.5 (3s, 3C$_{arom}$), 165.2 (s, C$_{pyrim}$), 168.9 (s, CO), 170.7 (s, C$_{pyrim}$), 192.9 (s, CO). MS (EI) *m*/*e*: 412 ([M]$^+$, 25), 294 (20), 293 (100), 261 (14), 260 (48), 171 (8), 105 (52), 91 (71), 77 (44), 65 (13). Anal. calcd. for $C_{25}H_{20}N_2O_2S$ (412.12): C, 72.79; H, 4.89; N, 6.79; S, 7.77. Found: C, 72.57; H, 5.00; N, 6.56; S, 8.09%.

Grignard Additions. General Procedure. To a solution of **13a** (1 equiv) in dry THF (3 mL/mmol), a 1 M solution in THF of methyl- and phenylmagnesium bromide (1.3 equiv) was added dropwise at room temperature. The reaction mixture was stirred for 2 h. at room temperature under a positive pressure of dry N_2. A solution of saturated NH_4Cl (2 mL/mmol) was added. The solvent was evaporated, and the residue was partitioned between H_2O and AcOEt. The organic layer was separated, and the aqueous one washed with AcOEt (2×). The combined organic layers were washed with brine (1×) and dried over anhydrous MgSO4. Filtration and removal of the solvent under reduced pressure afforded crude **14a** or **14b** that was further purified by flash-chromatography (*n*-hexane/AcOEt).

Synthesis of 1-(2-Benzylsulfanylpyrimidin-4-yloxy)-2-phenylpropan-2-ol (14a). According to the general procedure described above, reaction between **13a** (325 mg, 0.967 mmol) and methylmagnesium bromide (1.26 mL, 1.25 mmol) in dry THF (3 mL) resulted in 309 mg (90%) of **14a**. Isolated as a colorless oil. IR (film): 3409br, 3058m, 3030m, 2979m, 2938m, 1561s, 1440s, 1371m, 1221m, 1019s, 952m, 822m, 766m, 705m. ^{1}H NMR ($CDCl_3$): δ 1.66 (s, 3H, CH$_3$), 2.91 (s, 1H, OH), 4.42 (s, 2H, PhC*H*$_2$S), 4.46 (d, J = 11.2 Hz, 1H, CH$_2$O), 4.57 (d, J = 11.2 Hz, 1H, CH$_2$O), 6.42 (d, J = 5.8 Hz, 1H, CH$_{pyrim}$), 7.3−7.5 (m, 10H$_{arom}$), 8.26 (d, J = 5.6 Hz, 1H, CH$_{pyrim}$). ^{13}C NMR ($CDCl_3$): δ 26.6 (q, CH$_3$), 35.3 (t, PhCH$_2$S), 73.6 (s, R$_3$*C*OH), 73.7 (t, CH$_2$O), 103.9 (d, CH$_{pyrim}$), 125.1, 127.1, 127.3, 128.3, 128.4, 128.8 (6d, 10CH$_{arom}$), 137.4, 144.4 (2s, 2C$_{arom}$), 157.5 (d, CH$_{pyrim}$),

168.5, 171.2 (2s, $2C_{pyrim}$). MS (EI) *m*/*e*: 352 ($[M]^+$, 42), 232 (21), 218 (89), 199 (19), 186 (23), 185 (96), 121 (41), 105 (19), 92 (19), 91 (100). Anal. calcd. for $C_{20}H_{20}N_2O_2S$ (352.12): C, 68.16; H, 5.72; N, 7.95; S, 9.10. Found: C, 68.44; H, 5.92; N, 8.12; S, 9.37%.

Synthesis of 2-(2-Benzylsulfanylpyrimidin-4-yloxy)-1,1-diphenylethanol (14b). According to the general procedure described above, reaction between **13a** (550 mg, 1.64 mmol) and phenylmagnesium bromide (1.96 mL, 1.96 mmol) in dry THF (5 mL) resulted in 610 mg (90%) of **14b**. Isolated as colorless solid. mp: 77−78 °C. IR (KBr): 3390br, 3059w, 3030w, 2926w, 1562s, 1438s, 1314s, 1224m, 1018m, 821w, 764w, 700m.^{1}H NMR ($CDCl_3$): δ 3.57 (s, 1H, OH), 4.42 (s, 2H, $PhCH_2S$), 4.90 (s, 2H, CH_2O), 6.36 (d, J = 5.8 Hz, 1H, CH_{pyrim}), 7.3−7.5 (m, $15H_{arom}$), 8.22 (d, J = 5.8 Hz, 1H, CH_{pyrim}). ^{13}C NMR ($CDCl_3$): δ 35.2 (t, $PhCH_2S$), 71.7 (t, CH_2O), 77.4 (s, R_3CO), 104.0 (d, CH_{pyrim}), 126.4, 127.0, 127.4, 127.9, 128.2, 128.3, 128.4, 128.5, 128.7 (d, $15CH_{arom}$), 137.4, 143.4, 143.5 (3s, $3C_{arom}$), 157.5 (d, CH_{pyrim}), 168.2 (s, C_{pyrim}), 171.2 (s, C_{pyrim}). MS (EI) *m*/*e*: 414 ($[M]^+$, 9), 232 (36), 218 (57), 199 (13), 185 (46), 183 (28), 167 (21), 165 (24), 105 (92), 91 (100). Anal. calcd. for $C_{25}H_{22}N_2O_2S$ (414.14): C, 72.44; H, 5.35; N, 6.76; S, 7.74. Found: C, 72.21; H, 5.08; N, 6.96; S, 7.46%.

Oxidations with *m*-CPBA. General Procedure. To a cooled (0 °C) solution of pyrimidine derivatives **14a** and **14b** (1 equiv) in CH_2Cl_2 (5 mL/mmol), 2.5 equiv of *m*-CPBA was added in small portions. The reaction mixture was stirred at 0 °C for 2 h until total consumption of the starting materials (TLC monitoring). The reaction mixture was diluted with CH_2Cl_2 and *i*-PrOH, and the mixture was adsorbed over silica gel. The solvent was evaporated until dryness, and the crude product was adsorbed over silica purified by flash chromatography (*n*-hexane/AcOEt).

Synthesis of 2-Phenyl-1-(2-phenylmethanesulfonylpyrimidin-4-yloxy)-propan-2-ol (15a). According to the general procedure described above, the reaction of **14a** (260 mg, 0.74 mmol) and *m*-CPBA (531 mg, 1.85 mmol) in CH_2Cl_2 (4 mL), resulted in **15a** (231 mg, 82%). Isolated as a colorless solid. mp: 47−48 °C. IR (KBr): 3505br, 3087w, 3061w, 3032w, 2980m, 2932w, 1583s, 1538m, 1470m, 1448s, 1326s, 1251m, 1125s, 1012s, 986m, 848m, 769m, 698s. ^{1}H NMR ($CDCl_3$): δ 1.67 (s, 3H, CH_3), 2.70 (s, 1H, OH), 4.56 (d, J = 11.2 Hz, 1H, CH_2O), 4.69 (d, J = 11.2 Hz, 1H, CH_2O), 4.74 (2, 2H, $PhCH_2SO_2$), 6.89 (d, J = 5.8 Hz, 1H, CH_{pyrim}), 7.3−7.5 (m, $10H_{arom}$), 8.57 (d, J = 5.8 Hz, 1H, CH_{pyrim}). ^{13}C NMR ($CDCl_3$): δ 26.6 (q, CH_3), 57.6 (t, $PhCH_2SO_2$), 73.6 (s, R_3COH), 74.9 (t, CH_2O), 111.4 (d, CH_{pyrim}), 125.1 (d, $2CH_{arom}$), 126.7 (s, C_{arom}), 127.5, 128.4, 128.7, 128.9, 131.42 (5d, $8CH_{arom}$), 143.8 (s, C_{arom}), 157.8 (d, CH_{pyrim}), 164.3 (s, C_{pyrim}), 170.1 (s, CH_{pyrim}). MS $(FAB)^+$ *m*/*e*: 385 ($[M + 1]^+$, 19), 368 (23), 367 (100), 251 (24), 187 (78), 154 (40), 138 (20), 137 (52), 136 (54), 135 (20). Anal. calcd. for $C_{20}H_{20}N_2O_4S$ (384.11): C, 62.48; H, 5.24; N, 7.29; S, 8.34. Found: C, 62.21; H, 5.38; N, 7.00; S, 8.60%.

Synthesis of 1,1-Diphenyl-2-(2-phenylmetahnesulfonylpyrimidin-4-yloxy)-ethanol (15b). According to the general procedure described above, the reaction of **14b** (490 mg, 1.18 mmol) and *m*-CPBA (851 mg, 2.96 mmol) in CH_2Cl_2 (6 mL), resulted in **15b** (440 mg, 84%). Isolated as a colorless solid. mp: 117−118 °C. IR (KBr): 3422br, 3098w, 3060w, 3032w, 1585s, 1540w, 1451s, 1324s, 1133m, 1001m, 758m, 690m. ^{1}H NMR ($CDCl_3$): δ 3.24 (s, 1H, OH), 4.76 (s, 2H, $PhCH_2SO_2$), 5.00 (s, 2H, CH_2O), 6.85 (d, J = 5.8 Hz, 1H, CH_{pyrim}), 7.3−7.5 (m, $15H_{arom}$), 8.56 (d, J = 5.8 Hz, 1H, CH_{pyrim}). ^{13}C NMR ($CDCl_3$): δ 57.5 (t, $PhCH_2SO_2$), 72.9 (t, CH_2O), 77.4 (s, R_3COH), 111.4 (d, CH_{pyrim}), 126.4 (d, $2CH_{arom}$), 126.7 (s, C_{arom}), 127.7, 128.4, 128.7, 128.8, 131.2 (5s, $13CH_{arom}$), 142.9 (s, $2C_{arom}$), 158.0 (d, CH_{pyrim}), 164.3 (s, C_{pyrim}), 169.8 (s, C_{pyrim}). MS (FAB) *m*/*e*: 447 ($[M + 1]^+$, 8), 430 (28), 429 (100), 251 (48), 197 (39), 187 (93), 183 (20), 180 (28), 179 (24), 178 (25). Anal. calcd. for $C_{25}H_{22}N_2O_4S$ (446.13): C, 67.25; H, 4.97; N, 6.27; S, 7.18. Found: C, 66.99; H, 5.11; N, 6.52; S, 7.44%.

Ipso Substitution Reaction of Pyrimidinyl Sulfone Derivatives with Primary and Secondary Amines. General Procedure. To a solution of the corresponding pyrimidinyl sulfones **15a** and **15b** (1 mmol) in dioxane (3 mL), the corresponding primary or secondary amine was added (1.1 mmol). The reaction mixture was heated at 80 °C with good stirring until total consumption of the starting material (4−24 h, TLC monitoring). The solvent was removed under reduced pressure, and the residue was purified by flash-chromatography (*n*-hexane/AcOEt).

Synthesis of 2-(2-Butylaminopyrimidin-4-yloxy)-1,1-diphenylethanol (16a). According to the general procedure described above, reaction between **15b** and *n*-butylamine resulted in **16a** in 86% yield. Isolated as a colorless solid. mp: 130−131 °C. IR (KBr): ν 3535m, 3254m, 3162w, 3055w, 2955m, 2925m, 1605s, 1581s, 1529s, 1417s, 1307s, 1221m, 1024m, 797m, 697s. ^{1}H NMR ($CDCl_3$): δ 0.98 (t, J = 7.2 Hz, 3H, CH_3), 1.35−1.70 (m, 4H, $2CH_2$), 3.41 (q, J = 6.5 Hz, 2H, CH_2N), 4.57 (s, br, 1H, exchangeable with D_2O), 4.90 (s, 2H, CH_2O), 5.20 (s, br, 1H, exchangeable with D_2O), 5.95 (d, J = 5.6 Hz, 1H, CH_{pyrim}), 7.3−7.5 (m, $10H_{arom}$), 7.98 (d, J = 5.6 Hz, 1H, CH_{pyrim}). ^{13}C NMR ($CDCl_3$): δ 13.8 (q, CH_3), 20.0, 31.6 (2 t, $2CH_2$), 41.1 (t, CH_2N), 71.4 (t, CH_2O), 77.6 (s, R_3COH), 97.0 (d, CH_{pyrim}), 126.6, 127.3, 128.1 (3d, $10CH_{arom}$), 144.0 (s, $2C_{arom}$), 158.4 (d, CH_{pyrim}), 162.1, 169.5 (2s, $2C_{pyrim}$). MS (EI) *m*/*e*: 363 ($[M]^+$, 2), 183 (69), 181 (99), 180 (25), 163 (51), 152 (39), 139 (37), 138 (55), 125 (40), 124 (49), 105 (100). Anal. calcd. for $C_{22}H_{25}N_3O_2$ (363.19): C, 72.70; H, 6.93; N, 11.56. Found: C, 72.99; H, 6.69; N, 11.36%.

Synthesis of 1,1-Diphenyl-2-{2-[4-(3-trifluoromethylphenyl)-piperazin-1-yl]-pyrimidin-4-yloxy}ethanol (16b). According to the general procedure described above, reaction between **15b** and 1-(3-trifluoromethylphenyl)-piperazine resulted in **16b** in 88% yield. Isolated as a colorless solid. mp: 169−170 °C. IR (KBr): ν 3369br, 2885w, 2853w, 2813w, 1575s, 1493s, 1439s, 1306s, 1230s, 1159m, 1115s, 1011m, 951m, 697m. ^{1}H NMR ($CDCl_3$): δ 3.33 (t, J = 5.0 Hz, 4H, CH_2N), 3.85 (s, 1H, OH), 4.01 (t, J = 5.0 Hz, 4H, CH_2N), 4.91 (s, 2H, CH_2O), 6.02 (d, J = 5.6 Hz, 1H, CH_{pyrim}), 7.1−7.5 (m, $14H_{arom}$), 8.11 (d, J = 5.6 Hz, 1H, CH_{pyrim}). ^{13}C NMR ($CDCl_3$): 43.6, 48.7 (2t, $4CH_2N$), 71.2 (t, CH_2O), 77.6 (s, R_3COH), 97.2 (d, CH_{pyrim}), 112.5 (d, CH_{arom}), 116.2 (d, CH_{arom}), 119.1 (d, $1CH_{arom}$), 124.2 (s, CF_3), 126.6, 127.5, 128.3, 129.6 (4d, $11CH_{arom}$), 131.6 (s, C_{arom}), 143.9, 151.3 (2s, $3C_{arom}$), 158.4 (d, CH_{pyrim}), 161.3 (s, C_{pyrim}),

169.4 (s, C_{pyrim}). MS (EI) *m*/*e*: 520 ([M]$^+$, 22), 333 (25), 320 (55), 302 (100), 201 (53), 200 (26), 179 (31), 178 (31), 173 (25), 172 (58), 165 (30). Anal. calcd. for $C_{29}H_{27}F_3N_4O_2$ (520.21): C, 66.91; H, 5.23; N, 10.76. Found: C, 67.15; H, 5.41; N, 11.02%.

Synthesis of 2-Phenyl-1-{2-[4-(3-trifluoromethylphenyl)-piperazin-1-yl]-pyrimidin-4-yloxy}-propan-2-ol (16c). According to the general procedure described above, reaction between **15a** and 1-(3-trifluoromethylphenyl)-piperazine resulted in **16c** in 91% yield. Isolated as a colorless solid. mp: 134−135 °C. IR (KBr): ν 3374br, 2983w, 2885w, 2851m, 1582s, 1497s, 1442s, 1367m, 1337m, 1310s, 1233s, 1159m, 1122s, 1069m, 1028m, 1000m, 952m, 788m, 699m. ^{1}H NMR ($CDCl_3$): δ 1.70 (s, 3H, CH_3), 3.33 (t, J = 5.1 Hz, 4H, CH_2N), 3.41 (s, 1H, OH), 4.00 (t, J = 5.1 Hz, 4H, CH_2N), 4.47 (d, J = 11.2 Hz, 1H, CH_2O), 4.58 (d, J = 11.2 Hz, 1H, CH_2O), 6.07 (d, J = 5.6 Hz, 1H, CH_{pyrim}) 7.1−7.6 (m, 9H_{arom}), 8.13 (d, J = 5.6 Hz, 1H, CH_{pyrim}). ^{13}C NMR ($CDCl_3$): δ 26.7 (q, CH_3), 43.6, 48.70 (2t, 4CH_2N), 73.4 (t, CH_2O), 73.9 (s, R_3*C*OH), 97.1 (d, CH_{pyrim}), 112.5, 116.2, 119.1 (3d, 3CH_{arom}), 124.2 (s, CF_3), 125.2, 127.2, 128.3, 129.6 (4d, 6CH_{arom}), 131.5 (s, C_{arom}), 144.7, 151.4 (2s, 2C_{arom}), 158.4 (d, CH_{pyrim}), 161.3, 169.6 (2s, 2C_{pyrim}). MS (EI) *m*/*e*: 458 ([M]$^+$, 19), 271 (35), 259 (17), 258 (100), 241 (12), 240 (71), 201 (48), 200 (19), 173 (22), 172 (53). Anal. calcd. for $C_{24}H_{25}F_3N_4O_2$ (458.19): C, 62.87; H, 5.50; N, 12.22. Found: C, 62.62; H, 5.39; N, 12.47%.

Solid-Phase Synthesis of 19a−l. General Procedure. High-loaded Merrifield resin **1**, 2.0 g. (6.8 mmol) was swollen for 5 min with 35 mL of CH_2Cl_2, and the solvent was drained. Dry DMF (35 mL) and the corresponding 2-mercaptopyrimidones **2a**−**b** (21 mmol) were added. To this suspension, Et_3N (21 mmol) was added dropwise at room temperature with constant shaking for a period of 1 h. After additional vortexing at room temperature for 15 h, the mixture was washed successively with DMF (3 × 20 mL), MeOH (3 × 20 mL), dioxane (3 × 20 mL), MeOH (3 × 20 mL), CH_2Cl_2(3 × 20 mL), and *n*-pentane (2 × 20 mL). The resins **3a**−**b** were collected and dried at 40 °C/high vacuum overnight. IR (on bead **3a**): 2926m, 1675s, 1576m, 1458m, 1388m, 1259w, 1093m, 816m. IR (on bead **3b**): 2921m, 28032, 1664s, 1568m, 1440m, 1379m, 1300w, 1198m, 1060w, 935w. The polymer-bound pyrimidinones **3a**−**b** were swollen with CH_2Cl_2 (5 mL/mmol) for 5 min and then the solvent was flushed. Dry DMF (5 mL/mmol) and TMG (4 equiv) were added. The reaction mixture was shaken at room temperature for 30 min. Then a solution of the corresponding phenacyl bromides **12a**−**c** (4 equiv) in DMF (3 mL/mmol) was added dropwise. The mixture was shaken at room temperature for an additional 20 h. The excesses of reagents were removed by filtration, and the resins **17a**−**d** were washed successively with DMF (3×), CH_2Cl_2 (3×), MeOH (3×) and *n*-pentane (2×) (10 mL/mmol of resin). Resins **17a**−**d** were collected and dried at 40 °C/high vacuum overnight. IR (on bead **17a**): 3026m, 2916m, 2853m, 1696s, 15582, 1443m, 1320m, 1211m, 971m, 816m, 753m; IR (on bead **17b**): 3022w, 2919m, 2853w, 1704s, 1568m, 1533m, 1445m, 1379m, 1300w, 1195m, 981m, 835w; IR (on bead **17c**): 3022m, 2919m, 2850m, 1704s, 1560s, 1528s, 1444m, 1343s, 1218m, 1012w, 813m; IR (on bead **17d**): 2920m, 1693s, 1637m, 1557s, 1442m, 1316m, 1210m, 1085w. The polymer-bound pyrimidines **17a**−**d**, were swollen with CH_2Cl_2 (5 mL/mmol), and then the solvent was drained. CH_2Cl_2 (5 mL/mmol) and *m*-CPBA (3 equiv) were added. The reaction mixture was shaken at room temperature for 15 h. Resins **18a**−**d** were washed successively with CH_2Cl_2 (3×), *i*-PrOH (3×), CH_2Cl_2 (3×), and *n*-pentane (2×) (10 mL/mmol of resin). Resins **18a**−**d** were collected and dried at 40 °C/high vacuum overnight. The corresponding polymer-bound sulfones **18a**−**d** were then suspended in dioxane (3 mL/mmol) and treated with 1.2 equiv of different primary and secondary amines at 60−80 °C for 8 h. The corresponding pyrimidines **19a**−**l** liberated from the resins were collected individually, and the resins were further washed with small portions of dioxane. The solvent was evaporated, and the residue was filtered through a small plug of silica gel, affording pure **19a**−**l** (Table 2).

Synthesis of 2-(2-Butylamino-pyrimidin-4-yloxy)-1-phenyl-ethanone (19a). Isolated as a colorless solid. mp: 94−95 °C. IR (KBr): 3258m, 2958w, 2937w, 1708m, 1609s, 1536s, 1416m, 1317m, 1223m, 1076m, 963w, 805m, 758w. ^{1}H NMR ($CDCl_3$): 0.84 (t, 3H, J = 7.0 Hz, CH_3), 1.20−1.50 (m, 4H, 2CH_2), 3.19 (q, 2H, J = 5.8 Hz, CH_2N), 5.17 (s, br, 1H, NH), 5.54 (s, 2H, CH_2O), 6.19 (d, 1H, J = 5.6 Hz, CH_{pyrim}). 7.5−7.6 (m, 3H_{arom}), 7.9−8.0 (m, 2H_{arom}), 8.06 (d, 1H, J = 5.6 Hz, CH_{pyrim}). ^{13}C NMR ($CDCl_3$): 13.7 (q, CH_3), 19.9, 31.6 (2t, 2CH_2), 41.1 (t, CH_2N), 67.0 (t, CH_2O), 96.8 (d, CH_{pyrim}), 127.8, 128.7, 133.6 (3d, 5 CH_{arom}), 134.7 (s, C_{arom}), 158.6 (d, $CH_{pyrim.}$), 162.1, 168.7 (2s, 2$C_{pyrim.}$), 193.6 (s, C═O). MS (EI) *m*/*e*: 285 ([M]$^{\bullet+}$, 14), 256 (23), 243 (40), 242 (64), 229 (21), 166 (91), 124 (38), 119 (32), 105 (100), 91 (82).

Synthesis of 2-[2-(3,4-Dihydro-1*H*-isoquinolin-2yl)-pyrimidin-4-yloxy]-1-phenyl-ethanone (19b). Isolated as a colorless solid. mp: 95−96 °C. IR (KBr): 3063w, 3026w, 2933w, 2897w, 1692s, 1596s, 1562s, 1449s, 1344m, 1234s, 1088m, 969m, 747m. ^{1}H NMR ($CDCl_3$): 2.80 (t, 2H, J = 5.8 Hz, CH_2), 3.86 (t, 2H, J = 5.8 Hz, CH_2), 4.68 (s, 2H, CH_2), 5.52 (s, 2H, CH_2O), 6.20 (d, 1H, J = 5.6 Hz, CH_{pyrim}), 7.0−8.0 (m, 9H_{arom}), 8.17 (d, 1H, J = 5.6 Hz, CH_{pyrim}). ^{13}C NMR ($CDCl_3$): 28.7, 41.3, 46.0 (3t, 3CH_2), 67.2 (t, CH_2O), 96.2 (d, CH_{pyrim}), 126.0, 126.2, 126.3, 127.9, 128.4, 128.8, 133.6 (7d, 9CH_{arom}), 133.9, 134.9, 135.0 (3s, 3C_{arom}), 158.6 (s, CH_{pyrim}), 160.9, 168.2 (2s, 2C_{pyrim}), 194.1 (s, CO). MS (EI) *m*/*e*: 345 ([M]$^{\bullet+}$, 54), 227 (30), 226 (100), 132 (76), 130 (44), 117 (17), 115 (39), 105 (40), 104 (29), 103 (22), 95 (24), 91 (30).

Synthesis of 1-Phenyl-2-{2-[4-(3-trifluoromethyl-phenyl)-piperazin-1-yl]-pyrimidin-4-yloxy}-ethanone (19c). Isolated as a colorless solid. mp: 105−106 °C. IR (KBr): 2850w, 1700m, 1598s, 1475m, 1440s, 1369m, 1328m, 1308m, 1231s, 1155m, 1113s, 1002m, 979m, 688w. ^{1}H NMR ($CDCl_3$): 3.17 (t, 4H, J = 5.0 Hz, CH_2N), 3.82 (t, 4H, J = 5.0 Hz, CH_2N), 5.51 (s, 2H, CH_2O), 6.23 (d,1H, J = 5.6 Hz, CH_{pyrim}), 7.0−8.1 (m, 9H_{arom}), 8.15 (d, 1H, J = 5.6 Hz, CH_{pyrim}). ^{13}C NMR ($CDCl_3$): 43.5, 48.5 (2t, 4CH_2N), 67.4 (t, CH_2O), 96.9 (d, CH_{pyrim}), 112.4 (d, CH_{arom}), 116.1 (d, CH_{arom}), 119.0 (d, CH_{arom}), 124.2 (s, CF_3), 127.8, 128.8, 129.5 (3d, 5 CH_{arom}), 131.4 (s, C_{arom}−CF_3), 133.7 (d, CH_{arom}), 134.8, 151.3 (2s, 2C_{arom}), 158.6 (d, CH_{pyrim}), 161.1, 168.5

(2s, $2C_{pyrim}$), 193.9 (s, CO). MS (EI) *m*/*e*: 442 ($[M]^{\bullet+}$, 7), 323 (21), 243 (21), 242 (100), 172 (22), 136 (19), 119 (23), 105 (37), 91 (35).

Synthesis of 2-(2-Butylamino-6-phenyl-pyrimidin-4-yloxy)-1-phenyl-ethanone (19d). Isolated as a colorless solid. mp: 109−110 °C. IR (KBr): 3425m, 2946m, 2867w, 1702m, 1590s, 1548m, 1362s, 1208m, 767m, 693m. ^{1}H NMR ($CDCl_3$): 0.87 (t, 3H, J = 7.0 Hz, CH_3), 1.30−1.55 (m, 4H, $2CH_2$), 3.2−3.3 (m, 2H, CH_2N), 5.62 (s, 2H, CH_2O), 6.63 (s, 1H, CH_{pyrim}), 7.45−7.65 (m, $6CH_{arom}$), 8.00−8.05 (m, $4CH_{arom}$). ^{13}C NMR ($CDCl_3$): 13.7 (q, CH_3), 20.0, 31.6 (2t, $2CH_2$), 41.2 (t, CH_2N), 67.4 (t, CH_2O), 92.8 (d, CH_{pyrim}), 127.0, 127.8, 128.6, 128.8, 130.3, 133.7 (6d, $10CH_{arom}$), 134.6, 137.0 (2s, $2C_{arom}$), 161.6, 165.4, 169.9 (3s, $3C_{pyrim}$), 193.6 (s, CO). MS (EI) *m*/*e*: 361 ($[M]^{\bullet+}$, 20), 332 (45), 319 (54), 318 (71), 305 (38), 242 (100), 200 (75), 128 (49), 105 (99), 91 (87), 77 (76).

Synthesis of 1-Phenyl-2-{6-phenyl-2-[4-(3-trifluoromethyl-phenyl)-piperazin-1-yl]-pyrimidin-4-yloxy}-ethanone (19e). Isolated as a colorless solid. mp: 157−158 °C. IR (KBr): 2994w, 2894w, 2824m, 1692s, 1536s, 1489s, 1369s, 1308m, 1281m, 1238m, 1155m, 1117m, 982m, 773m, 693m. ^{1}H NMR ($CDCl_3$): 3.21 (t, 4H, J = 5.0 Hz, CH_2N), 3.93 (t, 4H, J = 5.0 Hz, CH_2N), 5.57 (s, 2H, CH_2O), 6.69 (s, 1H, CH_{pyrim}), 7.0−8.1 (m, $14H_{arom}$). ^{13}C NMR ($CDCl_3$): 43.6, 48.6 (2t, 4 CH_2N), 67.6 (2t, CH_2O), 92.4 (d, CH_{pyrim}), 112.3 (d, CH_{arom}), 116.0 (d, CH_{arom}), 119.0 (d, CH_{arom}), 124.3 (s, CF_3), 127.0, 127.9, 128.5, 128.8, 129.6, 130.2 (6d, $10CH_{arom}$), 131.4 (s, $C_{arom}-CF_3$), 133.7 (d, CH_{arom}), 134.9, 137.7 (2s, $2C_{arom}$), 161.0, 166.0, 169.7 (3s, $3C_{pyrim}$), 194.1 (s, CO). MS (EI):

Synthesis of 2-(2-Butylamino-pyrimidin-4-yloxy)-1-(3-nitro-phenyl)-ethanone (19f). Isolated as a colorless solid. mp: 117−118 °C IR (KBr): 3251s, 3082w, 2956m, 2952m, 2858d, 1708s, 1612s, 1586s, 1533s, 1475m, 1355m, 1311s, 1222s, 1073m, 1004m, 802s, 728m. ^{1}H NMR ($CDCl_3$): 0.85 (t, 3H, J = 7.1 Hz, CH_3), 1.24−1.27 (m, 2H, CH_2), 1.41−1.48 (m, 2H, CH_2), 3.19 (m, 2H, CH_2N), 5.30 (s, br, 1H, NH), 5.52 (s, 2H, CH_2O), 6.17 (d, 1H, J = 5.6 Hz, CH_{pyrim}), 7.74 (t, 1H, CH_{arom}, J = 8 Hz), 8.05 (d, 1H, J = 5.6 Hz, CH_{pyrim}), 8.33 (d, 1H, CH_{arom}, J = 8 Hz), 8.48 (d, 1H, CH_{arom}, J = 8 Hz), 8.83 (s, 1H, CH_{arom}). ^{13}C NMR ($CDCl_3$): 13.7 (q, CH_3), 19.9, 31.5 (2t, $2CH_2$), 41.1 (t, CH_2N), 67.3 (t, CH_2O), 96.6 (d, CH_{pyrim}), 122.8, 127.8, 130.1, 133.5 (4d, $4CH_{arom}$), 135.9, 148.4 (2s, $2C_{arom}$), 158.9 (d, CH_{pyrim}), 162.0, 168.3 (2s, $2C_{arom}$), 192.3 (s, CO). MS (EI) *m*/*e*: 330 ($[M]^{\bullet+}$, 6), 301 (23), 287 (100), 166 (65), 150 (47), 140 (22), 136 (46), 124 (34), 104 (22), 94 (34), 90 (33).

Synthesis of 1-(3-Nitro-phenyl)-2-{2-[4-(3-trifluoromethyl-phenyl)-piperazin-1-yl]pyrimidin-4-yloxy}-ethanone (19g). Isolated as a colorless solid. mp: 132−133 °C. IR (KBr): 3096w, 2925w, 2841m, 1718s, 1579s, 1490m, 1445s, 1350s, 1231s, 1110s, 793m. ^{1}H NMR ($CDCl_3$): 3.22 (t, 4H, J = 5.1 Hz, CH_2N), 3.83 (t, 4H, J = 5.1 Hz, CH_2N), 5.48 (s, 2H, CH_2O), 6.20 (d,1H, J = 5.6 Hz, CH_{pyrim}), 7.0−7.1 (m, 3H, CH_{arom}), 7.40 (t, 1H, J = 8 Hz, CH_{arom}), 7.7 (m, 1H, J = 8 Hz, CH_{arom}), 8.15 (d, 1H, J = 5.6 Hz, CH_{pyrim}), 8.34 (d, 1H, J = 7.8 Hz, CH_{arom}), 8.49 (double triplet, 1H, J = 7.4 Hz, J' = 0.8 Hz, CH_{arom}), 8.84 (s, 1H, CH_{arom}). ^{13}C NMR ($CDCl_3$): 43.5, 48.6 (2t, $4CH_2N$), 68.0 (t, CH_2O), 96.7 (d, CH_{pyrim}), 112.5 (d, CH_{arom}), 116.3 (d, CH_{arom}), 119.0, 122.8 (2d, $2CH_{arom}$), 124.2 (s, CF_3), 127.8, 129.6, 130.2 (3d, $3CH_{arom}$), 131.4 (s, $C_{arom}-CF_3$), 133.5 (d, CH_{arom}), 136.0, 148.4, 151.2 (3s, $3C_{arom}$), 158.9 (d, CH_{pyrim}), 160.1, 168.2 (2s, C_{pyrim}), 192.8 (s, CO). MS (EI) *m*/*e*: 487 ($[M]^{\bullet+}$, 4), 288 (15), 287 (100), 257 (25), 201 (16), 172 (22), 150 (17), 136 (21).

Synthesis of 2-(-2-Morpholin-4-yl-pyrimidin-4-yloxy)-1-(3-nitro-phenyl)-ethanone (19h). Isolated as a colorless solid. mp:111−112 °C. IR (KBr): 3073w, 2963w, 2921m, 2853m, 1695s, 1567s, 1453s, 1348s, 1293s, 1233s, 1104m, 1031m, 805m, 696m. ^{1}H NMR ($CDCl_3$): 3.65−3.75 (m, 8H, $4CH_2$), 5.44 (s, 2H, CH_2O), 6.17 (d, 1H, J = 5.4 Hz, CH_{pyrim}), 7.73 (t, 1H, J = 8 Hz, CH_{arom}), 8.10 (d, 1H, J = 5.4 Hz, CH_{pyrim}), 8.30 (d, 1H, J = 7 Hz, CH_{arom}), 8.46 (d, 1H, J = 8 Hz, CH_{arom}), 8.79 (s, 1H, CH_{arom}). ^{13}C NMR ($CDCl_3$): 44.1 (t, CH_2N), 66.6, 67.9 (2t, $2CH_2O$), 96.6 (d, CH_{pyrim}), 122.8, 127.8, 130.1, 133.4 (4d, $4CH_{arom}$), 136.0, 148.4 (2s, $2C_{arom}$), 158.8 (d, CH_{pyrim}), 161.1, 168.1 (2s, $2C_{pyrim}$), 192.8 (s, CO). MS (EI) *m*/*e*: 344 ($[M]^{\bullet+}$, 47), 343 (22), 316 (22), 314 (35), 313 (81), 287 (65), 286 (30), 180 (88), 164 (27), 162 (36), 15 (25), 150 (100).

Synthesis of 2-(2-Butylamino-pyrimidin-4-yloxy)-1-(4-chloro-phenyl)-ethanone (19i). Isolated as a colorless solid. mp: 117−118 °C. IR (KBr): 3238m, 2956m, 2929m, 2867m, 1694s, 1612s, 1586s, 1530s, 1432m, 1309m, 1223m, 1095m, 963m, 799m. ^{1}H NMR ($CDCl_3$): 0.85 (t, 3H, J = 6.8 Hz, CH_3), 1.25−1.45 (m, 4H, $2CH_2$), 3.2−3.25 (m, 2H, CH_2N), 5.21 (s, br, 1H, NH), 5.48 (s, 2H, CH_2O), 6.17 (d, 1H, J = 5.6 Hz, CH_{pyrim}), 7.49 (d, 2H, J = 8.6 Hz, $2CH_{arom}$), 7.94 (d, 2H, J = 8.6 Hz, $2CH_{arom}$), 8.06 (d, 1H, J = 5.6 Hz, CH_{pyrim}). ^{13}C NMR ($CDCl_3$): 13.7 (q, CH_3), 19.9, 31.5 (2t, $2CH_2$), 41.1 (t, CH_2N), 67.0 (t, CH_2O), 96.8 (d, CH_{pyrim}), 129.1, 129.2 (2d, $4CH_{arom}$), 132.9, 140.1 (2s, $2C_{arom}$), 158.7 (d, CH_{pyrim}), 162.0, 168.5 (s, $2C_{pyrim}$), 192.7 (s, CO). MS (EI) *m*/*e*: 319 ($[M]^{\bullet+}$, 10), 290 (20), 278 (20), 277 (32), 276 (53), 166 (96), 153 (23), 141 (32), 139 (100), 127 (25), 125 (79), 124 (46), 111 (39).

Synthesis of 1-(4-Chloro-phenyl)-2-{2-[4-(3-trifluoromethyl-phenyl)-piperazin-yl]-pyrimidin-4-yloxy}-ethanone (19j). Isolated as a colorless solid. mp: 144−145 °C. IR (KBr): 3124w, 2846w, 1702s, 1576s, 1476m, 1437s, 1330m, 1304m, 1230s, 1110m, 978m, 946m. ^{1}H NMR ($CDCl_3$): 3.18 (t, 4H, J = 4.8 Hz, CH_2N), 3.81 (t, 4H, J = 4.8 Hz, CH_2N), 5.44 (s, 2H, CH_2O), 6.21 (d, 1H, J = 5.6 Hz, CH_{pyrim}). 7.1−7.2 (m, 3H, CH_{arom}), 7.38 (t, 1H, J = 8.2 Hz, CH_{arom}), 7.51 (t, 2H, J = 8.4 Hz, CH_{arom}), 7.9−8.0 (m, 2H, CH_{arom}), 8.15 (d, 1H, J = 5.6 Hz, CH_{pyrim}). ^{13}C NMR ($CDCl_3$): 43.4, 48.5 (2t, $4CH_2N$), 67.5 (t, CH_2O), 96.8 (d, CH_{pyrim}), 112.4 (d, CH_{arom}), 116.2 (d, CH_{arom}), 119.0 (d, CH_{arom}), 124.2 (s, CF_3), 129.2, 129.3, 129.6 (3d, $5CH_{arom}$), 131.4 (s, $C_{arom}-CF_3$), 133.0, 140.2, 151.3 (3s, $3C_{arom}$), 158.7 (d, CH_{pyrim}), 161.0, 168.3 (2s, $2C_{pyrim}$), 193.0 (s, CO). MS (EI) *m*/*e*: 476 ($[M]^{\bullet+}$, 5), 323 (19), 278 (33), 276 (100), 172 (21), 139 (27), 136 (18), 125 (25).

Synthesis of 1-(4-Chloro-phenyl)-2-(2-morpholin-4-yl-pyrimidin-4-yloxy)-ethanone (19k). Isolated as a colorless solid. mp: 85−86 °C. IR (KBr): 2965m, 2921w, 2900m, 2857m, 1704s, 1591s, 1555s, 1508s, 1460m, 1307m, 1230m, 1089m, 969m. ^{1}H NMR ($CDCl_3$): 3.55−3.7 (m, 8H, $4CH_2$),

5.43 (s, 2H, CH_2O), 6.20 (d, 1H, $J = 5.6$ Hz, $CH_{pyrim.}$), 7.50 (dd, 2H, $J = 6.8$ Hz, $J' = 1.8$ Hz, CH_{arom}), 7.94 (dd, 2H, $J = 6.6$ Hz, $J' = 1.8$ Hz, CH_{arom}), 8.14 (d, 1H, $J = 5.6$ Hz, CH_{pyrim}).^{13}C NMR ($CDCl_3$): 44.2 (t, $2CH_2N$), 66.6, 67.5 (2t, $2CH_2O$), 96.8 (d, CH_{pyrim}), 129.2, 129.3 (2d, $4CH_{arom}$), 133.1, 140.2 (2s, $2C_{arom}$), 158.6 (d, CH_{pyrim}), 161.2, 168.3 (2s, $2C_{pyrim}$), 193.1 (s, CO). MS (EI) *m*/*e*: 332 ($[M]^{\bullet+}$, 56), 304 (37), 303 (43), 302 (80), 275 (67), 179 (92), 149 (88), 140 (65), 139(100), 125 (49), 111 (77).

Synthesis of 1-(4-Chloro-phenyl)-2-[2-(3,4-dimethoxy-phenylamino)-pyrimidin-4-yloxy]-ethanone (19l). Isolated as an orange solid. mp: 122−123 °C. IR (KBr): 3244m, 3182w, 3006w, 2936m, 1705m, 1582s, 1524s, 1466m, 1421s, 1295m, 1213m, 1086m, 974m, 793m. ^{1}H NMR ($CDCl_3$): 3.72 (s, 3H, CH_3O), 3.83 (s, 3H, CH_3O), 5.58 (s, 2H, CH_2O), 5.90 (d, 1H, $J = 8.2$ Hz, NH), 6.36 (d, 1H, $J = 5.2$ Hz, CH_{pyrim}), 6.44 (d, 1H, $J = 2.4$ Hz, CH_{arom}), 7.30 (s, 1H, CH_{arom}), 7.54 (d, 2H, $J = 8.2$ Hz, CH_{arom}), 7.77 (d, 1H, $J = 8.8$ Hz, CH_{arom}), 7.96 (d, 2H, $J = 8.2$ Hz, CH_{arom}), 8.20 (d, 1H, $J = 5.4$ Hz, CH_{pyrim}). ^{13}C NMR ($CDCl_3$): 55.4, 55.6 (2q, $2CH_3O$), 67.3 (t, CH_2O), 98.5 (d, CH_{arom}), 98.6 (d, CH_{pyrim}), 102.7, 120.3 (2d, $2CH_{arom}$), 121.9 (s, C_{arom}), 129.2, 129.3 (2d, $4CH_{arom}$), 132.9, 140.2, 149.7,155.4 (4s, $4C_{arom}$), 158.6 (d, CH_{pyrim}), 159.6, 168.5 (2s, C_{pyrim}), 192.2 (s, CO). MS (EI) *m*/*e*: 399 ($[M]^{\bullet+}$, 52), 369 (27), 368 (100), 216 (33), 215 (23), 139 (62), 138 (20), 125 (64), 110 (37).

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Supporting Information Available. Representative spectra of synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

Note Added after ASAP Posting

This article was inadvertently posted ASAP without the Supporting Information paragraph. The corrected version was posted with the issue.

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