Accepted Manuscript

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PII: S0040-4020(18)30447-2

DOI: 10.1016/j.tet.2018.04.058

Reference: TET 29473

To appear in: *Tetrahedron*

Received Date: 27 February 2018

Revised Date: 12 April 2018

Accepted Date: 17 April 2018

Please cite this article as: Sidhoum MA, El Kaïm L, Grimaud L, 4-Aminopyrimidine libraries from the Ugi-Smiles reaction of thiouracil, *Tetrahedron* (2018), doi: 10.1016/j.tet.2018.04.058.

Graphical Abstract

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4-Aminopyrimidine Libraries from the Ugi-Smiles Reaction of Thiouracil

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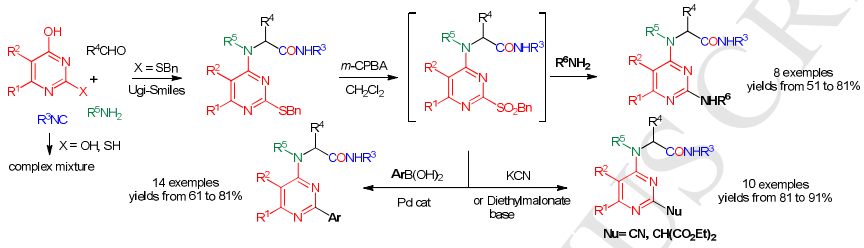

Tetrahedron
journal homepage: www.elsevier.com

4-Aminopyrimidine Libraries from the Ugi-Smiles Reaction of Thiouracil.

Madjid Ait Sidhoum[a] , Laurent El Kaïm[a]* Laurence Grimaud[b]*

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Ugi-Smiles
pyrimidines
sulfone
Suzuki reaction

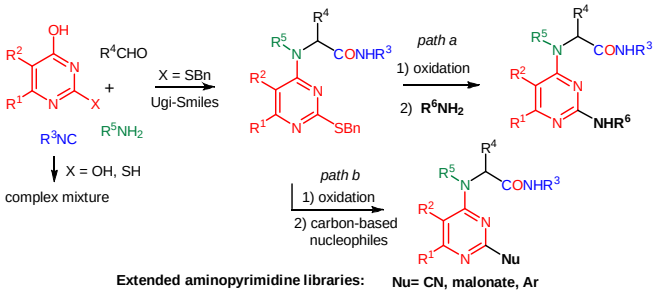
ABSTRACT

The Ugi-Smiles reaction of *S*-benzyl thiouracil have been exploited in several three-step sequences for the preparation of aminopyrimidine libraries with high diversity. After the 4-component coupling, oxidation of the thioether to sulfone is followed by displacement of the latter by various carbon-centered nucleophiles (cyanide, malonate, boronic acids) or amines. The efficiency of the whole sequence was further demonstrated with one-pot procedures.

1. Introduction

A few years ago, we reported a convenient access to 2,4-diaminopyrimidine derivatives using a Ugi-Smiles reaction of thiouracil derivatives (Scheme 1).[1] Pyrimidine derivatives are among the most important heterocyclic scaffolds displaying various biological activities.[2] Aminopyrimidines are widely represented among these in relation with their use for the synthesis of the backbone of both DNA and RNA bases (eg cytosine, adenine..) leading in particular to an impressive number of applications as anticancer agents.[3] The Ugi-Smiles coupling is a four-component reaction between isocyanides, aldehydes, primary amines and electron-poor phenols that is perfectly suited for the conversion of hydroxy and thio substituted six-membered nitrogen-based heterocycles into libraries of amino heterocycles.[4] Besides its interest for the preparation of libraries of DNA inhibitors, uracil appeared as a particularly attractive target for a Ugi-Smiles approach due to the selectivity issue brought by the two hydroxyl groups and the high diversity displayed by potential reactions at the two sites. After initial deceiving results obtained with both uracil and thiouracil, Ugi-Smiles couplings with masked-thiol substrates were successfully settled. The potential of the resulting adducts to behave as a platform for the preparation of pyrimidine-based libraries was demonstrated by a short sequence leading to diaminopyrimidines (Scheme 1, path a). We now wish to give a full account on this project together with extensions of the strategy to more diverse pyrimidines using carbon-based nucleophiles (Scheme 1, path b).

Scheme 1. Aminopyrimidine libraries from *S*-benzyl thiouracil.



2. Results and discussion

When Ugi-Smiles couplings of uracil with allyl amine, cyclohexyl isocyanide, and isovaleraldehyde were attempted under our standard conditions (1 M, 60 °C in methanol or 80 °C in toluene), we failed to differentiate between the OH-2 and the OH-4 of uracil and intractable mixtures were obtained using either stoichiometric amounts or two-fold excess of reagents. Similar results were obtained with thiouracil, which was expected to display a better selectivity between the hydroxy group and the thiol functionality. To address these selectivity issues, we decided to protect one of the two functional groups

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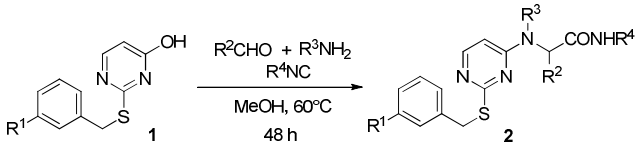
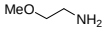
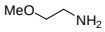
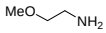
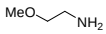
and selected thiouracil to pursue the study due to a possible *S*-selective alkylation. Thus, the latter was treated in EtOH at 50°C with benzyl bromide and 3-fluorobenzyl bromide in the presence of a stochiometric amount of sodium hydroxide to give after 3 hours pyrimidines **1a** and **1b** in 75% and 72% yields respectively. The Ugi-Smiles coupling with both protected thiouracils turned out to be rather efficient when performed in MeOH as shown by the various aminopyrimidines **2** prepared from a set of amines, aldehydes and isocyanides (Table 1). Aliphatic and aromatic aldehydes could be used with similar yields together with cyclohexyl or 4-benzyl isocyanides (Table 1, entries 1-3, 7-12). Isocyanoesters gave slightly lower yields in agreement with their reduced nucleophilicity (Table 1, entries 10-12).

Table 1. Ugi-Smiles coupling of *S*-benzyl thiouracil

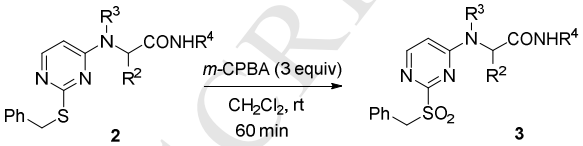


Entry	R^1	R^2	R^3NH_2	R^4NC	Product	Yield
1	H	*i*-Bu		*p*-ClBnNC	**2a**	91%
2	H	*i*-Bu		CyNC	**2b**	86%
3	H	H		CyNC	**2c**	72%
4	H	*i*-Bu	*p*-ClBnNH$_2$	CyNC	**2d**	71%
5	H	*i*-Pr		CyNC	**2e**	82%
6	H	*i*-Pr	*p*-ClBnNH$_2$	CyNC	**2f**	88%
7	H	Ph		CyNC	**2g**	72%
8	H	Et	*p*-ClBnNH$_2$	*p*-ClBnNC	**2h**	85%
9	H	Et		*t*-BuNC	**2i**	85%
10	H	H		MeOOCCH$_2$NC	**2j**	45%
11	H	H		MeOOCCH$_2$NC	**2k**	47%
12	H	H		EtOOCCH$_2$NC	**2l**	51%
13	F	*i*-Bu		*p*-ClBnNC	**2m**	72%
14	F	Ph		CyNC	**2n**	85%
15	F	Ph		*p*-MeOBnNC	**2o**	77%
16	F	*i*-Bu		CyNC	**2p**	87%
17	F	*i*-Pr		CyNC	**2q**	98%
18	F	Et		*t*-BuNC	**2r**	53%

In order to showcase the synthetic potential of this first reaction, the ability to displace the thioether group by various nucleophiles was next envisioned. Though the direct displacement of a thioether moiety tethered at the 2-position of a nitrogenated heterocycle by carbon-based nucleophiles has been reported under various metal-catalyzed conditions,[5] we decided to first oxidize the thioether to a sulfone and to treat the latter with several nucleophiles. Even if more lengthy, we surmised that the proper selection of a good leaving group would lead to a flexible set of conditions with a wide scope of nucleophiles.

Various oxidizing agents have been reported for the conversion of thioethers into sulfones. Hydrogen peroxide is certainly the best reagent in terms of side-product formation, however, its use generally requires a further optimization due to the need of a metal catalyst.[6] Thus, *m*-CPBA was selected for its broad scope and simple use.[7] The oxidation step was optimized using the thioether **2g** as substrate with three equivalents of *m*-CPBA by varying the solvent of the reaction -using methanol, toluene or dichloromethane. The latter gave the best results in terms of yields and reaction time: 95% isolated yield within 30 minutes at rt compared to 90% over 5 hours in methanol and 70% for 6 hours in toluene. With these conditions in hand, a set of various Ugi-Smiles adducts were efficiently oxidized leading to sulfones **3** as presented in Table 2.

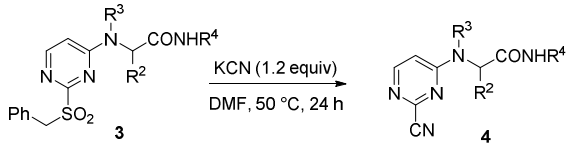
Table 2. Oxidation of Ugi-Smiles adducts



Entry	**2**	R^2	R^3	R^4	**3**	Yield
1	**2a**	*i*-Bu	allyl	*p*-ClBn	**3a**	87%
2	**2b**	*i*-Bu	allyl	Cy	**3b**	94%
3	**2c**	H	allyl	Cy	**3c**	89%
4	**2d**	*i*-Bu	*p*-ClBn	Cy	**3d**	88%
5	**2e**	*i*-Pr	allyl	Cy	**3e**	82%
6	**2f**	*i*-Pr	*p*-ClBn	Cy	**3f**	88%
7	**2g**	Ph	allyl	Cy	**3g**	95%
8	**2h**	Et	*p*-ClBn	*p*-ClBn	**3h**	85%
9	**2i**	Et	allyl	*t*-Bu	**3i**	85%

The potential of the new sulfones **3** was next evaluated towards different families of nucleophiles. According to seminal reports on nucleophilic substitution of heteroaryl sulfones, we decided to first test the reaction with cyanide[8] and malonate anions.[9]

Table 3. Cyanation of sulfones **3**

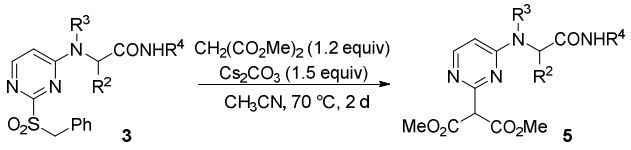


Entry	**2**	R^2	R^3	R^4	**3**	Yield
1	**3b**	*i*-Bu	allyl	Cy	**4b**	85%
2	**3e**	*i*-Pr	allyl	Cy	**4e**	81%
3	**3f**	*i*-Pr	*p*-ClBn	Cy	**4f**	82%
4	**3g**	Ph	allyl	Cy	**4g**	82%
5	**3h**	Et	*p*-ClBn	*p*-ClBn	**4h**	83%
6	**3i**	Et	allyl	*t*-Bu	**4i**	88%

Using 1.2 equiv of potassium cyanide as nucleophile with sulfone **3g**, best conditions were obtained in DMF as solvent and by heating the mixture at 50°C for one day. Under these optimized conditions, the desired cyano pyrimidine **4g** was

isolated in 82% yields (Table 3, entry 4). Lower temperature required increased reaction time and led to lower yields (DMF, rt, 3 days, 50%) whereas less polar solvents such as toluene or acetonitrile gave poor yields (around 10% within 2 days at reflux) in agreement with the poor solubility of potassium cyanide in these solvents. A set of six pyrimido sulfones **3** were submitted to these experimental conditions to afford cyano pyrimidines **4** in satisfying yields as displayed in Table 3. Similarly, addition of malonate were successfully tested. In this case, DMF could be replaced by acetonitrile as solvent using cesium carbonate to in situ generate the anion. Pyrimido sulfones **3** were converted into substituted malonates **5** in very good yields within 2 days (Table 4, entries 1-4).

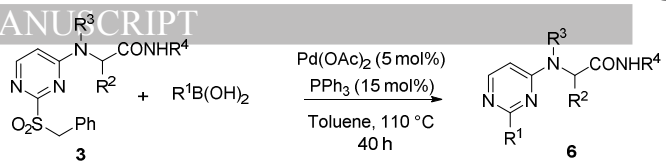
Table 4. Substitution by dimethyl malonate



3 **5**

Entry	**3**	R^2	R^3	R^4	**5**	Yield
1	**3a**	*i*-Bu	allyl	*p*-ClBn	**5a**	86%
2	**3b**	*i*-Bu	allyl	Cy	**5b**	87%
3	**3c**	H	allyl	Cy	**5c**	91%
5	**3e**	*i*-Pr	allyl	Cy	**5e**	83%

Following these additions of stabilized carbanions, we decided to examine whether more diversity could be achieved under transition metal-catalyzed reactions. Though few examples reported, we were not able to observe any substitution of the sulfonyl moiety of **3b** and **3g** by phenylacetylene or 4-methoxy substituted phenylacetylene under standard Sonogashira conditions ($PdCl_2(PPh_3)_2$, CuI, NEt_3 in DMF, CH_3CN, THF or NEt_3 as solvents). We next examined the possible substitution of the sulfonyl group according to a Suzuki-type reaction. The direct coupling of thioether with boronic acids has attracted much attention with the disclosure of efficient Pd/Cu co-catalyzed conditions to trigger the Liebeskind-Srogl coupling. The latter was also described for heterocyclic derivatives.[10] In contrast, there are only few examples of cross-coupling reactions between heteroaryl alkylsulfones and boronic acids. For instance, Liu and Robins have reported a Pd/NHC catalytic system to perform an efficient Suzuki reaction of a sulfonyl purine derivative.[11] Gratifyingly, when the sulfone **3a** was treated with 1.5 equiv of phenylboronic acid together with 5 mol% of $Pd(OAc)_2$ and 15 mol% of PPh_3 in refluxing toluene under argon, the formation of the desired arylamino pyrimidine **6a** was achieved in 75% yields. These simple conditions were not optimized further and a small library of fourteen aminoaryl pyrimidines was synthesized according to this procedure. Good yields were obtained using either electron-rich or electron-poor arylboronic acids as displayed in Table 5.



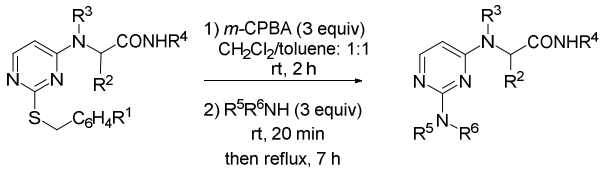
3 **6**

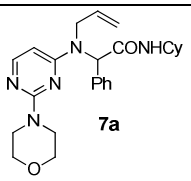
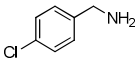
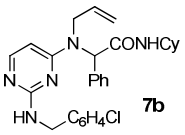
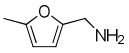
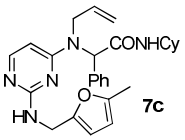
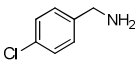
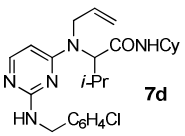
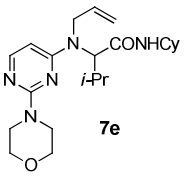
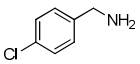
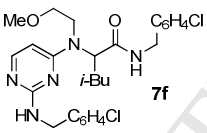
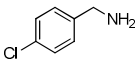
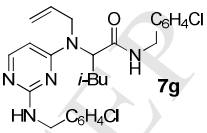
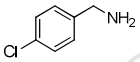
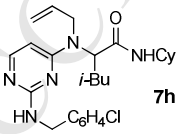
Entry	R^1	R^2	R^3	R^4	**3**	Yield
1	4-MeC_6H_4	*i*-Bu	allyl	*p*-ClBn	**6a**	75%
2	2-MeC_6H_4	*i*-Bu	allyl	Cy	**6b**	70%
3	Ph	*i*-Pr	allyl	Cy	**6c**	72%
4	4-MeC_6H_4	Ph	allyl	Cy	**6d**	60%
5	2-MeC_6H_4	*i*-Bu	*p*-ClBn	Cy	**6e**	69%
6	4-ClC_6H_4	*i*-Bu	allyl	Cy	**6f**	74%
7	3,4-$Cl_2C_6H_3$	*i*-Bu	allyl	Cy	**6g**	70%
8	4-FC_6H_4	*i*-Bu	allyl	Cy	**6h**	73%
9	4-MeOC_6H_4	*i*-Pr	allyl	Cy	**6i**	75%
10	2-MeOC_6H_4	*i*-Bu	allyl	Cy	**6j**	65%
11	2-MeOC_6H_4	*i*-Bu	*p*-ClBn	Cy	**6k**	61%
12	4-MeCOC_6H_4	Ph	allyl	Cy	**6l**	63%
13	4-EtC_6H_4	*i*-Pr	*p*-ClBn	Cy	**6m**	77%
14	4-*t*-BuC_6H_4	*i*-Pr	*p*-ClBn	Cy	**6n**	81%

We next examined the behavior of amines as nucleophiles. There are many examples concerning the displacement of sulfonyl groups tethered to nitrogen-based heterocycles by amines.[11] These reactions are usually performed in protic solvents such as ethanol whereas the oxidation step was formerly optimized in dichloromethane. Moreover, the use of an excess of oxidizing agent to form the sulfone prevents the development of a one-pot procedure. Indeed, amines are known to be readily oxidized to hydroxylamine by *m*-CPBA. Thus, direct addition of amines into the crude mixture after oxidation requires either prior destruction of the remaining oxidant or the use of a large excess of the amine. The latter solution was preferred together with the choice of relatively non-expensive amines. First attempts towards one-pot oxidation/amine addition starting from the Ugi-Smiles adduct **2n** and 3 equiv of morpholine with dichloromethane as sole solvent for both steps were rather deceiving as the expected diamino pyrimidine **7a** was obtained in a moderate 38% yield after 24 hours reflux. Controlled experiments demonstrated a very efficient oxidation followed by a sluggish second step in dichloromethane. When the same reaction was performed on isolated sulfone in refluxing toluene, the diaminopyrimidine could be isolated up to 80% yield. A 1:1 mixture of dichloromethane/toluene was then selected to balance the efficiency of both steps. The oxidation turned out to be slightly slower but still high yielding -up to 90% if the reaction mixture is left two hours at rt before adding the amine. The temperature was then slowly raised up to the boiling point of toluene while the dichloromethane distilled out of the mixture. To our delight, after 7 hours of reflux, the expected pyrimidine **7a** was isolated in 74% yield directly from **2n** (Table 6). Beside morpholine, primary amines such as 4-chlorobenzyl amine could be efficiently used in this one-pot process.

Table 5. Suzuki-type reaction of sulfones **3**

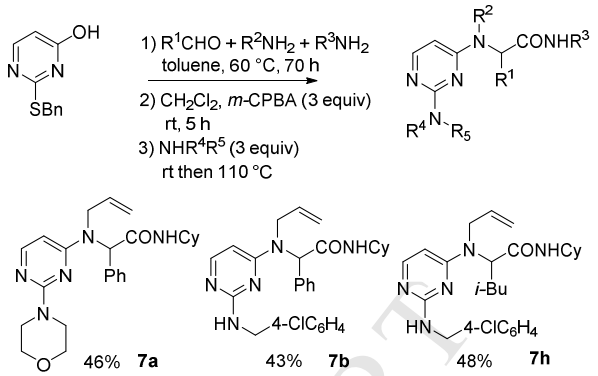
Table 6. One-pot diaminopyrimidine formation



Entry	2	R^5R^6NH	Product	Yield
1	**2n**		 **7a**	74%
2	**2n**		 **7b**	57%
3	**2n**		 **7c**	68%
4	**2q**		 **7d**	74%
5	**2q**		 **7e**	60%
6	**2m**		 **7f**	51%
7	**2a**		 **7g**	81%
8	**2b**		 **7h**	73%

Encouraged by this first successful one-pot two-step formation of diaminopyrimidines, we decided to examine the more challenging one-pot three-step version of the whole sequence including the multicomponent reaction. Thanks to the versatile efficiency of Ugi-Smiles couplings in both protic and aprotic solvents, methanol was thus replaced by toluene for the first Ugi-Smiles step. After completion, the mixture was diluted with dichloromethane followed by sequential addition of *m*-CPBA and amine. This sequence afforded **7a**, **7b** and **7h** in respectively 46, 43 and 48% yields (Scheme 2). Even though these results may be considered as moderate, they demonstrate the robustness of this three-step sequence with a 80% average yield per step.

Scheme 2. One-pot three-step diaminopyrimidine synthesis from *S*-benzyl thiouracil.



3. Conclusion

To conclude, we have disclosed a three-step procedure towards libraries of aminopyrimidine scaffolds, which are of important biological interest. The sequence displays as a key-step the Ugi-Smiles coupling of *S*-benzyl thiouracil. The thioether group is then exploited to raise the diversity of the whole transformation through substitution by various nucleophiles. The overall sequence showcases the synthetic potential of Ugi-Smiles couplings for the preparation of pyrimidine bases.

4. Experimental Part

4.1. General

NMR spectra were recorded at 298 K using a Bruker AVANCE 400 spectrometer. ^{1}H NMR spectra were recorded at 400 MHz and residual solvent peaks were used as an internal reference ($CDCl_3$ δ 7.26). Data are reported as follows: chemical shift in ppm, apparent multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet or overlap of nonequivalent resonances), coupling constants, integration. ^{13}C NMR spectra were recorded at 100 MHz and deuterated solvent peaks were used as an internal reference ($CDCl_3$ δ 77.16). Data are reported as follows: chemical shift in ppm, multiplicity deduced from DEPT experiments (CH_3, CH_2, CH, Cq), apparent multiplicity, coupling constants and integration where relevant. Analytical TLC was performed with Merck silica gel plates, pre-coated with silica gel 60 F254 (0.2 mm). Flash chromatography employed VWR (230–400 mesh) silica gel. Reactions were conducted under a positive pressure of dry nitrogen or argon Solvents were either obtained from commercial sources or dried with a MBRAUN Solvent Purification System SPS-800. Commercially available chemicals were used as purchased. IR spectra were recorded on a Perkin Elmer Spectrum 65 FT-IR Spectrometer. High-resolution (HRMS) mass spectra were performed on a JEOL JMS-Gcmate II, GC/MS system spectrometer using an electronic impact ionization source. The preparations and characterizations of **1a**, **1b**, **2a**, **2b**, **2c**, **2g**, **2j**, **2k**, **2l**, **2m**, **2n**, **2o**, **2p**, **2q**, **2r**, **7a**, **7b**, **7c**, **7d**, **7e**, **7f, 7g** and **7h** were already described previously,[1] the general procedures followed are just presented for these compounds.

4.2. *Synthesis of thiouracil derivative **1a** and **1b***

4.2.1. General procedure

A mixture of thiouracil (15 mmol, 1.92 g), alkylating agent (15 mmol), potassium carbonate (30 mmol, 4.15g) and Triton X-100

(0.04 mmol, 25 mg) in water (120 mL) was refluxed for 3 h. The aqueous layer was extracted with ethyl acetate (3x100 mL) and the combined organic extracts were dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure and the residue was chromatographed on silica gel. This procedure was followed using benzyl chloride (15 mmol, 1.89 gr) and m-fluorobenzyl chloride (15 mmol, 2.17 gr). The crude were purified by flash chromatography over silica gel (EtOAc/PE, 40:60) to afford **1a** (2.44 g, 75%) and **1b** (2,83 g, 80 %).

4.3. *Synthesis of Ugi adducts **2***

4.3.1. General procedure

To a 1 M solution of the aldehyde (1.0 mmol) in methanol was added successively 1.0 equiv of amine, 1.0 equiv of isocyanide, and 1.0 equiv of pyrimidine **1a** or **1b** under inert atmosphere. The resulting mixture was stirred until completion (TLC). It was then concentrated in vacuo, and the crude product was purified by flash chromatography on silica gel.

4.3.2.1: 2-*((4-chlorobenzyl)(2-(benzylthio)pyrimidin-4-yl)amino)-N-cyclohexyl-4-methylpentanamide (**2d**)*. The product was obtained as an oil (380 mg, 71%) after chromatography on silica gel (AcOEt/EP 60:40). **Rf** (AcOEt/EP 70: 30) 0.3. **^{1}H NMR** (400 MH_Z, $CDCl_3$) δ 8.04 (d, 1H, *J* =6.1 H_Z), 7.47 (d, 2H, *J* = 7.8 H_Z), 7.39-7.34 (m, 2H), 7.33-7.29 (m, 3H), 7.14 (d, 2H, *J* = 7.8 H_Z), 6.21 (br s, 1H), 6.00 (d, 1H, *J* = 6.1 H_Z), 5.33-5.28 (m, 1H), 4.67 (s, 2H), 4.45 (s, 2H), 3.74-3.62 (m, 1H), 1.99-1.91 (m, 1H), 1.88-1.82 (m, 1H), 1.73-1.66 (m, 2H), 1.64-1.48 (m, 4H), 1.39-1.29 (m, 2H), 1.24-1.10 (m, 2H), 1.06-0.97 (m, 1H), 0.93 (d, 3H, *J* = 6.6 H_Z), 0.90 (d, 3H, *J* = 6.6 H_Z).. **^{13}C NMR** (100 MH_Z, $CDCl_3$) δ 170.3, 169.4, 161.7, 156.0, 137.6, 135.7, 133.1, 129.0, 128.9, 128.6, 127.7, 127.3, 101.1, 56.1, 48.2, 48.0, 37.4, 35.2, 32.8, 32.7, 25.5, 25.3, 24.6, 22.8, 22.7. **IR** (thin film): 2933, 1740, 1589, 1471, 1342 cm^{-1}. **HRMS** Calculated for $C_{30}H_{37}ClN_4OS$: 536.2377, found: 536.2384.

4.3.2.2: *2-(allyl(2-(benzylthio)pyrimidin-4-yl)amino)-N-cyclohexyl-3-methylbutanamide (**2e**)*. The product was obtained as a yellow oil (430 mg, 98%) after chromatography on silica gel (Et_2O/EP 30:70). **Rf** (Et_2O/EP 50:50)) 0.5. **^{1}H NMR** (400 MH_Z, $CDCl_3$) δ 7.96 (d, 1H, *J* = 6.1 H_Z), 7.38 (d, 2H, *J* =7.6 H_Z), 7.27-7.22 (m, 2H), 7.21-7.15 (m, 1H), 6.09 (d, 1H, *J* = 6.1 H_Z), 5.92-5.67 (br s, 1H), 5.65-5.54 (m, 1H), 5.10-5.00 (m, 2H), 4.84-4.49 (br s, 1H), 4.29 (s, 2H), 4.00-3.91 (m, 2H), 3.62-3.51 (m, 1H), 2.36-2.22 (br s, 1H), 1.76 (d, 1H, *J* = 11.9 H_Z), 1.59 (d, 2H, *J* = 11.9 H_Z), 1.53-1.45 (m, 2H), 1.27-1.16 (m, 2H), 1.11-0.98 (m, 3H), 0.87 (d, 3H, *J* = 6.6 H_Z), 0.70 (d, 3H, *J* = 6.6 H_Z). **^{13}C NMR** (100.6 MH_Z, $CDC1_3$) 169.8, 169.0, 161.8, 155.6, 137.9, 132.9, 128.7, 128.6, 127.2, 117.4, 101.0, 63.0, 47.9, 46.6, 35.2, 32.9, 32.6, 26.8, 25.5, 24.7, 24.6, 19.8, 19.1. **IR** (thin film): 2933, 1740, 1573, 1367, 1220 cm^{-1}. **HRMS** Calculated for $C_{25}H_{34}N_4OS$: 438.2453, found: 438.2446.

4.3.2.3: 2-*((4-chlorobenzyl)(2-(benzylthio)pyrimidin-4-yl)amino)-N-cyclohexyl-4-methylbutanamide **(2f)***. The product was obtained as a yellow oil (360 mg, 68%) after chromatography on silica gel (Et_2O/EP 50:50). **Rf** (Et_2O/EP 50:50) 0.3. **^{1}H NMR** (400 MH_Z, $CDCl_3$) δ 7.96 (d, 1H, *J* = 6.1 H_Z), 7.48 (d, 2H, *J* = 7.6 Hz), 7.36 (t, 2H, *J* = 7.8 H_Z), 7.29-7.26 (m, 1H), 7.24 (d, 2H, *J* = 7.8 H_Z), 7.05 (d, 2H, *J* = 7.6 H_Z), 5.98-5.92 (m, 2H), 4.89 (br d, 1H, *J* = 16.9 H_Z), 4.67-4.48 (m, 2H), 4.45-4.33 (m, 2H), 3.68-3.57 (m, 1H), 2.50-2.32 (m, 1H), 1.91-1.81 (m, 1H), 1.73-1.65 (m, 3H), 1.63-1.56 (m, 1H), 1.33-1.27 (m, 2H), 1.19-1.11 (m, 3H), 0.98 (d, 3H, *J* = 6.3 Hz), 0.81 (d, 3H, *J* = 6.3 Hz). **^{13}C NMR** (100.6 MH_Z, $CDCl_3$) δ 169.9, 168.8, 162.0, 155.8, 137.8, 135.4, 132.8, 128.7, 128.6, 127.7, 127.3, 127.2 , 101.2, 63.5, 48.1, 47.4, 35.2, 33.0, 32.7, 27.5, 25.5, 24.7, 19.8, 19.2. **IR** (thin film): 2933, 1653, 1573, 1471, 1346 cm^{-1}. **HRMS** Calculated for $C_{29}H_{35}ClN_4OS$: 522.2220, found: 522.2215.

4.3.2.4: *N-(4-chlorobenzyl)-2-((4-chlorobenzyl)(2-(benzylthio) pyrimidin-4-yl)amino) butanamide (**2h**)*. The product was obtained as a green oil (350 mg, 64%) after chromatography on silica gel (Et_2O/EP 20:70). **Rf** (Et_2O/EP 50:50). 0.7. **^{1}H NMR** (400 MH_Z, $CDCl_3$) δ 8.01 (d, 1H, *J* = 6.1 Hz), 7.44 (d, 2H, *J* = 7.3 Hz), 7.35 (d, 2H, *J* = 7.3 Hz), 7.30-7.23 (m, 5H), 7.12-7.05 (m, 4H), 6.57 (br s, 1H), 6.00 (d, 1H, *J* = 6.1 Hz), 5.16 (br s, 1H), 4.75 (d, 1H, *J* = 17.4 Hz), 4.65-4.48 (m, 1H), 4.41-4.33 (m, 2H), 4.33-4.23 (m, 2H), 2.15-2.03 (m, 1H), 1.73-1.61 (m, 1H), 0.93 (t, 3H, *J* = 7.3 Hz). **^{13}C NMR** (100.6 MH_Z, $CDCl_3$) δ 170.3, 161.8, 156.1, .137.7, 136.5, 135.6, 133.2, 133.1, 129.0, 128.9, 128.8, 128.7, 127.5, 127.3, 100.9, 59.1, 48.1, 42.7, 35.2, 22.1, 11.1. **IR** (thin film): 2974, 1573, 1534, 1471, 1346 cm^{-1}. **HRMS** Calculated for $C_{29}H_{28}C_{12}N_4OS$: 550.1361, found: 550.1371.

4.3.2.5: *2-(allyl(2-(benzylthio)pyrimidin-4-yl)amino)-N-tert-butylbutanamide (**2i**)*. The product was obtained as a yellow solid (210 mg, 54%) after chromatography on silica gel (Et_2O/EP 30:70). **MP** = 93-94 °C. **Rf** (Et_2O/EP 30:70) 0.2. **^{1}H NMR** (400 MH_Z, $CDCl_3$) δ 8.08 (d, 1H, *J* = 6.1 H_Z), 7.46 (d, 2H, *J* = 7.6 H_Z), 7.37-7.31 (m, 2H), 7.27 (t, 1H, *J* = 7.1 H_Z), 6.25 (br s, 1H), 6.20 (d, 1H, *J* = 6.1 H_Z), 5.85-5.74 (m, 1H), 5.23 (d, 1H, *J* = 9.1 H_Z), 5.20 (d, 1H, *J* = 15.7 H_Z), 5.08-4.87 (br s, 1H), 4.41 (s, 2H), 4.09 (dd, 1H, *J* = 17.4, 5.1 H_Z), 3.94 (br d, 1H, *J* = 17.4 H_Z), 1.73-1.65 (m, 2H), 1.30 (s, 9H), 0.89 (t, 3H, *J* = 7.3 H_Z). **^{13}C NMR** (100.6 MH_Z, $CDCl_3$) δ 170.0, 169.7, 161.5, 155.6, 137.7, 133.1, 128.8, 128.5, 127.2, 117.4, 100.9, 59.4, 51.1, 47.2, 35.2, 28.7, 21.5, 10.9. **IR** (thin film): 2972, 1744, 1573; 1367; 1213 cm^{-1}. **HRMS** Calculated for $C_{22}H_{30}N_4OS$: 398.2140, found: 398.2140.

4.4. *Synthesis of sulfone Ugi adducts **3***

4.4.1. General procedure

To a stirred solution Ugi-Smiles adduct **2** (1.0 mmol) in dichloromethane (15 mL) was added *m*-CPBA (3.0 equiv, 3.0 mmol) at 0°C. The mixture was then allowed to warm to room temperature. After 60 min, a saturated aqueous solution of $Na_2S_2O_3$ was added to the reaction mixture and the resulting aqueous layer was extracted 3 times with dichloromethane. The combined organic phases were washed with a saturated aqueous solution of sodium bicarbonate, followed by brine, dried over anhydrous $MgS0_4$, filtered and the solvent removed in vacuo. The product was purified by flash chromatography.

4.4.2.1: *N-(4-chlorobenzyl)-2-(allyl(2-(benzylsulfonyl)pyrimidin-4-yl)amino)-4-methylpentanamide (**3a**)*. The product was obtained as a yellow solid (460 mg, 87%) after chromatography on silica gel (AcOEt/EP 25:75). **MP** = 153-154°C. **Rf** (AcOEt/EP 50:50) 0.6. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.27 (d, 1H, *J* = 6.1 Hz), 7.35-7.25 (m, 5H), 7.19 (d, 2H, *J* = 8.3 H_Z), 7.10 (d, 2H, *J* = 8.3 H_Z), 6.52 (d, 1H, *J* = 6.1 H_Z), 5.76-5.65 (m, 1H), 5.29-5.23 (m, 1H), 5.22 (d, 1H, *J* = 10.6 H_Z), 5.11 (d, l H, *J* = 17.4 H_Z), 4.68 (d, 1H, *J* = 13.6 H_Z), 4.61 (d, 1H, *J* = 13.6 H_Z), 4.32-4.18 (m, 2H), 4.17-4.10 (m, 1H), 3.95 (br d, lH, *J* = 17.7 H_Z), 2.00-1.92 (m, 1H), 1.65-1.56 (m, 1H), 1.55-1.44 (m, 1H), 0.93 (d, 3H, *J* = 6.6 H_Z), 0.90 (d, 3H, *J* = 6.6 H_Z). **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 170.0, 163.3, 162.2, 155.8, 136.9, 132.8 , 131.9, 131.2, 129.1, 128.9, 128.7, 128.6, 127.0, 117.7, 107.1, 57.4, 56.4, 47.5, 42.6, 37.3, 25.0, 22.8, 22.6. **IR** (thin

film): 2958, 1740, 1674, 1489, 1217 cm^{-1}. **HRMS** Calculated for $C_{27}H_{31}ClN_4O_3S$: 526.1805, found: 526.1828.

4.4.2.1: *2-(allyl(2-(benzylsulfonyl)pyrimidin-4-yl)amino)-N-cyclohexyl -4-methylpentanamide (**3b**)*. The product was obtained as a yellow oil (450 mg, 94%) after chromatography on silica gel (Et_2O/EP 35:65). **Rf** (Et_2O/EP 50:50) 0.5. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.22 (d, 1H, *J* = 6.1 H_Z), 7.29-7.21 (m, 5H), 6.59 (d, 1H, *J* = 7.6 Hz), 6.44 (d, 1H, *J* = 6.1 H_Z), 5.74-5.61 (m, 1H), 5.16 (d, 1H, *J* = 10,4 Hz), 5.12-5.07 (br s, 1H), 5.04 (d, 1 H , *J* = 17.7 H_Z), 4.74 (d, 1 H , *J* = 13.9 H_Z), 4.56 (d, 1 H , *J* = 13.9 H_Z), 4.20 (d, 1H, *J* = 17.4 H_Z), 3.88 (d, 1H, *J* = 17.4 H_Z), 3.56-3.50 (m, 1H), 1.90-1.81 (m, 1H), 1.75 (d, 1H, *J* = 10.9 H_Z), 1.64-1.56 (m, 1H), 1.53-1.36 (m, 5H), 1.25-0.95 (m, 5H), 0.84 (d, 3H, *J* = 6.3 H_Z), 0.81 (d, 3H, *J* = 6.3 H_Z). **^{13}C NMR** (100.6 MH_Z, $CDCl_3$) δ 168.7, 163.4, 162.2, 155.7, 132.1, 131.2, 128.8,128.7, 127.1, 117.4, 107.1, 57.3, 56.2, 48.5, 47.3, 37.1, 32.7, 32.3, 25.3, 25.1, 24.9, 22.9, 22.7. **IR** (thin film): 2933, 1635, 1587, 1489, 1119 cm^{-1}. **HRMS** Calculated for $C_{26}H_{36}N_4O_3S$: 484.2508, found: 484.2484.

4.4.2.3: *2-(allyl(2-(benzylsulfonyl)pyrimidin-4-yl)amino)-N-cyclohexylacetamide (**3c**)*. The product was obtained as an oil (380 mg, 89%) after chromatography on silica gel (Et_2O/EP 30:70). **Rf** (Et_2O/EP 50:50) 0.6. **^{1}H NMR** (400 MH_Z, $CDCl_3$) δ 8.23 (d, 1H, *J* = 5.8 H_Z), 7.30-7.19 (m, 5H), 6.61 (br s, 1H), 6.47 (d, 1H, *J* = 5.8 H_Z), 5.78-5.67 (m, 1H), 5.18 (d, 1H, J = 10.4 H_Z), 5.04 (d, 1H, *J* = 16.7 H_Z), 4.62 (s, 2H), 4.17-4.05 (m, 2H), 3.97 (s, 2H), 3.70-3.45 (m, 1H), 1.69-1.45 (m, 5H), 1.21-1.11 (m, 2H), 1.04-0.92 (m, 3H). **^{13}C NMR** (100.6 MHz, $CDC1_3$) δ 167.0, 163.7, 161.7, 156.0, 131.3, 130.2, 128.8, 128.7, 127.1, 117.7, 105.8, 57.3, 52.6, 52.4, 48.7, 32.6, 25.3, 25.0. **IR** (thin film): 2933, 1740, 1590,1370, 1217 cm^{-1}. **HRMS** Calculated for $C_{22}H_{28}N_4O_3S$: 428.1882, found: 428.1881

4.4.2.4: *2-((4-chlorobenzyl)(2-(benzylsulfonyl)pyrimidin-4-yl)amino)-N-cyclohexyl-4-methylpentanamide (**3d**)*. The product was obtained as a yellow oil (500 mg, 88%) after chromatography on silica gel (AcOEt/EP 70:30). **Rf** (AcOEt/EP 70:30) 0.3. **^{1}H NMR** (400 MH_Z, $CDCl_3$) δ 8.17 (d, 1H, *J* = 6.1 H_Z), 7.35 (d, 2H, *J* = 7.3 H_Z), 7.28-7.21 (m, 5H), 6.95 (d, 2H, *J* = 7.3 H_Z), 6.67 (br s, 1H), 6.20 (d, 1H, *J* = 6.1 H_Z), 5.12 (br s, 1H), 4.88-4.76 (m, 2H), 4.57 (d, 1H, *J* = 13.9 H_Z), 4.48 (d, 1H, *J* = 16.9 H_Z), 3.57-3.44 (m, 1H), 1.94-1.87 (m, 1H), 1.83-1.72 (m, 1H), 1.64-1.56 (m, 1H), 1.52- 1.38 (m, 4H), 1.37-1.28 (m, 1H), 1.23-1.02 (m, 4H), 0.86-0.84 (m, 1H), 0.81 (d, 3H, *J* = 6.3 H_Z), 0.79 (d, 3H, *J* = 6.3 H_Z). **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 168.8, 163.4, 162.5, 156.1, 134.5, 133.5, 131.3, 129.2, 128.9, 128.7, 128.3, 127.1, 107.1, 57.3, 56.7, 48.7, 48.1, 37.5, 32.7, 32.3, 25.5, 25.4, 25.3, 24.9, 23.0, 22.6. **IR** (thin film): 2933, 1656, 1590, 1492, 1321 cm^{-1}. **HRMS** Calculated for $C_{30}H_{37}ClN_4O_3S$: 568.2275, found: 568.2278.

4.4.2.5: *2-(allyl(2-(benzylsulfonyl)pyrimidin-4-yl)amino)-N-cyclohexyl-4-methylbutanamide (**3e**)*. The product was obtained as a yellow oil (390 mg, 82%) after chromatography on silica gel (Et_2O/EP 30:70). **Rf** (Et_2O/EP 50:50) 0.5. **^{1}H NMR** (400 MH_Z, $CDCl_3$) δ 8.23 (d, 1H, *J* = 6.1 H_Z), 7.30-7.26 (m, 2H), 7.25-7.22 (m, 3H), 6.48 (d, 1H, *J* = 6.1 H_Z), 5.67-5.56 (m, 1H), 5.15 (d, 1 H , *J* = 10.6 H_Z), 5.10 (d, 1H, *J* =17.2 H_Z), 4.74 (d, 1H, *J* = 13.9 H_Z), 4.56 (d, 1H, *J* =13.9 H_Z), 4.55-4.46 (br s, 1H), 4.08 (d, 2 H , *J* = 4.3 H_Z), 3.56-3.45 (m, 1H), 2.40-2.28 (br s, 1H), 1.74 (br d, 1H, *J* =11.1 H_Z), 1.60 (br d, 1H, *J* =13.1 H_Z), 1.53-1.39 (m, 3H), 1.22-1.13 (m, 2H), 1.12-0.98 (m, 3H), 0.89 (d, 3H, *J* = 6.6 H_Z), 0.71 (d, 3H, *J* = 6.6 H_Z). **^{13}C NMR** (100.6 MH_Z, $CDC1_3$) δ 168.3, 163.4, 162.6, 155.6, 132.0, 131.2, 128.8, 128.7, 127.3, 118.3, 107.4, 64.5, 57.4, 48.3, 47.3, 32.7, 32.3, 26.8, 25.3, 24.9, 24.8, 19.5,19.2. **IR** (thin film): 2933, 1737, 1590, 1374, 1217 cm^{-1}. **HRMS** Calculated for $C_{25}H_{34}N_4O_3S$: 470.2352; found: 470.2331.

4.4.2.6: *2-((4-chlorobenzyl)(2-(benzylsulfonyl)pyrimidin-4-yl) amino)-N-cyclohexyl-4-methylbutanamide (**3f**)*. The product was obtained as a yellow oil (490 mg, 88%) after chromatography on silica gel (Et_2O/EP 40:60). **Rf** (Et_2O/EP 50:50) 0.3. **^{1}H NMR** (400 MH_Z, $CDCl_3$) δ 8.24 (d, 1H, *J* = 6.1 H_Z), 7.48-7.33 (m, 5H), 7.31-7.25 (m, 2H), 7.09-6.98 (m, 2H), 6.69 (br s, 1H), 6.31 (d, 1H, *J* = 6.1 H_Z), 4.98-4.94 (m, 3H), 4.72-4.63 (m, 2H), 3.73-3.57 (m, 1H), 2.54-2.37 (m, 1H), 1.92-1.81 (m, 1H), 1.77-1.72 (m, 1H), 1.66-1.55 (m, 3H), 1.33-1.28 (m, 1H), 1.27-1.21 (m, 2H), 1.21-1.18 (m, 1H), 1.01 (d, 3H, *J* = 6.3 H_Z), 0.97-0.92 (m, 1H), 0.79 (d, 3H, *J* = 6.3 H_Z). ^{13}C NMR (100.6 MH_Z, $CDCl_3$) δ 168.2, 163.4, 162.8, 155.9, 134.0, 133.2, 131.2, 129.0, 128.9, 128.7, 127.7, 127.2, 107.5, 64.9, 57.4, 48.4, 47.8, 32.8, 32.5, 27.5, 25.3, 24.9, 19.6, 19.3. **IR** (thin film): 2937, 1740, 1587, 1370, 1213 cm^{-1}. **HRMS** Calculated for $C_{29}H_{35}ClN_4O_3S$: 554.2118, found: 554.2110.

4.4.2.7: *2-(allyl(2-benzylsulfonyl)pyrimidin-4-yl)amino)-N-cyclohexyl-2-phenylacetamide (**3g**)*. The product was obtained as a yellow oil (480 mg, 95%) after chromatography on silica gel (Et_2O/EP 50:50). **Rf** (Et_2O/EP 50:50) 0.3. **^{1}H NMR** (400 MH_Z, $CDCl_3$) δ 8.32 (d, 1H, *J* = 6.1 H_Z), 7.41-7.33 (m, 10H), 6.62 (d, 1H, *J* = 6.1 H_Z), 6.44 (br s, 1H),6.30 (d, 1H, *J* = 7.8 H_Z), 5.56-5.44 (m, 1H), 5.06 (d, 1H, *J* = 10.8 H_Z), 5.02 (d, 1H, *J* = 18.7 H_Z), 4.70 (s, 2H), 4.15 (dd, 1H, *J* =15.2, 7.1 H_Z), 4.10-4.00 (m, 1H), 3.82-3.72 (m, 1H), 1.92 (d, 1H, *J* = 11.5 H_Z), 1.80 (d, 1H, *J* = 11.5 H_Z), 1.72-1.63 (m, 2H), 1.63-1.55 (m, 1H), 1.31-1.26 (m, 2H), 1.15-1.05 (m, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 168.4, 163.6, 162.3, 155.7, 134.5, 132.3, 131.3, 129.7, 128.9, 128.8, 128.7, 127.1, 117.4, 107.1, 62.4, 57.5, 49.1, 48.9, 32.8, 32.5, 25.4, 24.9, 24.8. **IR** (thin film): 2937, 1740, 1587, 1489, 1220 cm^{-1}. **HRMS** Calculated for $C_{28}H_{32}N_4O_3S$: 504.2195, found: 504.2218.

4.4.2.8: *N-(4-chlorobenzyl)-2-((4-chlorobenzyl)(2-(benzylsulfonyl)pyrimidin-4-yl)amino)butanamide (**3h**)*. The product was obtained as a yellow oil (500 mg, 85%) after chromatography on silica gel (Et_2O/EP 20:80). **Rf** (Et_2O/EP 50:50) 0.7. **^{1}H NMR** (400 MH_Z, $CDCl_3$) δ 8.29 (d, 1H, *J* = 6.1 H_Z), 7.48-7.44 (m, 1H), 7.38-7.36 (m, 4H), 7.33-7.32 (m, 1H), 7.31-7.29 (m, 1H), 7.25- 7.23 (m, 1H), 7.22-7.20 (m, 1H), 7.11 (d, 2H, *J* = 8.3 H_Z), 7.05 (d, 2H, *J* = 8.3 H_Z), 6.35 (d, 1H, *J* = 6.1 H_Z), 5.01-4.89 (m, 2H), 4.80-4.74 (m, 1H), 4.70-4.64 (m, 1H), 5.57-4.48 (m, 1H), 4.36 (dd, 1H, *J* = 14.7, 6.1 H_Z), 4.11 (dd, 1H, *J* = 14.7, 6.1 H_Z), 2.14-2.07 (m, 1H), 1.66-1.58 (m, 1H), 0.90 (t, 3H, *J* =7.3 H_Z). **^{13}C NMR** (100.6 MH_Z, $CDC1_3$) δ 169.7, 163.3, 162.5, 156.3, 136.8, 134.5, 133.5, 133.0, 131.3, 129.3, 129.2, 129.0, 128,8, 128.6, 127.1, 107.0, 60.1, 57.3, 48.4, 42.7, 22.1, 10.7. **IR** (thin film): 2940, 1740, 1594, 1370, 1217 cm^{-1}. **HRMS** Calculated for $C_{29}H_{28}Cl_2N_4O_3S$: 582.1259, found: 582.1277.

4.4.2.9:*2-(allyl(2-(benzylsulfonyl)pyrimidin-4-yl)amino)-N-tert-butyl butanamide (**3i**)*. The product was obtained as an yellow oil (370 mg, 85%) after chromatography on silica gel (Et_2O/EP 30:70). **Rf** (Et_2O/EP 30:70) 0.2. **^{1}H NMR** (400 MH_Z, $CDCl_3$) δ 8.22 (d, 1H, *J* = 6.3 H_Z), 7.28-7.24 (m, 2H), 7.24-7.20 (m, 3H), 6.44 (d, 1H , *J* = 6.3 H_Z), 6.40-6.34 (br s, 1H), 5.72-5.62 (m, 1H), 5.14 (d, 1H, *J* = 10.6 H_Z), 5.02 (d, 1H, *J* = 17.4 H_Z), 4.77-4.68 (m, 2H), 4.55 (d, 1H, *J* = 13.9 H_Z), 4.21 (br d, 1H, *J* = 18.2 H_Z), 3.86 (br d, 1H, *J* = 18.2 H_Z), 2.02-1.89 (m, 1H), 1.63-1.51 (m, 1H), 1.11 (s, 9H), 0.80 (t, 3H, *J* = 7.3 H_Z). NMR ^{13}C (100.6 MH_Z, $CDCl_3$) δ

169.1, 163.4, 162.2, 155.7, 132.1, 131.3, 128.8, 128.7, 127.3, 117.4, 107.1, 59.9, 57.3, 51.5, 47.2, 28.5, 21.8, 10.6. **IR** (thin film): 2972, 1740, 1485, 1367, 1217 cm^{-1}. **HRMS** Calculated for $C_{22}H_{30}N_4O_3S$: 430.2039, found: 430.2043

4.5. *Substitution of the sulfonyl group by CN*

4.5.1. General procedure

To a solution of pyrimidine **3** (0.2 mmol) in dry DMF (2 mL) was added KCN (1.2 equiv, 0.24 mmol). The reaction mixture was stirred at 55 ^{O}C under argon for 24 h. After water addition and extraction with Et_2O, the cyanopyrimidines **4** were isolated by flash column chromatography on silica gel.

4.5.2.1: *2-(allyl(2-cyanopyrimidin-4-yl)amino)-N-cyclohexyl-4-methylpentanamide (**4b**)*. The product was obtained as a yellow solid (60 mg, 85%) after chromatography on silica gel (Et_2O/EP 20:80). **Rf** (Et_2O/EP 50:50) 0.8. **MP** = 100-101 °C. **^{1}H NMR** (400 MH_Z, $CDCl_3$) δ 8.15 (d, 1H, *J* = 6.1 Hz), 6.50 (d, 1H, *J* = 6.1 Hz), 5.97 (d, 1H, *J* = 6.3 Hz), 5.76-5.61 (m, 1 H), 5.27-5.04 (m, 3H), 4.11 (d, 1H, *J* = 17.2 Hz), 3.94 (d, 1H, *J* = 17.2 Hz), 3.69-3.58 (m, 1H), 1.88-1.77 (m, 2H), 1.73-1.67 (m, 2H), 1.59-1.39 (m, 4H), 1.31-1.21 (m, 2H), 1.15-1.07 (m, 2H), 1.04-0.98 (m, 1H), 0.88 (d, 3H, *J* = 6.6 Hz), 0.86 (d, 3H, *J* = 6.6 Hz). NMR ^{13}C (100.6 MH_Z, $CDCl_3$) δ 168.9, 161.6, 155.7, 143.8, 132.1, 117.9, 1 16.1, 107.4, 55.9, 48.3, 47.3, 37.6, 32.9, 32.8, 25.4, 25.0, 24.7, 22.7, 22.6. **IR** (thin film): 2933, 1740, 1580, 1485, 1213 cm^{-1}. **HRMS** Calculated for $C_{20}H_{29}N_5O$: 355.2372, found: 355.2381.

4.5.2.2: *2-(allyl(2-cyanopyrimidin-4-yl)amino)-N-cyclohexyl-3-methylbutanamide (**4e**)*. The product was obtained as a white solid (50 mg, 81%) after chromatography on silica gel (Et_2O/EP 20:80). **Rf** (Et_2O/EP 50:50) 0.7. **MP** = 101-102 °C. **^{1}H NMR** (400 MH_Z, $CDCl_3$) δ 8.14 (d, 1H, *J* = 6.1 H_Z), 6.52 (d, 1H, *J* = 6.1 H_Z), 5.95 (s, 1H), 5.67-5.54 (m, 1H), 5.16 (d, 1H, *J* = 10.4 H_Z), 5.09 (d, 1H, *J* = 16.9 H_Z), 4.86-4.74 (m, 1H), 4.19 (br d, 1H, *J* = 17.4 H_Z), 4.01 (dd, 1H, *J* = 17.4, 5.8 H_Z), 3.70-3.59 (m, 1H), 2.39-2.29 (m, 1H), 1.85 (d, 1H, *J* = 10.6 H_Z), 1.72-1.60 (m, 2H), 1.58-1.47 (m, 2H), 1.31-1.21 (m, 2H), 1.18-1.11 (m, 2H), 1.01 (d, 1H, *J* = 10.6 H_Z), 0.95 (d, 3H, *J* = 6.6 H_Z), 0.74 (d, 3H, *J* = 6.6 H_Z). **^{13}C NMR** (100.6 MH_Z, $CDCl_3$) δ 168.3, 161.8, 155.6, 143.8, 131.8, 118.1, 116.2, 107.4, 63.7, 48.2, 46.9, 32.9, 32.7, 27.3, 25.4, 24.7, 24.6, 19.5, 18.9. **IR** (thin film): 2930, 1667, 1527, 1482, 1388 cm^{-1}. **HRMS** Calculated for $C_{19}H_{27}N_5O$: 341.2216, found: 341.2219.

4.5.2.3: *2-((4-chlorobenzyl)(2-cyanopyrimidin-4-yl)amino)-N-cyclohexyl-3methylbutanamide (**4f**)*. The product was obtained as a yellow solid (60 mg, 82%) after chromatography on silica gel (Et_2O/EP 30:70). **Rf** (Et_2O/EP 50:50) 0.5. **MP** = 130-131 °C. **^{1}H NMR** (400 MH_Z, $CDCl_3$) δ 8.03 (d, 1H, *J* = 6.1 H_Z), 7.21-7.15 (m, 2H), 6.99-6.90 (m, 2H), 6.22 (d, 1H, *J* = 6.1 H_Z), 6.05 (br s, 1H), 5.13-4.86 (m, 2H), 4.43 (d, 1H, *J* = 16.7 H_Z), 3.68-6.56 (m, 1H), 2.45-2.31 (m, 1H), 1.89-1.81 (m, 1H), 1.74-1.47 (m, 4H), 1.31-1.21 (m, 2H), 1.16-1.04 (m, 3H), 0.96 (d, 3H, *J* = 6.8 H_Z), 0.75 (d, 3H, *J* = 6.8 H_Z). ^{13}C NMR (100.6 MH_Z, $CDCl_3$) δ 168.2, 162.0, 155.9, 143.8, 134.0, 133.3, 129.1, 127.5, 116.1, 107.5, 64.1, 48.4, 47.5, 33.0, 32.8, 28.0, 25.4, 24.7, 19.1. **IR** (thin film): 2933, 1740, 1663, 1485, 1217 cm^{-1}. HRMS Calculated for $C_{23}H_{28}ClN_5O$: 425.1982, found: 425.1974.

4.5.2.4: *2-(allyl(2-cyanopyrimidin-4-yl)amino)-N-cyclohexyl-2-phenylacetamide (**4g**)*. The product was obtained as a white solid (62 mg, 82%) after chromatography on silica gel (Et_2O/EP 30:70). **Rf** (Et_2O/EP 50:50) 0.5. **MP** = 168-169 °C. **^{1}H NMR** (400 MH_Z, $CDCl_3$) δ 8.15 (d, 1H, *J* = 6.3 Hz), 7.32 (m, 5H), 6.54 (d, 1H, 6.3 Hz), 6.29 (s, 1H), 5.63 (d, 1H, *J* = 7.6 Hz), 5.43-5.31 (m, 1H), 4.96-4.91 (m, 2H), 4.02-3.87 (m, 2H), 3.80-3.70 (m, 1H), 1.86 (d, 2H, *J* = 11.9 Hz), 1.67-1.57 (m, 2H), 1.56-1.49 (m, 1H), 1.32-1.24 (m, 2H), 1.13-1.04 (m, 3H). **^{13}C NMR** (100.6 MH_Z, $CDCl_3$) δ 168.3, 161.6, 155.7, 143.8, 134.5, 132.2, 129.8, 129.1, 117.5, 116.2, 107.2, 62.7, 49.1, 48.9, 32.9, 24.8. **IR** (thin film): 2933, 1740, 1580; 1384, 1227 cm^{-1}. **HRMS** Calculated for $C_{22}H_{25}N_5O$: 375.2059, found: 375.2048.

4.5.2.5: *N-(4-chlorobenzyl)-2-((4-chlorobenzyl)(2-cyano-pyrimidin-4yl)amino)butanamide (**4h**)*. The product was obtained as a white solid (75 mg, 83%) after chromatography on silica gel (Et_2O/EP 40:60). **Rf** (Et_2O/EP 50:50) 0.3. **MP** = 178-179 °C. **^{1}H NMR** (400 MH_Z, $CDCl_3$) δ 8.06 (d, 1H, *J* = 6.1 H_Z), 7.23-7.17 (m, 4H), 7.07 (d, 2H, *J* = 7.6 H_Z), 7.02 (d, 2H, *J* = 6.8 H_Z), 6.62 (br s, 1H), 6.28 (d, 1H, *J* = 6.1 H_Z), 5.26-5.06 (m, 1H), 4.88-4.71 (m, 1H), 4.66-4.45 (m, 1H), 4.37-4.23 (m, 2H), 2.05-1.96 (m, 1H), 1.73-1.59 (m, 1H), 0.87 (t, 3H, *J* = 7.1 H_Z). **^{13}C NMR** (100.6 MH_Z, $CDCl_3$) δ 169.9, 161.9, 156.2, 143.8, 136.2, 134.3, 133.5, 129.3, 129.1, 129.0, 127.3, 116.0, 107.4, 59.6, 48.4, 42.9, 23.9, 10.9. **IR** (thin film): 2937, 1744, 1587, 1384; 1249 cm^{-1}. **HRMS** Calculated for $C_{23}H_{21}C1_2N_5O$: 453.1123, found: 453.1119.

4.5.2.6: *2-(allyl(2-cyanopyrimidin-4-yl)amino)-N-tert-butyl butanamide (**4i**)*. The product was obtained as a yellow oil (53 mg, 88%) after chromatography on silica gel (Et_2O/EP 20:80). **Rf** (Et_2O/EP 50:50) 0.9. **^{1}H NMR** (400 MH_Z, $CDCl_3$) δ 8.15 (d, 1H, *J* = 6.3 H_Z), 6.50 (d, 1H, *J* = 6.3 H_Z), 5.98 (br s, 1H), 5.76-5.61 (m, 1H), 5.17 (d, 1H, 10.6 H_Z), 5.10 (d, 1H, *J* = 17.4 H_Z), 4.99-4.82 (br s, 1H), 4.13 (d, 1H, 16.4 H_Z), 4.00-3.87 (m, 1H), 2.05-1.89 (m, 2H), 1.25 (s, 9H), 0.86-0.82 (m, 3H). ^{13}C NMR (100.6 MH_Z, $CDCl_3$) δ 169.0, 161.5, 155.7, 143.8, 132.0, 117.8, 116.1, 107.3, 59.9, 51.6, 47.2, 28.7, 22.0, 10.7. **IR** (thin film): 2972, 1740, 1677, 1485, 1227 cm^{-1}. **HRMS** Calculated for $C_{16}H_{23}N_5O$: 301.1903, found: 301.1908.

4.6. *Substitution of the sulfonyl group by a dimethylmalonyl ester group*

4.6.1. General procedure

To a solution of dimethylmalonate (1.2 equiv, 0.24 mmol) in dry acetonitrile (0.1 M) at rt under argon was added Cs_2CO_3 (1.5 equiv, 0.3 mmol). After 30 min, pyrimidinesulfone **3** (0.2 mmol) was added and the mixture was heated at 70°C for 48 h. After water addition and extraction with CH_2Cl_2, the pyrimidines **5** were isolated by flash column chromatography on silica gel.

4.6.2.1: *dimethyl 2-(4-((1-(4-chlorobenzylamino)-4-methyl-1-oxopentan-2-yl)(allyl)amino) pyrimidin-2-yl)malonate (**5a**)*. The product was obtained as a yellow oil (86 mg, 86%) after chromatography on silica gel (Et_2O/EP 50:50). **Rf** (Et_2O/EP 50:50) 0.2. **^{1}H NMR** (400 MH_Z, $CDCl_3$) δ 8.12 (d, 1H, *J* = 6.3 H_Z), 7.44 (br s, 1H), 7.12 (d, 2H, *J* = 8.3 H_Z), 7.03 (d, 2H, *J* = 8.3 H_Z), 6.29 (d, 1H, *J* = 6.3 H_Z), 5.60-5.48 (m, 1H), 5.47-5.35 (br s, 1H), 5.10-5.03 (m, 2H), 4.87 (s, 1H), 4.30 (dd, 1H, J_{AB} = 14.4, 5.3 H_Z), 4.19 (dd, 1H, J_{AB} = 14.4, 5.3 H_Z), 4.09-4.00 (m, 1H), 3.70-3.67 (m, 1H), 3.67 (s, 3H), 3.64 (s, 3H), 1.85-1.75 (m, 1H), 1.60-1.54 (m, 1H), 1.50-1.41 (m, 1H), 0.84 (d, 3H, *J* = 6.3 H_Z),

0.80 (d, 3H, J = 6.3 H_Z). **^{13}C NMR** (100.6 MH_Z, $CDCl_3$) δ 170.4, 167.5, 167.4, 161.9, 161.2, 156.1, 137.6, 132.6, 129.1, 128.4, 117.4, 103.8, 61.0, 54.0, 53.0, 46.8, 42.5, 36.4, 24.9, 22.6, 22.5. **IR** (thin film): 2954, 1740, 1587, 1367, 1217 cm^{-1}. **HRMS** Calculated for $C_{25}H_{31}ClN_4O_5$: 502.1983, found: 502.1995.

4.6.2.2: *dimethyl 2-(4-(allyl(1-(4-cyclohexylamino)-4-methyl-1-oxopentan-2-yl)amino) pyrimidin-2-yl)malonate (**5b**)*. The product was obtained as a yellow oil (80 mg, 87%) after chromatography on silica gel (Et_2O/EP 40:60). **Rf** (Et_2O/EP 50:50) 0.3. **^{1}H NMR** (400 MH_Z, $CDCl_3$) δ 8.12 (d, 1H, J = 6.1 H_Z), 6.36 (br s, 1H), 6.29 (d, 1H, J = 6.1 H_Z), 5.76-5.61 (m, 1H), 5.53 (br s, 1H), 5.13 (d, 1H, J = 10.4 H_Z), 5.10 (d, 1H, J = 17.2 H_Z), 4.88 (s, 1H),4.11 (d, 1H, J = 17.9 H_Z), 3.81-3.76 (m, 1H), 3.74 (s, 3H), 3.73 (s, 3H), 3.62-3.54 (m, 1H), 1.84-1.72 (m, 2H), 1.66-1.47 (m, 5H), 1.46-1.30 (m, 1H), 1.23-1.14 (m, 3H), 1.08-0.95 (m, 2H), 0.85 (d, 3H, J = 6.6 H_Z), 0.81 (d, 3H, J = 6.6 H_Z). **^{13}C NMR** (100.6 MH_Z, $CDCl_3$) δ 169.4, 167.5, 167.2, 161.8, 161.4, 156.1, 132.9, 117.8, 103.5, 61.2, 54.3, 53.0, 52.9, 48.3, 46.7, 36.9, 32.7, 32.5, 25.5, 25.2, 25.0, 24.9, 22.7, 22.5. **IR** (thin film): 2933, 1740, 1583, 1370, 1217 cm^{-1}. **HRMS** Calculated for $C_{24}H_{36}N_4O_5$: 460.2686, found: 460.2696.

4.6.2.3: *dimethyl 2-(4-(allyl(2-(cyclohexylamino)-2-oxoethyl) amino) pyrimidin-2-yl)malonate (**5c**)*. The product was obtained as a colorless oil (86 mg, 86%) after chromatography on silica gel (Et_2O/EP 50:50). **Rf** (Et_2O/EP 50:50) 0.2. **^{1}H NMR** (400 MH_Z, $CDCl_3$) δ 8.17 (d, 1H, J = 5.8 H_Z), 6.39-6.15 (m, 2H), 5.80-5.67 (m, 1H), 5.17 (d, 1H, J = 10.6 H_Z), 5.11 (d, 1H, J = 17.4 H_Z), 4.86 (s, 1H), 4.09-3.98 (m, 4H), 3.74 (s, 6H), 3.70-3.58 (m, 1H), 1.79-1.72 (m, 2H), 1.63-1.57 (m, 2H), 1.55-1.49 (m, 1H), 1.27-1.21 (m, 2H), 1.10-0.99 (m, 3H). **^{13}C NMR** (100.6 MH_Z, $CDCl_3$) δ 166.7, 166.2, 161.0, 160.4, 155.4, 129.6, 117.0, 101.1, 60.3, 51.9, 51.2, 50.5, 47.4, 32.5, 25.5, 25.0. **IR** (thin film): 2937, 1740, 1590, 1367, 1217 cm^{-1}. **HRMS** Calculated for $C_{20}H_{28}N_4O_5$: 404.2060, found: 404.2055.

4.6.2.4: *dimethyl 2-(4-(allyl(1-(cyclohexylamino)-3-methyl-1-oxobutan-2-yl)amino)pyrimidin-2-yl)malonate (**5e**)*. The product was obtained as a yellow oil (74 mg, 83%) after chromatography on silica gel (Et_2O/EP 40:60). **Rf** (Et_2O/EP 50:50) 0.3. **^{1}H NMR** (400 MH_Z, $CDCl_3$) δ 8.12 (d, 1H, J = 6.1 H_Z), 6.31 (d, 1H, J = 6.1 H_Z), 6.24 (br s, 1H), 5.69-5.57 (m, 1H), 5.15-5.08 (m, 2H), 4.88 (s, 1H), 4.85-4.74 (m, 1H), 4.06 (dd, 1H, J = 17.7, 5.6 H_Z), 4.00-3.95 (m, 1H), 3.75 (s, 3H), 3.74 (s, 3H), 3.64-3.57 (m, 1H), 2.40-2.25 (m, 1H), 1.84-1.77 (m, 1H), 1.67-1.48 (m, 4H), 1.27-1.13(m, 3H), 1.07-0.96 (m, 2H), 0.91 (d, 3H, J = 6.6 H_Z), 0.73 (d, 3H, J = 6.6 H_Z). **^{13}C NMR** (100.6 MH_Z, $CDCl_3$) δ 168.9, 1676, 167.2, 161.9, 161.3, 156.0, 132.7, 117.8, 103.6, 62.9, 61.2, 53.0, 52.9, 48.2, 46.7, 32.8, 32.5, 26.4, 25.5, 25.1, 25.0, 19.9, 19.2. **IR** (thin film): 2933, 1740, 1670, 1541, 1482 cm^{-1}. **HRMS** Calculated for $C_{23}H_{34}N_4O_5$: 446.2529, found: 446.2516.

4.7. *Palladium catalyzed couplings of **3** with boronic acids*

4.7.1. *General procedure*

To a solution 0.05 M of (benzylsulfonyl)pyrimidine **3** (0.1 mmol) in toluene (2 mL) were successively added under inert atmosphere $Pd(OAc)_2$ (5.0 mol %), triphenylphosphine (15 mol %) followed by the boronic acid (1.2 equiv, 0.12 mmol) and Cs_2CO_3 (1.5 equiv, 0.15 mmol). The reaction mixture was stirred under reflux for 40 h. After water addition and extraction with CH_2Cl_2, the pyrimidines **6** were isolated by flash column chromatography on silica gel.

4.7.2.1: *2-(allyl(2-p-tolylpyrimidin-4-yl)amino)N-(4-chloro benzyl)-4-methylpentanamide (**6a**)*. The product was obtained as a yellow oil (35 mg, 75%) after chromatography on silica gel (Et_2O/EP 40:60). **Rf** (Et_2O/EP 50:50) 0.3. **^{1}H NMR** (400 MH_Z, $CDCl_3$) δ 8.03 (d, 1H, J = 6.1 H_Z), 7.18 (d, 2H, J = 8.3 H_Z), 6.96 (d, 2H, J = 8.3 Hz), 6.90 (d, 2H, J = 8.3 H_Z), 6.85 (d, 2H, J = 8.3 H_Z), 6.1 (d, 1H, J = 6.1 H_Z), 6.02-5.92 (br s, 1H), 5.69-5.57 (m, 1H), 5.10 (d, 1H, J = 12.1 H_Z), 5.06 (d, 1H, J =18.4 H_Z), 4.94-4.80 (m, 1H), 4.16 (dd, 1H, J = 14.9, 6.1 H_Z), 4.09 (dd, 1H, J = 17.4, 5.6 Hz), 4.03 (dd, 1H, J = 14.9, 6.1 H_Z), 3.74 (br d, 1H, J = 17.4 H_Z), 2.16 (s, 3H), 1.83-1.74 (m, 1H), 1.44-1.31 (m, 2H), 0.78 (d, 3H, J = 6.3 Hz), 0.76 (d, 3H, J = 6.3 H_Z). **^{13}C NMR** (100.6 MH_Z, $CDCl_3$) δ 170.6, 164.9, 163.5, 158.3, 150.9, 136.4, 135.0, 133.1, 130.0, 128.7, 128.6, 121.9, 117.2, 99.6, 54.6, 47.3, 42.4, 37.1, 24.9, 22.8, 22.0, 20.8. **IR** (thin film): 2954, 1677, 1590, 1384, 1206 cm^{-1}. **HRMS** Calculated for $C_{27}H_{31}C1N_4O$: 462.2186, found: 462.2185.

4.7.2.2: *2-(allyl(2-o-tolylpyrimidin-4-yl)amino)N-cyclohexyl-3-methylpentanamide (**6b**)*. The product was obtained as a yellow oil (30 mg, 70%) after chromatography on silica gel (Et_2O/EP 40:60). **Rf** (Et_2O/EP 60:40) 0.4. **^{1}H NMR** (400 MH_Z, $CDCl_3$) δ 8.01 (d, 1H, J = 6.1 H_Z), 7.20-7.18 (m, 1H), 7.16 (d 1H, J = 8.1 H_Z), 7.12-7.07 (m, 1H), 7.04 (d, 1H, J = 8.1 Hz), 6.07 (d, 1H, J = 6.1 H_Z), 5.70-5.59 (m, 1H), 5.48 (d, 1H, J = 6.8 H_Z), 5.11 (d, 1H, J = 13.4 H_Z), 5.07 (d, 1H, J = 17.9 H_Z), 4.91 (br s, 1H), 4.09-3.95 (m, 1H), 3.78 (d, 1H, J = 17.7 H_Z), 3.57-3.47 (m, 1H), 2.13 (s, 3H), 1.72-1.64 (m, 2H), 1.62-1.48 (m, 4H), 1.46-1.38 (m, 1H), 1.36-1.27 (m, 1H), 1.25-1.16 (m, 2H), 1.07-1.01 (m, 1H), 0.95-0.81 (m, 2H), 0.75 (d, 3H, J = 6.3 H_Z), 0.74 (d, 3H, J = 6.3 H_Z). **^{13}C NMR** (100.6 MH_Z, $CDCl_3$) δ 169.5, 164.4, 163.6, 158.2, 151.7, 133.2, 131.3, 130.8, 127.1, 125.5, 122.3, 117.2, 99.5, 54.4, 47.9, 47.0, 37.2, 33.0, 32.9, 25.6, 24.9, 24.8, 22. 6, 22.5, 16.5. **IR** (thin film): 2930, 1740, 1590, 1381, 1217 cm^{-1}. **HRMS** Calculated for $C_{26}H_{36}N_4O$: 420.2889, found: 420.2858.

4.7.2.3: *2-(allyl(2-phenylpyrimidin-4-yl)amino)N-cyclohexyl-3-methylbutanamide (**6c**)*. The product was obtained as a yellow oil (28 mg, 72%) after chromatography on silica gel (Et_2O/EP 30:70). **Rf** (Et_2O/EP 50:50) 0.5. **^{1}H NMR** (400 MH_Z, $CDCl_3$) δ 7.98 (d, 1H, J = 6.1 Hz), 7.39-7.34 (m, 2H), 7.20-7.16 (m, 1H), 7.12 (d, 2H, J = 7.6 H_Z), 6.11 (d, 1H, J = 6.1 H_Z), 5.71-5.46 (m, 2H), 5.10 (d, 1H, J = 7.8 H_Z), 5.07 (d, 1H, J = 15.7 H_Z), 4.61-4.41 (br s, 1H), 4.06-3.94 (m, 2H), 3.60-3.49 (m, 1H), 2.29-2.20 (m, 1H), 1.70 (br d, 1H, J = 11.6 H_Z), 1.62-1.55 (m, 2H), 1.53-1.46 (m, 2H), 1.28-1.20 (m, 2H), 1.09-1.04 (m, 1H), 0.97-0.84 (m, 2H), 0.80 (d, 3H, J = 6.6 H_Z), 0.70 (d, 3H, J = 6.6 H_Z). **^{13}C NMR** (100.6 MH_Z, $CDCl_3$) δ 168.9, 164.6, 163.8, 157.8, 153.3, 132.9, 129.5, 125.3, 122.2, 1175, 100.0, 63.0, 47.7, 47.0, 33.0, 32.7, 26.7, 25.5, 24.7, 24.6, 19.6, 19.1. **IR** (thin film): 2930, 1670, 1587, 1381, 1206 cm^{-1}. **HRMS** Calculated for $C_{24}H_{32}N_4O$: 392.2576, found: 392.2522.

4.7.2.4: *2-(allyl(2-p-tolylpyrimidin-4-yl)amino)N-cyclohexyl-2-phenylbutanamide (**6d**)*. The product was obtained as a white solid (26 mg, 60%) after chromatography on silica gel (Et_2O/EP 40:60). **MP** = 159-160°C. **Rf** (Et_2O/EP 50:50) 0.3. **^{1}H NMR** (400 MH_Z, $CDCl_3$) δ 7.98 (d, 1H, J = 6.1 H_Z), 7.30-7.18 (m, 5H), 7.11 (d, 2H, J = 8.3 H_Z), 7.00 (d, 2H, J = 8.3 H_Z), 6.28 (s, 1H), 6.15 (d, 1H, J = 6.1 H_Z), 5.46 (d, 1H, J = 7.3 H_Z) 5.43-5.32 (m, 1H), 4.99-4.87 (m, 2H), 4.01-3.85 (m, 2H), 3.75-3.65 (m, 1H), 2.27(s, 3H), 1.85-1.72 (m, 2H), 1.60 (br d, 2H, J = 11.8 H_Z), 1.53 (br d, 1H, J =12.6 H_Z), 1.26 (br d, 2H, J = 12.6 H_Z), 1.05-0.90 (m, 3H). **^{13}C NMR** (100.6 MH_Z, $CDCl_3$) δ 168.7, 164.7, 163.8, 157.7, 151.0, 135.5, 134.5, 133.5, 129.9, 129.6, 128.8, 128.5, 121.8,

116.8, 99.8, 61.4, 48.9, 32.9, 32.8, 25.5, 24.8, 21.0. **IR** (thin film): 2930, 1740, 1587, 1384, 1206 cm^{-1}. **HRMS** Calculated for $C_{28}H_{32}N_4O$: 440.2576, found: 440.2562.

4.7.2.5: *2-((4-chlorobenzyl)(2-o-tolylpyrimidin-4-yl)amino)N-cyclohexyl-2-methylpentanamide (**6e**)*. The product was obtained as a yellow oil (35 mg, 69%) after chromatography on silica gel (Et_2O/EP 40:60). **Rf** (Et_2O/EP 50:50) 0.3. **^{1}H NMR** (400 MH_Z, $CDCl_3$) δ 7.94 (d, 1H, *J* = 6.1 H_Z), 7.23-7.19 (m, 4H), 7.12 (d, 1H, *J* = 7.3 H_Z), 7.08 (d, 1H, *J* = 8.1 H_Z), 6.97 (d, 2H, *J* = 7.6 H_Z), 5.85 (d, 1H, *J* = 6.1 H_Z), 5.54 (br s, 1H), 5.06-4.97 (br s, 1H), 4.74-4.59 (m, 1H), 4.50-4.36 (m, 1H), 3.58-3.47 (m, 1H), 2.16 (s, 3H), 1.78-1.65 (m, 2H), 1.63-1.49 (m, 4H), 1.34-1.16 (m, 4H), 1.09-1.02 (m, 1H), 0.94-0.84 (m, 2H), 0.74 (d, 3H, *J* = 5.3 H_Z), 0.70 (d, 3H, *J* = 5.3 H_Z). **^{13}C NMR** (100.6 MH_Z, $CDCl_3$) δ 169.3, 164.3, 163.9, 158.5, 151.6, 135.6, 132.9, 131.4, 130.8, 128.9, 127.5, 127.1, 125.6, 122.3, 99.7, 55.1, 48.0, 47.9, 37.5, 33.0, 32.9, 25.5, 25.1, 24.8, 22.8, 22.3, 16.6. **IR** (thin film): 2930, 1674, 1590, 1489, 1182 cm^{-1}. **HRMS** Calculated for $C_{30}H_{37}ClN_4O$: 504.2656, found: 504.2674.

4.7.2.6: *2-((4-chlorobenzyl)(2-o-tolylpyrimidin-4-yl)amino)N-cyclohexyl-2-methylpentanamide (**6f**)*. The product was obtained as a yellow oil (33 mg, 74%) after chromatography on silica gel (Et_2O/EP 30:70). **Rf** (Et_2O/EP 60:40) 0.5. **^{1}H NMR** (400 MH_Z, $CDCl_3$) δ 8.00 (d, 1H, *J* = 6.1 H_Z), 7.30 (d, 2H, *J* = 8.6 H_Z), 7.07 (d, 2H, *J* = 8.6 H_Z), 6.12 (d, 1H, *J* = 6.1 H_Z), 5.71-5.59 (m, 2H), 5.12 (d, 1H, *J* = 11.1 H_Z), 5.08 (d, 1H, *J* = 17.7 H_Z), 4.97 (br s, 1H), 4.05 (d, 1H, *J* = 16.9 H_Z), 3.81 (d, 1H, *J* = 16.9 H_Z), 3.59-3.49 (m, 1H), 1.75-1.66 (m, 2H), 1.62-1.54 (m, 2H), 1.53-1.43 (m, 3H), 1.40-1.34 (m, 1H), 1.28-1.17 (m, 2H), 1.11-1.03 (m, 1H), 0.95-0.83 (m, 2H), 0.79 (d, 3H, *J* = 6.3 H_Z), 0.78 (d, 3H, *J* = 6.3 H_Z). **^{13}C NMR** (100.6 MH_Z, $CDCl_3$) δ 169.5, 164.3, 163.6, 157.8, 151.6, 132.9, 130.6, 129.6, 123.6, 117.4, 100.1, 54.9, 47.9, 47.1, 37.1, 32.9, 32.7, 25.5, 24.9, 24.7, 24.6, 22.6, 22.4. **IR** (thin film): 2937, 1740, 1590, 1370, 1213 cm^{-1}. **HRMS** Calculated for $C_{25}H_{33}ClN_4O$: 440.2343, found: 440.2336.

4.7.2.7: *2-(allyl(2-(3,4-dichlorophenyl)pyrimidin-4-yl)amino)N-cyclohexyl-4-methylpentanamide (**6g**)*. The product was obtained as a yellow oil (33 mg, 70%) after chromatography on silica gel (Et_2O/EP 30:70). **Rf** (Et_2O/EP 60:40) 0.5. **^{1}H NMR** (400 MH_Z, $CDCl_3$) δ 7.99 (d, 1H, *J* = 6.1 H_Z), 7.4.1 (d, 1H, *J* = 8.6 H_Z), 7.27 (d, 1H, *J* = 2.5 H_Z), 7.01 (dd, 1H, *J* = 8.6, 2.5 H_Z), 6.14 (d, 1H, *J* = 6.1 H_Z), 5.73-5.57 (m, 2H), 5.14 (d, 1H, *J* = 11.4 H_Z), 5.09 (d, 1H, *J* = 18.2 Hz), 5.05-4.92 (br s, 1H), 4.10-3.98 (m, 1H), 3.83 (br d, 1H, *J* = 16.4 H_Z), 3.61-3.50 (m, 1H), 1.77-1.67 (m, 2H), 1.63-1.55 (m, 2H), 1.54-1.45 (m, 3H), 1.42-1.35 (m, 1H), 1.24-1.17 (m, 2H), 1.11-1.05 (m, 1H), 0.96-0.84 (m, 2H), 0.80 (d, 3H, *J* = 6.3 H_Z), 0.79 (d, 3H, *J* = 6.3 Hz). **^{13}C NMR** (100.6 MH_Z, $CDCl_3$) δ 169.3, 164.0, 163.7, 157.9, 151.9, 133.0, 132.9, 130.8, 129.1, 124.4, 121.9, 117.5, 100.4, 55.0, 47.9, 47.2, 37.2, 32.9, 32.7, 25.4, 24.9, 24.7, 24.6, 22.5. **IR** (thin film): 2933, 1740, 1590, 1337, 1213 cm^{-1}. **HRMS** Calculated for $C_{25}H_{32}Cl_2N_4O$: 474.1953, found: 474.1946.

4.7.2.8: *2-(allyl(2-(4-fluorophenyl)pyrimidin-4-yl)amino)N-cyclohexyl-4-methylpentanamide (**6h**)*. The product was obtained as a yellow oil (31 mg, 73%) after chromatography on silica gel (Et_2O/EP 30:70). **Rf** (Et_2O/EP 60:40) 0.5. **^{1}H NMR** (400 MH_Z, $CDCl_3$) δ 8.00 (d, 1H, *J* = 6.1 H_Z), 7.11-7.06 (m, 2H), 7.05-6.99 (m, 2H), 6.10 (d, 1H, *J* = 6.1 H_Z), 5.72-5.58 (m, 2H), 5.13 (d, 1H, *J* = 12.1 H_Z), 5.08 (d, 1H, *J* = 18.2 H_Z), 5.03-4.92 (m, 1H), 4.04 (br d, 1H , *J* = 17.7 H_Z), 3.80 (br d, 1H, *J* = 17.7 H_Z), 3.60-3.50 (m, 1H), 1.75-1.69 (m, 2H),1.62-1.56 (m, 2H), 1.53-1.45 (m, 3H), 1.39-1.35 (m, 1H), 1.27-1.20 (m, 2H), 1.09-1.03 (m, 1H), 0.95-0.84 (m, 2H), 0.79 (d, 3H, *J* = 6.3 H_Z), 0.77 (d, 3H, *J* = 6.3 H_Z). **^{13}C NMR** (100.6 MH_Z, $CDCl_3$) δ 169.4, 164.6, 163.6, 159.6 ($J_{C\text{-}F}$ = 244.4 H_Z), 158.0, 148.9 ($J_{C\text{-}F}$ = 2.2 H_Z), 133.0, 1235 ($J_{C\text{-}F}$ = = 8.1 H_Z), 117.4, 116.2 ($J_{C\text{-}F}$ = 23.4 H_Z), 99.9, 54.8, 47.8, 47.1, 37.1, 32.9, 32.8, 25.5, 24.9, 24.7, 24.6, 22.6, 22.5. **IR** (thin film): 2933, 1737, 1590, 1503, 1192 cm-1. **HRMS** Calculated for $C_{25}H_{33}FN_4O$: 424.2638, found: 424.2620.

4.7.2.9: *2-(allyl(2-(4-methoxyphenyl)pyrimidin-4-yl)amino)-N-cyclohexyl-4-methylbutanamide (**6i**)*. The product was obtained as a yellow oil (32 mg, 75%) after chromatography on silica gel (Et_2O/EP 50:50). **Rf** (Et_2O/EP 50:50) 0.2. **^{1}H NMR** (400 MH_Z, $CDCl_3$) δ 7.98 (d, 1H, *J* = 6.1 H_Z), 7.07-7.02 (m, 2H), 6.89-6.85 (m, 2H), 6.10 (d, 1H, *J* = 6.1 H_Z), 5.69-5.54 (m, 2H), 5.12-5.04 (m, 2H), 4.58 (br s, 1H), 3.99 (br d, 2H, *J* = 4.0 H_Z), 3.75 (s, 3H), 3.62-3.51 (m, 1H), 2.34-2.20 (m, 1H), 1.72 (d, 1H, *J*= 11.6 H_Z), 1.63-1.56 (m, 2H), 1.54-1.46 (m, 2H), 1.30-1.21 (m, 2H), 1.10-1.03 (m, 1H), 0.97 (d, 1H, *J* = 11.6 Hz,), 0.91-0.86 (m, 1H), 0.83 (d, 3H, *J* = 6.6 H_Z), 0.72 (d, 3H, *J* = 6.6 H_Z). **^{13}C NMR** (400 MH_Z, $CDCl_3$) δ 168.9, 164.9, 163.9, 157.7, 156.8, 146.7, 132.9, 122.9, 117.5, 114.4, 99.9, 63.2, 55.6, 47.7, 46.9, 33.0, 32.7, 26.7, 25.5, 24.7, 24.6, 19.7, 19.1. **IR** (thin film): 2933, 1744, 1590, 1384, 1206 cm^{-1}. **HRMS** Calculated for $C_{25}H_{34}N_4O_2$: 422.2682, found: 422.2691.

4.7.2.10: *2-(allyl(2-(2-methoxyphenyl)pyrimidin-4-yl)amino)-N-cyclohexyl-4-methylpentanamide (**6j**)*. The product was obtained as a yellow oil (28 mg, 65%) after chromatography on silica gel (Et_2O/EP 50:50). **Rf** (Et_2O/EP 50:50) 0.2. **^{1}H NMR** (400 MH_Z, $CDCl_3$) δ 7.99 (d, 1H, *J* = 6.1 H_Z), 7.14 (t, 1H, *J* = 7.6 H_Z), 7.09 (d, 1H, *J* = 7.6 H_Z), 6.96-6.89 (m, 2H), 6.07 (d, 1H, *J* = 6.1 H_Z), 5.78 (d, 1H, *J* = 7.3 H_Z), 5.70-5.59 (m, 1H), 5.11 (d, 1H, *J* = 10.1 H_Z), 5.07 (d, 1H, *J* = 17.4 H_Z), 4.95 (br s, 1H), 4.02 (dd, 1H, *J* = 17.7, 4.0 H_Z), 3.77 (d, 1H, *J* = 17.7 H_Z), 3.70 (s, 3H), 3.59-3.48 (m, 1H), 1.74-1.55 (m, 5H), 1.54-1.41 (m, 2H), 1.38-1.30 (m, 1H), 1.27-1.16 (m, 2H), 1.08-1.02 (m, 1H), 1.00-0.84 (m, 2H), 0.75 (d, 3H, *J* = 6.8 Hz), 0.72 (d, 3H, *J* = 6.8 Hz). **^{13}C NMR** (100.6 MH_Z, $CDCl_3$) δ 169.6, 164.4, 163.9, 158.0, 151.9, 142.3, 133.2, 126.3, 123.2, 121.1, 117.2, 113.2, 99.6, 56.2, 54.4, 47.9, 47.0, 37.0, 33.0, 32.8, 25.6, 24.8, 24.7, 22.6, 22.4. **IR** (thin film): 2933, 1677, 1499, 1388, 1206 cm^{-1}. **HRMS** Calculated for $C_{26}H_{36}N_4O_2$: 436.2838, found: 436.2830.

4.7.2.11: *2-((4-chlorobenzyl(2-(2-methoxyphenyl)pyrimidin-4-yl)amino)-N-cyclohexyl-4-methylpentanamide (**6k**)*. The product was obtained as a green oil (32 mg, 61%) after chromatography on silica gel (Et_2O/EP 50:50). **Rf** (Et_2O/EP 50:50) 0.2. **^{1}H NMR** (400 MH_Z, $CDCl_3$) δ 7.92 (d, 1H, *J*= 5.8 H_Z), 7.22-7.18 (m, 3H), 7.15-7.11 (m, 1H), 6.99 (d, 2H, *J*= 8.8 H_Z), 6.96 (d, 2H, *J*= 8.8 H_Z), 5.95-5.87 (br s, 1H), 5.85 (d, 1H, *J* = 5.8 H_Z), 5.04 (br s, 1H), 4.65 (d, 1H, *J*= 16.4 H_Z), 4.49-4.36 (m, 1H), 3.73 (s, 3H), 3.59-3.48 (m, 1H), 1.77-1.67 (m, 2H), 1.63-1.50 (m, 4H), 1.35-1.28 (m, 2H), 1.27-1.21 (m, 2H), 1.10-1.04 (m, 1H), 0.98-0.86 (m, 2H), 0.73 (d, 3H, *J* = 6.3 Hz), 0.70 (d, 3H, *J* = 6.3 Hz). **^{13}C NMR** (100.6 MH_Z, $CDCl_3$) δ 169.4, 164.4, 164.0, 158.3, 151.9, 142.2, 135.8, 132.9, 129.9, 127.5, 126.4, 123.2, 121.2, 113.3, 99.9, 56.2, 55.1, 48.0, 47.9, 37.3, 33.0, 32.8, 25.6, 25.1, 24.8, 22.7, 22.4. **IR** (thin film): 2933, 1740, 1594, 1384, 1206 cm^{-1}. **HRMS** Calculated for $C_{30}H_{37}C1N_4O_2$: 520.2605, found: 520.2615

4.7.2.12: *2-((2-(4-acetylphenyl)pyrimidin-4-yl)(allyl)amino)-N-cyclohexyl-2-phenylacetamide (**6l**)*. The product was obtained as a yellow oil (30 mg, 63%) after chromatography on silica gel (Et_2O/EP 40:60). **Rf** (Et_2O/EP 40:60) 0.2. **^{1}H NMR** (400 MH_Z,

$CDCl_3$) δ 7.98 (d, 1H, *J*= 6.1 H_Z), 7.93 (d, 2H, *J* = 7.8 H_Z), 7.29-7.23 (m, 5H), 7.20 (d, 2H, *J* = 7.8 H_Z), 6.27 (br s, 1H), 6.21 (d, 1H, *J* = 6.1 H_Z), 5.52 (br d, 1H, *J*= 8.8 H_Z), 5.43-5.32 (m, 1H), 4.93-4.85 (m, 1H), 4.01-3.87 (m, 1H), 3.77-3.66 (m, 1H), 2.52 (s, 3H), 1.85-1.72 (m, 2H), 1.63-1.48 (m, 3H), 1.29-1.22 (m, 2H), 1.06-0.92 (m, 3H). **^{13}C NMR** (100.6 MH_Z, $CDCl_3$) δ 196.9, 168.6, 164.0, 163.9, 157.5, 157.2, 135.2, 133.8, 133.2, 130.0, 129.6, 128.9, 128.6, 121.8, 117.0, 100.6, 61.9, 49.1, 48.7, 32.8, 32.5, 26.6, 25.4, 24.8, 24.7. **IR** (thin film): 2933, 1737, 1594, 1489, 1213 cm^{-1}. **HRMS** Calculated for $C_{29}H_{32}N_4O_2$: 468.2525, found: 468.2539.

4.7.2.13: *2-((4-chlorobenzyl(2-(4-ethylphenyl)pyrimidin-4-yl)amino)-N-cyclohexyl-3-methylbutanamide (**6m**)*. The product was obtained as a green oil (39 mg, 77%) after chromatography on silica gel (Et_2O/EP 30:70). **Rf** (Et_2O/EP 50:50) 0.4. **^{1}H NMR** (400 MH_Z, $CDCl_3$) δ 7.98 (d, 1H, *J*= 5.8 Hz), 7.19 (d, 2H, *J* = 8.1 H_Z), 7.14 (d, 2H, *J* = 8.3 H_Z), 7.04 (d, 2H, *J* = 8.1 H_Z), 6.93 (d, 2H, *J* = 8.3 H_Z), 5.82 (d, 1H, *J*= 5.8 Hz), 5.64 (br s, 1H), 4.76 (d, 1H, *J*= 17.4 H_Z), 4.66 (br s, 1H), 4.45 (d, 1H, *J* = 17.4 H_Z), 3.59-3.48 (m, 1H), 2.60 (q, 2H, *J* = 7.6 H_Z), 2.35-2.19 (m, 1H), 1.75-1.67 (m, 1H), 1.64-1.49 (m, 4H), 1.26-1.13 (m, 5H), 1.11-1.05 (m, 1H), 0.99-0.89 (m, 2H), 0.81 (d, 3H, *J* = 6.3 Hz), 0.69 (d, 3H, *J* = 6.3 H_Z). **^{13}C NMR** (100.6 MH_Z, $CDCl_3$) δ 168.8, 164.8, 164.0, 158.1, 151.1, 141.2, 135.3, 132.8, 128.8, 128.7, 127.7, 121.9, 100.6, 63.7, 47.8, 47.5, 33.1, 32.8, 28.4, 27.3, 25.5, 24.7, 19.6, 19.2, 15.8. **IR** (thin film): 2933, 1737, 1594, 1489, 1208 cm^{-1}. **HRMS** Calculated for $C_{30}H_{37}C1N_4O$: 504.2656, found: 504.2642.

4.7.2.14: *2-((4-chlorobenzyl(2-(4-tert-butylphenyl)pyrimidin-4-yl)amino)-N-cyclohexyl-3-methylbutanamide (**6n**)*. The product was obtained as a green oil (43 mg, 81%) after chromatography on silica gel (Et_2O/EP 30:70). **Rf** (Et_2O/EP 50:50) 0.5. **^{1}H NMR** (400 MH_Z, $CDCl_3$) δ 7.89 (d, 1H, *J* = 6.1 H_Z), 7.38 (d, 2H, *J* = 8.6 H_Z), 7.14 (d, 2H, *J* = 8.3 H_Z), 7.05 (d, 2H, *J* = 8.6 H_Z), 6.92 (d, 2H, *J* = 8.3 H_Z), 5.82 (d, 1H, *J* = 6.1 H_Z), 5.61 (br s, 1H), 4.73 (d, 1H, *J* = 17.4 H_Z), 4.61 (br s, 1H), 4.62 (d, 1H, *J* = 17.4 H_Z), 3.57-3.46 (m, 1H), 2.32-2.19 (m, 1H), 1.75-1.66 (m, 1H), 1.64-1.48 (m, 4H), 1.27 (s, 9H), 1.23-1.18 (m, 2H), 1.12-1.05 (m, 1H), 1.00-0.92 (m, 2H), 0.77 (d, 3H, *J* = 6.3 H_Z), 0.68 (d, 3H, *J* = 6.3 H_Z). **^{13}C NMR** (100.6 MH_Z, $CDCl_3$) δ 168.8, 164.8, 164.0, 158.2, 150.9, 148.1, 135.2, 132.8, 128.7, 127.7, 126.4, 121.5, 100.0, 63.6, 47.9, 47.3, 34.5, 33.2, 32.8, 32.5 , 27.2, 25.5, 24.7, 19.6, 19.2. **IR** (thin film): 2933, 1674, 1594, 1384, 1210 cm^{-1}. **HRMS** Calculated for $C_{32}H_{41}C1N_4O$: 532.2969, found: 532.2984.

4.8. *General procedure for one-pot formation of diaminopyrimidines **7** from **2***

To a 0.1 M DCM/toluene (1:1) solution of Ugi-Smiles adduct **2** (1.0 mmol) is added 3.0 equiv of *m*-CPBA (3.0 mmol). The reaction mixture was stirred under argon at rt for 2 h. Then amine (3.0 equiv) was added and the mixture left further 20 min at rt before raising the temperature to 110°C (distillation of the DCM). After 7 hours, the toluene was evaporated under reduced pressure and the crude material was purified by flash chromatography on silica gel. This procedure was applied for all diaminopyrimidines **7** presented in Table 6.

4.9. *General procedure for the one-pot three-step formation of diaminopyrimidines **7**.*

To a solution of the aldehyde (l.0 mmol) in toluene (1 mL) under argon was successively added the amine (l.0 mmol), the isocyanide (l.0 mmol), and **1a** (l.0 mmol). The resulting mixture was heated at 80°C for 3 days before adding dichloromethane (l mL) at room temperature. The mixture was treated with 3 equiv of *m*-CPBA (3.0 mmol) and left at room temperature for 5 h. The second amine (3.0 equiv, 3.0 mmol) was then added and the mixture was left at room temperature for 20 min (time long-enough to destroy the remaining *m*-CPBA) before increasing the temperature up to 110°C, which led to the distillation of the DCM out of the reaction mixture. After 7 hours, toluene was evaporated under reduced pressure and the crude material was purified by flash chromatography on silica gel. This procedure was applied to the preparation of **7a**, **7b** and **7h** which were obtained in 46, 43 and 48% isolated yields.

Acknowledgments

We thank ENSTAParistech for financial support and the Ministry of higher education and scientific research of Algeria for scholarship.

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