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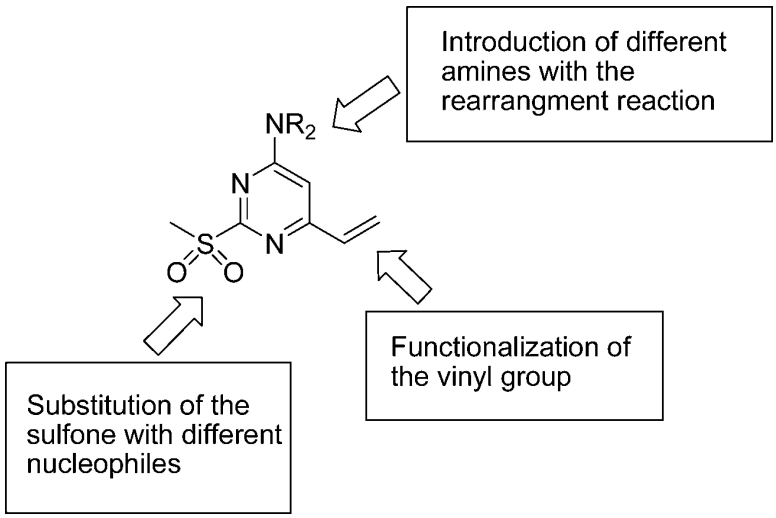

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Parallel Solution-Phase Synthesis of 4-Dialkylamino-2-methylsulfonyl-6-vinylpyrimidines

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A simple and straightforward methodology for the parallel, solution-phase synthesis of novel 4-dialkylamino-2-methylsulfonyl-6-vinylpyrimidines **9a**−**j** has been developed. Starting from 2-methylthio-6-[2-(*p*-toluensulfonyloxy)ethan-1-yl]-4(3*H*)-pyrimidinone (**6**), a three-step procedure (namely, tosylate substitution by amines, base-catalyzed rearrangement, and sulfide to sulfone oxidation) using a Büchi Sincore synthesizer gave the final products in high yield after simple ethyl acetate extraction and without further purification. Interestingly, when the final oxidation step was performed on 4-arylpiperazine derivatives **8g**−**j**, the corresponding highly polar piperazine *N*-oxides **9g**−**j** were obtained, which conversely needed chromatographic purification in order to give the pure products.

Introduction

High-speed chemical techniques have recently become an important tool for the rapid identification of new lead compounds.[1,2] Solid- and solution-phase synthesis, as well as microwave assisted techniques, represent nowadays the main tools for rapid lead structure identification. Particularly, solution-phase strategies have recently become very popular due to their many advantages over solid-phase approaches, such as the use of traditional analytical techniques (TLC, HPLC, GC/MS and NMR) for reaction monitoring.[3] Although parallel solution-phase chemistry has proven to be useful for lead generation and lead optimization, the rapid purification or isolation of desired compounds from a reaction mixture represents a bottleneck in the synthetic procedure. For this reason, solid-supported reagents and scavengers have been finding increasingly wider application as tools for faster isolation of pure compounds in solution-phase synthesis of compound libraries.[4]

The present work is an extension of our ongoing efforts toward the development of new methodologies for the synthesis of pyrimidine and pyrimidinone derivatives as potential nonnucleoside reverse transcriptase inhibitors (NNRTIs) of human immunodeficiency virus (HIV).[5] The HIV-RT is an attractive target for the development of selective inhibitors, since the nonnucleoside inhibitor binding site (NNIBS) is elastic, and its conformation depends on the size, chemical structure, and binding mode of the specific NNRTI.[6] The rapid emergence of drug-resistant viral variants in HIV-1-infected patients is the primary cause of treatment failure in long-term administration. Therefore, with the aim of identifying new lead compounds for the development of novel NNRTIs capable of overcoming the effects of resistant mutations, we have set up a simple and efficient methodology for the parallel solution-phase synthesis of a small library of pyrimidine derivatives.

Results and Discussion

With the aim of finding a methodology for the cleavage of pyrimidine derivatives from the Merrifield resin, we synthesized compound **1**,[7] bearing in position 2 a side chain mimicking the spacer we used in previous works for the solid-phase synthesis of similar compounds.[8] A possible method to release 2-aminopyrimidines from polymer-supported 2-alkylthiopyrimidines entails oxidation of the sulfur atom to sulfone, followed by nucleophilic displacement by amines.[9] Accordingly, compound **1** (Scheme 1) was reacted with Oxone in a 1:1 mixture of MeOH/H_2O to give the sulfone **2** which, upon treatment with pyrrolidine at 80 °C, was expected to provide **3**. Quite surprisingly, however, no trace of **3** was detected in the reaction medium because the only cleavage product was compound **4**.

The formation of **4** can be explained assuming that the sulfone moiety may confer Michael acceptor properties to the vinyl group of **2**: in fact, when **1** was treated with pyrrolidine, neither displacement nor addition reaction occurred. This result suggested testing the ability of activated 6-vinyl derivatives to bind covalently to the basic amino acid residues of HIV-1 RT active site in order to find new NNRTIs. We decided, therefore, to develop a methodology for the solution-phase parallel synthesis of pyrimidine derivatives bearing both the 6-vinyl and 2-methylsulfonyl moieties and to introduce, in the first instance, a single variation in C-4 position using different amines, according

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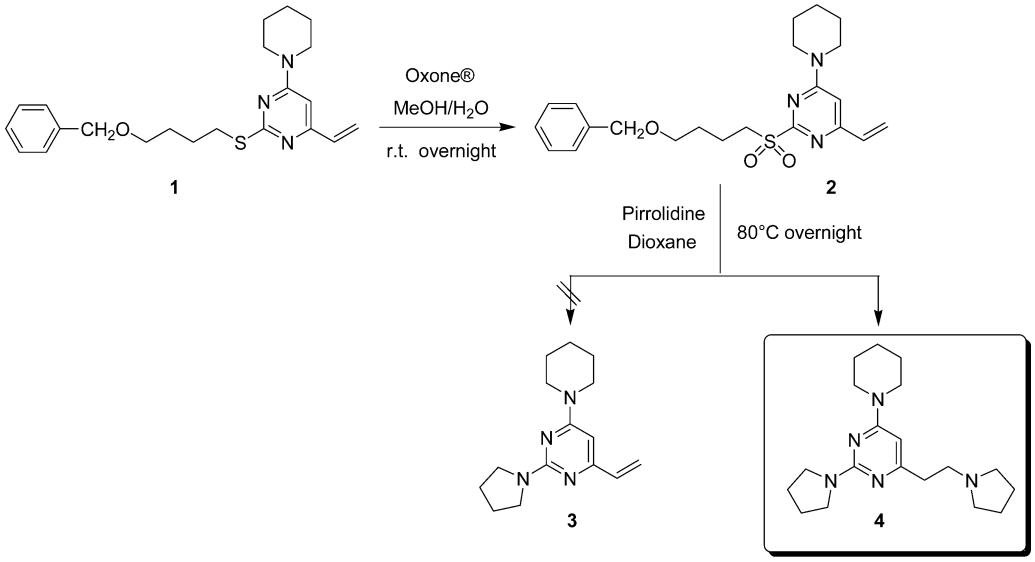
Scheme 1



to a previously reported procedure.[10] This approach would lead eventually to a general core structure suitable for further lead optimization (Figure 1); thus, the 6-vinyl group could

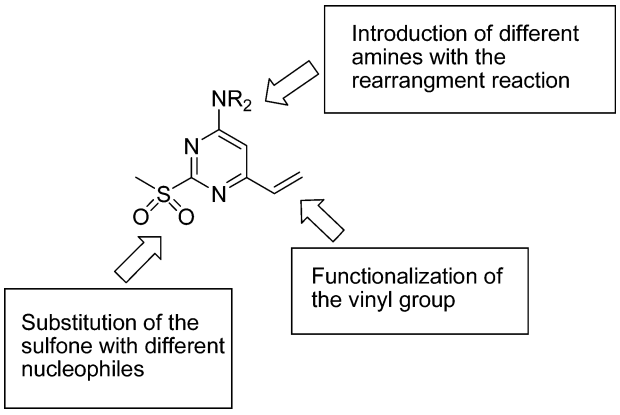
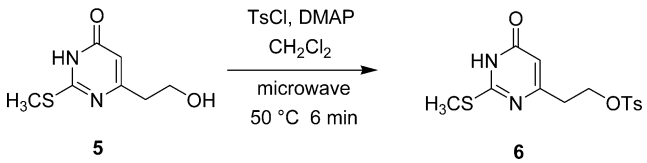


Figure 1.

be functionalized by alkylation reactions, epoxidation followed by ring opening, Diels−Alder reactions, and so on, while the 2-methylsulfonyl moiety could ideally be substituted with different nucleophiles.

As the starting material for our synthesis, we prepared tosylate **6** (Scheme 2) according to a procedure previously

Scheme 2



developed in our group[10] and which was further optimized by performing the tosylation reaction under microwave-assisted conditions. In this way, **6** could be obtained in only 6 min instead of the 24 h required by the original procedure.

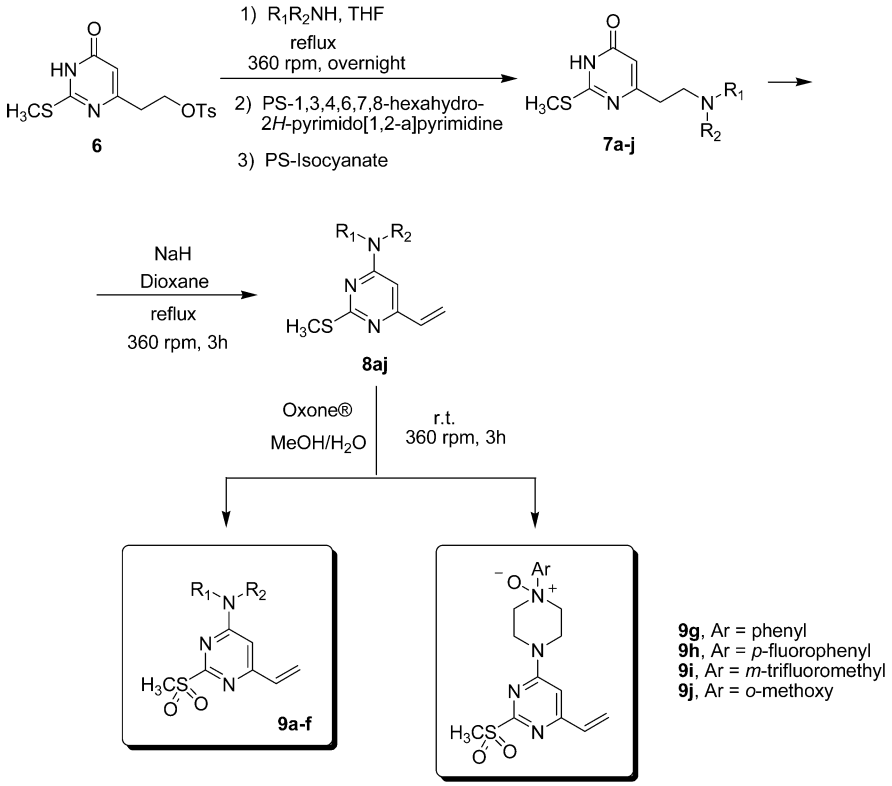
The tosyl derivative **6** was then submitted to a three-step parallel procedure (Scheme 3) using a Büchi Syncore synthesizer. In the first step, compound **6** was partitioned into 10 separate reaction vessels and then reacted with 10 different amines in a 2-fold excess in order to drive the reactions to completion. Once HPLC analysis revealed that all the reactions were finished, two solid-supported scavengers for nucleophiles were added to remove excess reagents and side products. The PS-1,3,4,6,7,8-hexahydro-2*H*-pyrimido[1,2-*a*]pyrimidine scavenger was added to bind the *p*-toluensulfonic acid released in the reaction medium as side product, while the excess of secondary amines was removed using a PS-isocyanate scavenger. After simple parallel filtration, compounds **7a**−**j** were obtained in more than 95% purity, as shown by HPLC/MS analysis.

Compounds **7a**−**j** were then treated with NaH in refluxing dioxane. After removing volatiles under reduced pressure, the reaction mixtures were taken up in CH_2Cl_2 and subjected to parallel filtration to afford compounds **8a**−**j** as pure products.

This rearrangement reaction, proceeding through a very efficient tandem Hofmann-like elimination (C-6 side chain) followed by C-4 hydroxy (oxo) substitution by dialkylamino nucleophiles,[10] provides a selective entry to substituted 6-vinylpyrimidine derivatives, whose synthesis is not easy to carry out using alternative approaches. In fact, protection at N-1 or N-3 positions and Pd-assisted cross-coupling reaction are required to obtain 6-vinyl derivatives in moderate to good yield.[11] Moreover, the contemporary introduction of both a vinyl moiety at C-6 and an amino group at C-4 positions of pyrimidine bases requires more than one synthetic step: C-6 formylation and subsequent Wittig reaction are used to elaborate the 6-vinyl group,[12] while the introduction of a leaving group in C-4 and its subsequent nucleophilic displacement are necessary to introduce the C-4 dialkylamino moiety.[13] Chemical evidence as well as some infrared and ultraviolet data led us to hypothesize a concerted intermolecular four-center mechanism for this unprecedented rearrangement reaction.[10]

Finally, compounds **8a**−**j** were converted into corresponding sulfones **9a**−**j**, without undesidered epoxidation of the vinyl group, by treatment with Oxone, which has proven to be very efficient for selective sulfur oxidation.[14] However, while compounds **8a**−**f** were transformed into the corre-

Scheme 3



sponding sulfones **9a**−**f** after 3 h at room temperature and were obtained as pure products after ethyl acetate extraction, compounds **8g**−**j**, containing a phenylpiperazino moiety at the C-4 position, upon treatment with Oxone gave compounds **9g**−**j**, resulting from overoxidation of the piperazine nitrogen directly bound to the nonheterocyclic aromatic ring. Interestingly, only the nitrogen linked to the nonetherocyclic ring gives rise to the corresponding *N*-oxide, because no overoxidation product formed on treatment of **8f** with Oxone. Since the *N*-oxide derivatives proved to be very polar compounds, it was hard to obtain them as pure products by simple extraction, and chromatographic purification was required to obtain pure **9g**−**j** in good yield (Table 1). All the synthesized compounds were submitted to biological evaluation as HIV-1 RT inhibitors according to a procedure previously described;[5c] some of them showed inhibitory activity in the micromolar range. Further studies for lead structure optimization are currently in progress and will be published in due course.

Conclusion

In summary, a simple and efficient methodology for the parallel synthesis of 2,4,6-trisubstituted pyrimidine derivatives **9a**−**j** in high yield and purity has been developed. By means of this procedure, a set of secondary amines (dialkylamines, diallylamines, benzylamines, and substituted piperazines) has been introduced into the C-4 position of the pyrimidine nucleus in only one synthetic step. The combinatorial potential of this methodology is further enhanced by the possibility of displacing the methyl sulfone group with different nucleophiles as well as of functionalizing in many different ways the vinyl group of compounds **9** to get libraries of new potential NNRTIs.

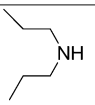
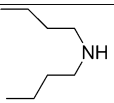
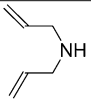
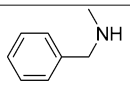
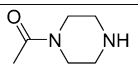
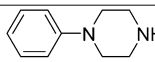
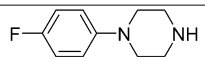
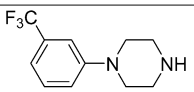
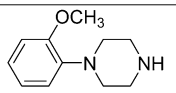
Experimental Section

General. All commercially available chemicals were used as purchased. CH_2Cl_2 was dried over calcium hydride, THF and dioxane was dried over Na/benzophenone prior to use. Anhydrous reactions were run under a positive pressure of dry N_2. IR spectra were recorded on a Perkin-Elmer BX FT-IR system, using KBr pellets. TLC was carried out using Merck TLC plates silica gel 60 F254. Chromatographic purifications were performed on columns packed with Merck 60 silica gel, 23−400 mesh, for flash technique. ^{1}H and ^{13}C NMR spectra were recorded at 200 MHz on a Bruker AC200F spectrometer. Chemical shifts are reported relative to $CDCl_3$ at δ 7.24 ppm and tetramethylsilane at δ 0.00 ppm. Büchi Syncore polyvap was used for parallel synthesis, filtration, and evaporation. Elemental analyses (C, H, N) were performed in-house using a Perkin-Elmer Elemental Analyzer 240C.

HPLC and MS Analysis. The purity of compounds was assessed by reversed-phase liquid chromatography and mass spectrometer (Agilent series 1100 LC/MSD) with a UV detector at $\lambda = 254$ nm and an electrospray ionization source (ESI). The LC elution method (using a Zorbax Eclipse XDB, 4.6 × 150 mm, 5-μm C8 column) was the following: 10-min method at 25 °C, mobile phase composed of (A) 1% ammonium acetate 0.01 M in water and (B) 99% MeOH at a flow rate of 0.4 mL/min (all solvents were HPLC grade, Fluka).

Mass spectral (MS) data were obtained using an Agilent 1100 LC/MSD VL system (G1946C) with a 0.4 mL/min flow rate using a binary solvent system of 95:5 methyl alcohol/water. UV detection was monitored at 254 nm. Mass spectra were acquired in positive mode scanning over the mass range

Table 1. Synthesized Derivatives **9a**−**l** through Parallel Liquid-Phase Synthesis

Entry	R_1R_2NH	Compound	Yield (%)
i		**9a**	93
ii		**9b**	95
iii		**9c**	95
iv		**9d**	92
v		**9e**	90
vi		**9f**	90
vii		**9g**	82
viii		**9h**	88
ix		**9i**	87
x		**9j**	80

of 50−1500. The following ion source parameters were used: drying gas flow, 9 mL/min; nebulizer pressure, 40 psig; drying gas temperature, 350 °C.

Microwave Irradiation Experiments. Microwave reactions were conducted using a CEM Discover Synthesis Unit (CEM Corp., Matthews, NC). The machine consists of a continuous focused microwave power delivery system with operator-selectable power output from 0 to 300 W. The temperature of the contents of the vessel was monitored using a calibrated infrared temperature control mounted under the reaction vessel. All experiments were performed using a stirring option whereby the contents of the vessel are stirred by means of a rotating magnetic plate located below the floor of the microwave cavity and a Teflon-coated magnetic stir bar in the vessel.

2-{1-[(4-Benzyloxy)butyl]sulfonyl}-4-(piperidin-1-yl)-6-vinylpyrimidine (2). Compound **1**[7] (1 mmol) was placed in a round-bottom flask and dissolved in 10 mL of methanol. A solution of Oxone (3 equiv/mol) in water (10 mL) was added dropwise, and the resulting mixture was stirred at room temperature overnight. The reaction mixture was diluted with water and extracted with CH_2Cl_2; the organic phase was then washed with brine, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. Purification of the crude product by flash chromatography (CH_2Cl_2/CH_3OH, 98:2) gave **2** in 85% yield. ^{1}H NMR ($CDCl_3$): δ 1.50−1.88 (m, 8H), 1.90−2.15 (m, 2H), 3.35−357 (m, 4H), 3.58−3.82 (m, 4H), 4.46 (s, 2H), 5.56 (dd, J_{cis} = 9.8 Hz, J_{gem} = 1.8 Hz), 6.30−6.70 (m, 3H), 7.12−7.48 ppm (m, 5H). MS (ESI) *m*/*z* 416 $[M + H]^+$, 438 $[M + Na]^+$.

2-(Pyrrolidin-1-yl)-4-(piperazin-1-yl)-6-[2-(pyrrolidin-1-yl)ethyl]pirimidine (4). Compound **2** (1 mmol) was dissolved in anhydrous dioxane (10 mL), then pyrrolidine (2 equiv/mol) was added, and the reaction mixture was heated overnight at reflux. To the cooled solution, PS-isocyanate scavenger (2 equiv/mol) was added, and the mixture was stirred for 2 h at room temperature, then filtered, and the resulting solution was evaporated to dryness under reduced pressure. Purification of the crude product by flash chromatography (CH_2Cl_2/CH_3OH, 95:5) gave product **4** in 67% yield. ^{1}H NMR ($CDCl_3$): δ 1.48−1.78 (m, 6H), 1.85−2.0 (m, 4H), 2.0−2.15 (m, 4H), 3.25 (t, 2H, J = 7.0 Hz), 3.32−3.50 (m, 6 H), 3.52−3.78 (m, 8H), 6.13 ppm (s, 1H). MS (ESI) *m*/*z* 330 $[M + H]^+$.

2-Methylthio-6-[2-(*p*-toluensulfonyloxy)ethan-1-yl]-4(3*H*)-pyrimidinone (6). Substrate **5**[10] (1 mmol), DMAP (1 equiv/mol) and *p*-toluensulfonyl chloride (1 equiv/mol) were dissolved in anhydrous CH_2Cl_2 (10 mL), and the mixture was irradiated in the microwave oven for 6 min at 50 °C (two runs). The reaction mixture was washed with 2 N HCl and brine, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. Purification of the crude residue by flash chromatography ($CHCl_3$/MeOH, 9.5:0.5) gave product **6** in 95% yield. ^{1}H NMR ($CDCl_3$): δ 2.30 (s, 3H), 2.39 (s, 3H), 2.84 (t, 2H), 3.89 (t, 2H), 6.56 (s, 1H), 7.30 (d, 2H), 7.80 ppm (d, 2H). IR $(CHCl_3)_{\nu max}$ (cm^{-1}) 3019, 1637, 1572. MS (ESI) *m*/*z* 341 $[M + H]^+$. Anal. Calcd for $C_{13}H_{15}N_2O_4S_2$: C, 47.69; H, 4.62; N, 8.56. Found: C, 47.83; H, 4.57; N, 8.35.

Parallel Synthesis of 6-[2-(Dialkylamino)ethan-1-yl]-2-methylthio-4(3*H*)-pyrimidinones (7a−j). General Procedure. Substrate **6** (1 mmol), divided into 10 different vessels, was placed in the Büchi Syncore and dissolved in anhydrous THF (5 mL) under a positive pressure of dry N_2. The appropriate amines (2 equiv/mol) were added, and the reaction mixtures were heated at reflux temperature at 360 rpm overnight. To the cooled solutions, PS-1,3,4,6,7,8-hexahydro-2*H*-pyrimido[1,2-*a*]pyrimidine scavenger was added (2 equiv/mol), and the mixtures were stirred (360 rpm) for 2 h at room temperature. Then the PS-isocyanate scavenger (2 equiv/mol) was added, and the mixtures were stirred (360 rpm) for an additional 2 h at room temperature. Finally, the reaction mixtures were filtered in parallel with a specific filtration unit, and the scavengers were washed twice with 5 mL of CH_2Cl_2 and then evaporated to dryness with the same apparatus. Compounds **7a**−**j** were identified by LC/MS analysis and proved to be pure enough to be used in the next step without further purification.

Parallel Synthesis of 4-Dialkylamino-2-methylthio-6-vinylpyrimidines (8a−j). General Procedure. Compounds **7a**−**j** (1 mmol) were placed in the Büchi Syncore and dissolved in 5 mL of anhydrous dioxane. To the resulting

solutions, NaH (2 equiv/mol) was added, and the reaction mixtures were heated at reflux at 360 rpm for 3 h. All reaction mixtures were cooled and then filtered in parallel with a specific filtration unit; the resulting solutions were evaporated to dryness in parallel to afford compounds **8a**−**j**, which could be used in the next step without purification.

4-Diethylamino-2-methylthio-6-vinylpyrimidine (8a). ^{1}H NMR ($CDCl_3$): δ 1.19 (t, 6H), 2.48 (s, 3H), 3.30−3.70 (m, 4H), 5.45 (dd, 1H, J_{cis} = 9.8 Hz, J_{gem} = 1.6 Hz), 5.95 (s, 1H), 6.39−6.50 ppm (m, 2H). MS (ESI) *m*/*z* 246 $[M + Na]^+$.

4-Dipropylamino-2-methylthio-6-vinylpyrimidine (8b). ^{1}H NMR ($CDCl_3$): δ 0.92 (t, 6H), 1.49−1.67 (m, 4H), 2.48 (s, 3H), 3.32−3.51 (m, 4H), 5.45 (dd, 1H, J_{cis} = 9.8 Hz, J_{gem} = 1.8 Hz), 5.95 (s, 1H), 6.38−6.50 ppm (m, 2H). MS (ESI) *m*/*z* 252 $[M + H]^+$.

4-Dibutylamino-2-methylthio-6-vinylpyrimidine (8c). ^{1}H NMR ($CDCl_3$): δ 0.93 (t, 6H), 1.23−1.45 (m, 4H), 1.47−1.63 (m, 4H), 2.48 (s, 3H), 3.25−3.53 (m, 4H), 5.45 (dd, 1H, J_{cis} = 9.7 Hz, J_{gem} = 1.8 Hz), 5.95 (s, 1H), 6.39−6.51 ppm (m, 2H). MS (ESI) *m*/*z* = 280 $[M + H]^+$.

4-Diallylamino-2-methylthio-6-vinylpyrimidine (8d). ^{1}H NMR ($CDCl_3$): δ 2.50 (s, 3H), 3.45−4.15 (m, 4H), 5.05−5.20 (m, 4H), 5.55 (dd, 1H, J_{cis} = 9.5 Hz, J_{gem} = 2.0 Hz), 5.65−5.80 (m, 2H), 6.00 (s, 1H), 6.35−6.65 ppm (m, 2H). MS (ESI) *m*/*z* 270 $[M + Na]^+$.

4-[(*N*-Benzyl-methylamino)]-2-methylthio-6-vinylpyrimidine (8e). ^{1}H NMR ($CDCl_3$): δ 2.51 (s, 3H), 3.15 (s, 3H), 4.80 (s, 2H), 5.56 (dd, 1H, J_{cis} = 9.8 Hz, J_{gem} = 1.5 Hz), 6.00 (s, 1H), 6.40−6.60 (m, 2H), 7.05−7.41 ppm (m, 5H). MS (ESI) *m*/*z* 294 $[M + Na]^+$.

4-[(4-Acetyl)piperazin-1-yl]-2-methythio-6-vinylpyrimidine (8f). ^{1}H NMR ($CDCl_3$): δ 2.12 (s, 3H), 2.54 (s, 3H), 3.55−3.87 (m, 8H), 5.64 (dd, 1H, J_{cis} = 9.7 Hz, J_{gem} = 1.8 Hz), 6.46 (s, 1H), 6.41−6.78 ppm (m, 2H). MS (ESI) *m*/*z* 279 $[M + H]^+$.

2-Methylthio-4-[(4-phenyl)piperazin-1-yl]-6-vinylpyrimidine (8g). ^{1}H NMR ($CDCl_3$): δ 2.53 (s, 3H), 3.25 (t, 4H, *J* = 5.25 Hz), 3.81 (t, 4H, *J* = 5.25 Hz), 4.10−4.75 (m, 4H), 5.51 (d, 1H, J_{cis} = 9.8 Hz), 6.15 (s, 1H), 6.38−6.53 (m, 2H), 6.85−7.31 ppm (m, 5H). MS (ESI) *m*/*z* 335 $[M + Na]^+$.

4-[4-(4-Fluorophenyl)-piperazin-1-yl]-2-methylthio-6-vinylpyrimidine (8h). ^{1}H NMR ($CDCl_3$): δ 2.52 (s, 3H), 3.14 (t, 4H, *J* = 4.97 Hz), 3.80 (t, 4H, *J* = 4.97 Hz), 4.10−4.65 (m, 4H), 5.51 (d, 1H, J_{cis} = 9.8 Hz), 6.15 (s, 1H), 6.40−6.68 (m, 2H), 6.89−6.97 ppm (m, 4H). MS (ESI) *m*/*z* 353 $[M + Na]^+$.

2-Methylthio-4-[4-(3-trifluorophenyl)piperazin-1-yl]-6-vinylpyrimidine (8i). ^{1}H NMR ($CDCl_3$): δ 2.52 (s, 3H), 3.24 (t, 4H, *J* = 6.12 Hz), 3.79 (t, 4H, *J* = 6.12 Hz), 5.51(d, 1H, J_{cis} = 9.9 Hz), 6.15 (s, 1H), 6.36−6.72 (m, 2H), 6.83−7.34 ppm (m, 4H). MS (ESI) *m*/*z* 403 $[M + Na]^+$.

4-[4-(2-Methoxyphenyl)piperazin-1-yl]-2-methylthio-6-vinylpyrimidine (8j). ^{1}H NMR ($CDCl_3$): δ 2.52 (s, 3H), 3.02−3.20 (m, 4H), 3.80−3.86 (m, 4H), 3.88 (s, 3H), 5.49 (d, 1H, J_{cis} = 9.4 Hz), 6.16 (s, 1H), 6.45−6.67 (m, 2H), 6.81−7−09 ppm (m, 4H). MS (ESI) *m*/*z* 365 $(M + Na)^+$.

Parallel Synthesis of 4-Dialkylamino-2-methylsulfonyl-6-vinylpyrimidines (9a−j). General Procedure. Compounds **8a**−**j** (1 mmol) were placed in the Büchi Syncore and dissolved in 2.5 mL of methanol. A solution of Oxone (3 equiv/mol) in water was added dropwise, and the resulting mixtures were shaken at room temperature at 360 rpm for 3h. The reactions were filtered in parallel with a specific filtration unit and then evaporated to dryness in parallel.

Compounds 9a−f. The crude material was diluted with ethyl acetate (20 mL), washed with water and brine, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure to give the final product (purity > 98%).

Compounds 9g−j. The crude material was purified by flash chromatography (CH_2Cl_2/CH_3OH, 9:1) to afford the final product (purity > 98%).

4-Diethylamino-2-methylsulfonyl-6-vinylpyrimidine (9a). HPLC t_R 4.15 min. ^{1}H NMR ($CDCl_3$): δ 1.19 (t, 6H), 3.27 (s, 3H), 3.35−3.8 (m, 4H), 5.58 (dd, 1H, J_{cis} = 9.8 Hz, J_{gem} = 1.6 Hz), 6.30 (s, 1H), 6.37−6.66 ppm (m, 2H). IR (CH_2Cl_2) (ν, cm^{-1}): 1136, 1264, 1589. MS (ESI) *m*/*z* 278 $[M + Na]^+$, 533 $[2M + Na]^+$.

4-Dipropylamino-2-methylsulfonyl-6-vinylpyrimidine (9b). HPLC t_R 4.42 min. ^{1}H NMR ($CDCl_3$): δ 0.92 (t, 6H), 1.62 (m, 4H), 3.25 (s, 3H), 3.3−3.7 (m, 4H), 5.58 (dd, 1H, J_{cis} = 9.8 Hz, J_{gem} = 1.8 Hz), 6.28 (s, 1H), 6.39−6.66 ppm (m, 2H). IR (CH_2Cl_2) (ν, cm^{-1}): 1136, 1264, 1588. MS (ESI) *m*/*z* 284 $[M + H]^+$, 589 $[2M + Na]^+$.

4-Dibutylamino-2-methylsulfonyl-6-vinylpyrimidine (9c). HPLC t_R 4.58 min. ^{1}H NMR ($CDCl_3$): δ 0.91 (t, 6H), 1.20−1.37 (m, 4H), 1.47−1.67 (m, 4H), 3.24 (s, 3H), 3.25−3.75 (m, 4H), 5.56 (dd, 1H, J_{cis} = 9.7 Hz, J_{gem} = 1.8 Hz), 6.27 (s, 1H), 6.37−6.65 ppm (m, 2H). IR (CH_2Cl_2) (ν, cm^{-1}): 1139, 1265, 1589. MS (ESI) *m*/*z* 312 $[M + H]^+$, 645 $[2M + Na]^+$.

4-Diallylamino-2-methylsulfonyl-6-vinylpyrimidine (9d). HPLC t_R 4.16 min. ^{1}H NMR ($CDCl_3$): δ 3.27 (s, 3H), 3.8−4.4 (m, 4H), 511−5.23 (m, 4H), 5.60 (dd, 1H, J_{cis} = 9.5 Hz, J_{gem} = 2.0 Hz), 5.69−5.88 (m, 2H), 6.32 (s, 1H), 6.39−6.66 ppm (m, 2H). IR (CH_2Cl_2) (ν, cm^{-1}): 1137, 1245, 1588. MS (ESI) *m*/*z* 302 $[M + Na]^+$, 581 $[2M + Na]^+$.

4-[(*N*-Benzyl-methylamino)]-2-methylsulfonyl-6-vinylpyrimidine (9e). HPLC t_R 4.15 min. ^{1}H NMR ($CDCl_3$): δ 2.90−3.45 (m, 6H). 4.82 (s, br, 2H), 5.59 (dd, 1H, J_{cis} = 9.8 Hz, J_{gem} = 1.5 Hz), 6.39 (s, 1H), 6.40−6.65 (m, 2H), 7.05−7.41 ppm (m, 5H). IR (CH_2Cl_2) (ν, cm^{-1}): 1137, 1185, 1590. MS (ESI) *m*/*z* 326 $[M + Na]^+$, 629 $[2M + Na]^+$.

4-[(4-Acetyl)piperazin-1-yl]-2-methylsulfonyl-6-vinylpyrimidine (9f). HPLC t_R 4.17 min. ^{1}H NMR ($CDCl_3$): δ 2.12 (s, 3H), 3.28 (s, 3H), 3.52−3.97 (m, 8H), 5.65 (dd, 1H, J_{cis} = 9.7 Hz, J_{gem} = 1.8 Hz), 6.46 (s, 1H), 6.40−6.68 ppm (m, 2H). IR (CH_2Cl_2) (ν, cm^{-1}): 1132, 1252, 1589, 1721. MS (ESI) *m*/*z* 311 $[M + H]^+$, 643 $[2M + Na]^+$.

4-[4-Phenyl-piperazin-1-yl 4-*N*-oxide]-2-methylsulfonyl-6-vinylpyrimidine (9g). HPLC t_R 4.05 min. ^{1}H NMR ($CDCl_3$): δ 3.28 (s, 3H), 3.30−3.52 (m, 2H), 3.75−4.03 (m, 2H), 4.10−4.75 (m, 4H), 5.66 (d, 1H, J_{cis} = 9.8 Hz), 6.44−6.69 (m, 3H), 7.45−7.49 (m, 3H). 7.94−7.98 ppm (m, 2H), ^{13}C NMR ($CDCl_3$): δ 39.2 (CH_3SO_2), 40.5 (2 × $CH_2N_{piperazine}$), 67.8 (2 × $CH_2NO_{piperazine}$), 103.9 ($C5_{pyrimidine}$), 114.0, 117.5 (3 × CH_{arom}), 123.9 ($CH_{2\ vinyl}$), 124.1 (CH_{vinyl}), 128.2 ppm

(CH_{arom}). IR (CH_2Cl_2) (ν, cm^{-1}): 1133, 1284, 1498, 1589. MS (ESI) *m/z* 383 $[M + Na]^+$, 743 $[2M + Na]^+$.

4-[4-(4-Fluorophenyl)-piperazin-1-yl 4-*N*-oxide]-2-methylsulfonyl-6-vinylpyrimidine (9h). HPLC t_R 4.06 min. ^1H NMR ($CDCl_3$): δ 3.29 (s, 3H), 3.39−3.57 (m, 2H), 3.75−4.02 (m, 2H), 4.10−4.65 (m, 4H), 5.68 (dd, 1H, $J_{cis} = 9.8$ Hz, $J_{gem} = 1.6$ Hz), 6.45−6.70 (m, 3H), 7.10−7.23 (m, 2H), 7.89−8.07 ppm (m, 2H). ^{13}C NMR ($CDCl_3$): δ 39.2 (CH_3SO_2), 40.5 (2 × $CH_2N_{piperazine}$), 67.8 (2 × $CH_2NO_{piperazine}$), 103.9 ($C5_{pyrimidine}$), 117.0, 117.5 (4 × CH_{arom}), 123.9 ($CH_{2\ vinyl}$), 124.1 (CH_{vinyl}), 135.5 ppm (CF_{arom}). IR (CH_2Cl_2) (ν, cm^{-1}): 1138, 1256, 1500, 1587. MS (ESI) *m/z* 401 $[M + Na]^+$, 779-$[2M + Na]^+$.

4-[4-(3-Trifluorophenyl)-piperazin-1-yl 4-*N*-oxide]-2-methylsulfonyl-6-vinylpyrimidine (9i). HPLC t_R 4.07 min.^1H NMR ($CDCl_3$): δ 3.27 (s, 3H), 3.32−3.58 (m, 2H), 3.83−4.09 (m, 2H), 4.15−4.73 (m, 4H) 5.67 (d, 1H, $J_{cis} = 9.9$ Hz), 6.39−6.80 (m, 3H), 7.55−7.88 (m, 2H), 8.10−8.30 (m, 1H), 8.37−8.50 ppm (m, 1H).^{13}C NMR ($CDCl_3$): δ 39.2 (CH_3SO_2), 40.5 (2 × $CH_2N_{piperazine}$), 67.9 (2 × CH_2-$NO_{piperazine}$), 103.9 ($C5_{pyrimidine}$), 112.5, 116.2, (2 × CH_{arom}), 119.1 (CH_{arom}), 123.9 ($CH_{2\ vinyl}$), 124.1 (CH_{vinyl}), 124.2 (CF_3), 128.1 ppm (CH_{arom}). IR (CH_2Cl_2) (ν, cm^{-1}): 1136, 1284, 1498, 1590. MS (ESI) *m/z* 451 $[M + Na]^+$, 879 $[2M + Na]^+$.

4-[4-(2-Methoxyphenyl)-piperazin-1-yl 4-*N*-oxide]-2-methylsulfonyl-6-vinylpyrimidine (9j). HPLC t_R 4.05 min.^1H NMR ($CDCl_3$): δ 3.02−3.25 (m, 2H), 3.33 (s, 3H), 3.91 (s, 3H), 4.15−4.50 (m, 2H), 4.52−4.83 (m, 4H), 5.68 (dd, 1H, $J_{cis} = 9.4$ Hz, $J_{gem} = 2.05$ Hz), 6.47−6.72 (m, 3H), 7.0 (d, 1H, $J = 7.9$ Hz), 7.16 (t, 1H, $J = 7.77$ Hz), 7.43 (t, 1H, $J = 7.9$ Hz), 8.8 ppm (d, 1H, $J = 7.9$ Hz). ^{13}C NMR ($CDCl_3$): δ 39.2 (CH_3SO_2), 40.5 (2 × $CH_2N_{piperazine}$), 55.9 (CH_3O), 67.9 (2 × $CH_2NO_{piperazine}$), 103.9 ($C5_{pyrimidine}$), 115.2, 115.3, 119.3, 122.0 (4 × CH_{arom}), 123.9 ($CH_{2\ vinyl}$), 124.1 ppm (CH_{vinyl}). IR (CH_2Cl_2) (ν, cm^{-1}): 1136, 1284, 1498, 1590. MS (ESI) *m/z* 413 $[M + Na]^+$, 803 $[2M + Na]^+$.

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