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Synthesis of *C*2-functionalized pyrimidines from 3,4-dihydropyrimidin-2(1*H*)-ones by the Mitsunobu coupling reaction

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ABSTRACT

The Biginelli 3,4-dihydropyrimidin-2(1*H*)-one was converted to various *C*2-multifunctionalized pyrimidines via the dehydrogenation and Mitsunobu reaction using amines, alcohols, phenols and carboxylic acids as nucleophiles. A possible mechanism was also proposed to rationalize the formation of products.

1. Introduction

Biginelli 3,4-dihydropyrimidin-2(1*H*)-ones (DHPMs)[1] are central subunits in a broad range of medicinal agents, which display interesting pharmacological and biological properties, such as calcium channel modulators, α_{1a}-adrenergic receptor antagonists, mitotic kinesin inhibitors and hepatitis B virus replication inhibitors.[2] The DHPM core was also found in several marine derived natural products, such as Crambine, Batzelladine B (potent HIV gp-120CD4 inhibitors) and Ptilomycalin alkaloids.[3] Additionally, the Biginelli DHPMs are important building blocks in synthesis of multifunctionalized pyrimidines. Although much effort has been paid on the development of methods for the synthesis of the pyrimidine derivatives,[4] few methodologies are available towards efficiently synthesis of 2-substituted pyrimidines. In general, *C*2-substituted pyrimidines were obtained from Biginelli DHPMs by a four-step strategy involving sequentially dehydrogenation, tautomerization, activation and coupling with a nucleophile[5,6] (Scheme 1). However, the harsh condition in chlorination using $POCl_3$ at high temperatures would threaten those substrates with sensitive functional groups (Scheme 1, Eq. 1).[5] Besides, S-alkylation was absolutely necessary for sulfide oxidation (Scheme 1, Eq. 2).[6b,e] Dehydrogenation of the Biginelli DHPMs is also a well known difficult process leading to low yield, when oxidizing agents, such as SeO_2, DDQ or HNO_3 were used.[7] It was not until 2005 that a more efficient approach was achieved by Kang et al., in which[8] Biginelli DHPMs were converted to the *C*2-functionalized pyrimidines via Kappe dehydrogenation[7c] and PyBroP-mediated coupling with nucleophiles at rt for 24 h (Scheme 1, Eq. 3). At the same time, Yamamoto et al.[9] developed a mild and practical procedure for dehydrogenation of DHPMs using *tert*-butylhydroperoxide (TBHP), which can be applied on a large scale.

However, some limitations still exist in the synthesis of *C*2-functionalized pyrimidines based on the methodologies mentioned above, such as elevating temperature, using of expensive catalyst, needing long reaction time or multistep. Thus, it is necessary to develop simpler and more efficient methods under mild reaction conditions to construct these compounds. To address this problem, we have developed a mild and rapid procedure to the synthesis of *C*2-substituted pyrimidines by sequential functionalization of 3,4-dihydropyrimidine-2(1*H*)-ones via oxidation and esterification followed by cross-coupling reaction with N, S and O nucleophiles at rt (Scheme 1, Eq. 4).[10] The results showed that the method is not essential for the reaction of pyrimidin-2-yl sulfonates with phenols to provide phenolic pyrimidine derivative. Herein we report a general and comprehensive strategy for the preparation of highly *C*2-functionalized pyrimidines (**4**, **6**, **8**) including phenolic pyrimidines through direct functionalization of the 2-hydroxy pyrimidine

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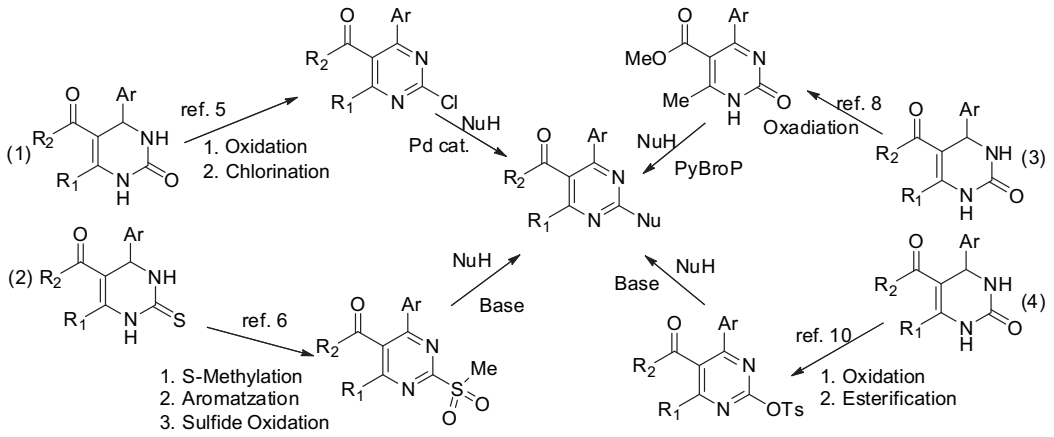
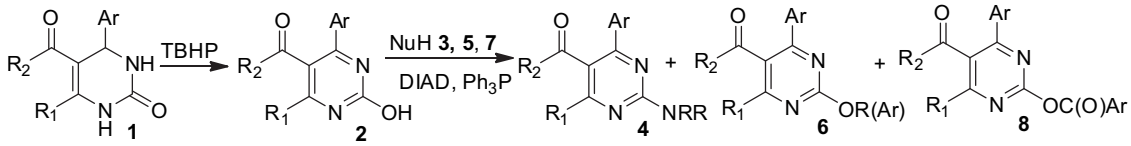


Scheme 1. Synthesis of the C-2 functionalized pyrimidines deriving from DHPMs.

core **2**, which obtained from Biginelli 3,4-dihydropyrimidine-2(1*H*)-ones **1** (Scheme 2). The OH group of the 2-hydroxy pyrimidine can be replaced by different nitrogen, oxygen and acid nucleophiles using amines **3**, alcohols (or phenols) **5** and benzoic acids **7** via Mitsunobu reaction.



Scheme 2. Preparation of *C*2-multifunctionalized pyrimidines.

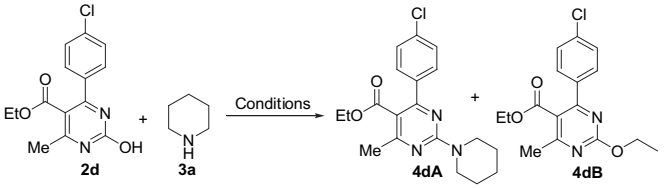
2. Results and discussion

The Biginelli DHPM **1** and their dehydrogenated compounds **2** were readily prepared according to the procedures reported by Fu et al.[11] and Yamamoto et al.[9] As a starting point in our investigations, we examined the Mitsunobu reaction between model substrate 2-hydroxy pyrimidine **2d** and piperidine **3a**. Firstly, we chose diethyl azodicarboxylate (DEAD) and triphenylphosphine (TPP) as Mitsunobu regents.[12] As expected, when the reaction was performed at rt for 12 h, the cross-coupling product **4dA** was obtained in low yield together with the isolation of a *C*2 ethoxy substituted pyrimidine **4dB** (Table 1, entries 1 and 2). When the reaction was performed at 0 °C to rt, the yield of **4dA** was increased obviously (entry 3). Diisopropyl azodicarboxylate (DIAD) exhibited the best activity and higher yields of **4dA** were obtained with shorter reaction time (entries 7 and 8). Survey of various conditions indicates that the optimum ratio of **2d**:**3a**:DIAD:Ph_3P is 1:1.5:1.5:1.5.

Next, the addition order of the reactants and solvents was evaluated. Initially, the reaction was conducted under the typical procedure of the Mitsunobu reaction as follows: DIAD was added dropwise to the mixture of TPP, **2d**, and **3a**, but the reaction did not occur smoothly and only 56% yield of **4dA** was achieved (entry 9). A survey of the adding order showed that the yield could be improved significantly according to the following order: at 0 °C, DIAD (1.5 mmol) was dissolved in THF (3 mL), followed by the addition of TPP with the formation of a suspension, then **2d** and **3a** were added (entry 8). The mixture was warmed to rt, and stirred for further 2.5 h to give **4dA** in 78% yield.

With the optimized conditions in hand, we then examined the scope of 2-hydroxy pyrimidine substrates by varying the substituents on the aromatic ring to explore the generality of this Mitsunobu reaction. The results were summarized in Table 2. No matter what substituent groups were on the aromatic rings of 2-hydroxy pyrimidine, the reactions proceeded smoothly, and the cross-coupling products were isolated in good yields. Cyclic secondary amines were the most successful in this process (entries 1–14). Acyclic amines also gave promising results (completed within 5 h), albeit a bit longer time was needed (entries 15). However, when aromatic amine was involved, the reaction became complicated, and most of the starting 2-hydroxy pyrimidine **2** was recovered (not shown in Table 2).

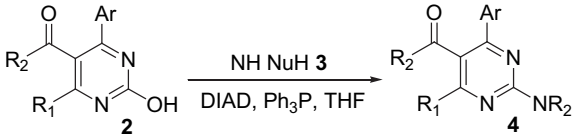
Table 1
Optimization of reaction conditions for product **4dA**[a]



Entry	Equiv of **2d**:**3a**	Reagent	Temp (°C)	Time (h)	Isolated yield (%)	
					4dA	**4dB**
1	1:1	DEAD	25	12	10	60
2	1:1.5	DEAD	25	12	11	63
3	1:1.5	DEAD	0–25	12	50	40
4	1:1.5	DEAD	60	12	10	68
5	1:1.5	DEAD	0–25	2.5	56	35
6[b]	1:1.5	DEAD	0–25	2.5	53	39
7	1:1	DIAD	0–25	12	56	—
8	1:1.5	DIAD	0–25	2.5	78	—
9[c]	1:1.5	DIAD	0–25	2.5	56	—

[a] Reaction conditions: at 0 °C, DIAD (1.5 mmol) was first dissolved in THF (3 mL), followed by the addition of TPP (1.5 mmol) with the forming of a suspension, then **2d** (1.0 mmol) and **3a** (1.5 mmol) were added. The temperature was increased to rt.
[b] CH_2Cl_2 was used as solvent.
[c] Reaction conditions: DIAD (1.5 mmol) was added dropwise to the mixture of TPP (1.5 mmol), **3a** (1.5 mmol) and **2d** (1.0 mmol).

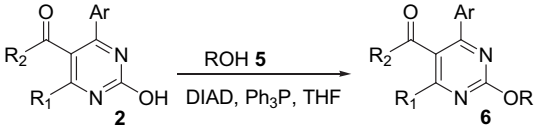
Table 2
Coupling of 2-hydroxy pyrimidines **2** with NH nucleophiles **3**[a]

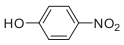
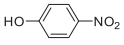
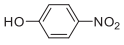
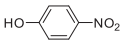
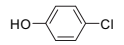
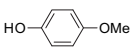


Entry	Ar/**2**	R_1	R_2	NH	**4**	Yield (%)[b]
1	Ph/**2a**	Me	OEt	 **3a**	**4a**	84
2	4-MeO–Ph/**2b**	Me	OEt	**3a**	**4b**	81
3	4-Me–Ph/**2c**	Me	OEt	**3a**	**4c**	83
4	4-Cl–Ph/**2d**	Me	OEt	**3a**	**4d**	78
5	4-Br–Ph/**2e**	Me	OEt	**3a**	**4e**	85
6	4-F–Ph/**2f**	Me	OEt	**3a**	**4f**	86
7	4-F–Ph/**2g**	*i*-Pr	OMe	**3a**	**4g**	80
8	Ph/**2a**	Me	OEt	 **3b**	**4h**	82
9	4-MeO–Ph/**2b**	Me	OEt	**3b**	**4i**	80
10	4-Me–Ph/**2c**	Me	OEt	**3b**	**4j**	80
11	4-Cl–Ph/**2d**	Me	OEt	**3b**	**4k**	83
12	4-Br–Ph/**2e**	Me	OEt	**3b**	**4l**	80
13	4-F–Ph/**2f**	Me	OEt	**3b**	**4m**	82
14	4-F–Ph/**2g**	*i*-Pr	OMe	**3b**	**4n**	84
15[c]	Ph/**2a**	Me	OEt	$CH_3CH_2NH_2$ **3c**	**4o**	77

[a] Reaction conditions: at 0 °C, DIAD (1.5 mmol) was first dissolved in THF (3 mL), followed by the addition of TPP (1.5 mmol) with the forming of a suspension, then **2** (1.0 mmol) and **3** (1.5 mmol) was added. The temperature was increased to rt and stirred for another 2.5 h.
[b] Isolated yields.
[c] Reaction was completed within 6 h.

Table 3
Coupling of 2-hydroxy pyrimidines **2** with OH nucleophiles **5**[a]



Entry	Ar	R_1	R_2	Time (h)	ROH **5**	**6**	Yield (%)[b]
1	Ph	Me	OEt	2	CH_3CH_2OH	**6a**	95
2	Ph	Me	OEt	2	$(CH_3)_2CHOH$	**6b**	93
3	Ph	Me	OEt	2	$PhCH_2OH$	**6c**	90
4	4-Cl–Ph	Me	OEt	2	CH_3CH_2OH	**6d**	96
5	Ph	Me	OEt	6		**6e**	82
6	4-MeO–Ph	Me	OEt	6		**6f**	95
7	4-Cl–Ph	Me	OEt	6		**6g**	86
8	4-F–Ph	*i*-Pr	OMe	6		**6h**	80
9	4-Cl–Ph	Me	OEt	6		**6i**	78
10	4-Cl–Ph	Me	OEt	12		**6j**	60[c]
11	4-Cl–Ph	Me	OEt	12		**6k**	Trace[d]

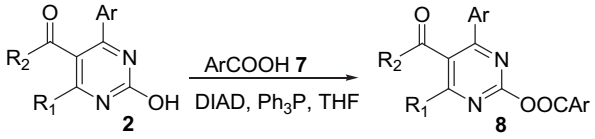
[a] Reaction conditions: at 0 °C, DIAD (1.5 mmol) was first dissolved in THF (3 mL), followed by the addition of TPP (1.5 mmol) with the forming of a suspension, then **2** (1.0 mmol) and **5** (1.5 mmol) was added. The temperature was increased to rt and stirred for another 6 h.
[b] Isolated yields.
[c] NMR yield is determined by ^{1}H NMR spectroscopy.
[d] Detected by TLC and ^{1}H NMR.

When this procedure was applied to the reaction between 2-hydroxy pyrimidine **2** and alcohols **5**, to our delight, the target molecules were obtained in excellent isolated yields (Table 3). As indicated in Table 3, the reaction could proceed smoothly (entries 1–4). Then alcohol was changed to phenols, and the reaction could also occur smoothly with phenols bearing electron-withdrawing groups, such as nitro and chloro, affording desired products **6e**–**i** good to excellent isolated yields (entries 5–9) with prolonged reaction time. Unfortunately, product **6j** could not be isolated from the reaction mixture by column chromatography and the corresponding yield was determined by ^{1}H NMR (entry 10). When phenols with an electron-donating group (such as CH_3O) were used, the reaction gave the desired product in trace yield (detected by TLC and ^{1}H NMR) (entry 11). The results implied that the phenols bearing electron-withdrawing groups were preferred in this reaction, which was in agreement with other Mitsunobu reactions. It is because that the phenols with lower pK_a value can accelerate this cross-coupling reaction.[12a]

To further demonstrate the utility of the Mitsunobu reaction, we also tested the reaction between 2-hydroxy pyrimidine **2** and carboxylic acids **7**. As we expected, Mitsunobu reaction occurred smoothly giving *C*2 benzoyloxy pyrimidines **8a**–**g** (Table 4). All substrates, either 2-hydroxy pyrimidines or carboxylic acids, with either electron-rich (CH_3O) or electron-deficient (NO_2, Cl) aryl groups, afforded the corresponding *C*2 benzoyloxy pyrimidines **8a**–**g** in good to high yields, in favor of the one with electron-deficient groups.

As mentioned above, the nuclephiles, such as phenols and carboxylic acids with lower pK_a prefer the cross-coupling reaction. Thus the mechanism was proposed for the formation of *C*2-multifunctionalized pyrimidines via the Mitsunobu reaction based on a general pathway as shown in Scheme 3. The first step is the irreversible formation of the Morrison–Brunn–Huisgen (MBH) betaine **9**.[13] In step 2, this betaine **9** deprotonates the nucleophile to form the ionic specie **10**, which reacted with the 2-hydroxy pyrimidine **2** providing the key alkoxyphosphonium salt **11** and the hydrazine $RO_2CNH–NHCO_2R$. After nucleophilic substitution and releasing of a molecule of triphenylphosphine oxide, the product, *C*2-multifunctionalized pyrimidine, is formed.

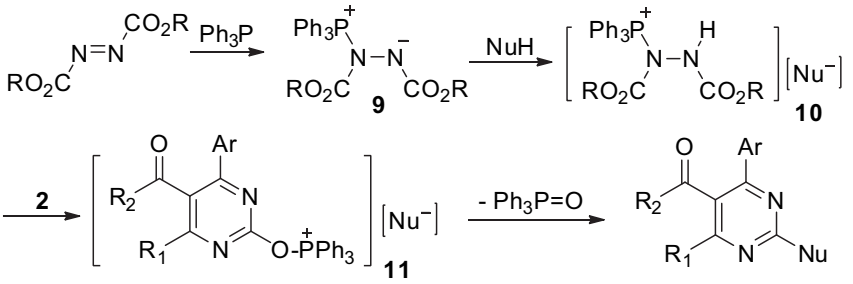
Table 4
Coupling of 2-hydroxy pyrimidines **2** with carboxylic nucleophlies **7**[a]



Entry	Ar	R_1	R_2	**7**	**8**	Yield (%)[b]
1	Ph	Me	OEt	PhCOOH	**8a**	70
2	4-MeO–Ph	Me	OEt	PhCOOH	**8b**	68
3	4-Cl–Ph	Me	OEt	PhCOOH	**8c**	69
4	4-F–Ph	*i*-Pr	OMe	PhCOOH	**8d**	63
5	4-Cl–Ph	Me	OEt	4-MeO–PhCOOH	**8e**	72
6	4-Cl–Ph	Me	OEt	4-NO_2–PhCOOH	**8f**	80
7	4-Cl–Ph	Me	OEt	4-Cl–PhCOOH	**8g**	79

[a] Reaction conditions: at 0 °C, DIAD (1.5 mmol) was first dissolved in THF (3 mL), followed by the addition of TPP (1.5 mmol) with the forming of a suspension, then **2** (1.0 mmol) and **7** (1.5 mmol) was added. The temperature was increased to rt and stirred for another 6 h.
[b] Isolated yields.

It is noteworthy that the study reported above, to our best knowledge, is the first general exploration of cross-coupling reaction of 2-hydroxy pyrimidines with N, O and acid nucleophiles to give *C*2-substituted pyrimidines under Mitsunobu reaction conditions. This cross-coupling reaction, in which only two steps needed using 3,4-dihydropyrimidinones as starting material, was superior to other reported processes.



Scheme 3. A proposed mechanism for the formation of *C*2-multifunctionalized pyrimidines.

3. Conclusion

In conclusion, we have developed a novel and efficient synthetic method to prepare *C*2-multifunctionalized pyrimidines by the Mitsunobu reaction between 2-hydroxy pyrimidine and alcohols, amines, phenols and carboxylic acids nucleophiles. Compared to previously known approaches, the simplicity (only two-step needed using 3,4-dihydropyrimidinones as starting material) and higher efficiency make this method particularly attractive. These results provided, as well as other reported studies, that Mitsunobu reaction conditions could be potentially applicable to other electron-deficient heterocyclic or aromatic systems. The present study also provides a readily accessible approach to construct multifunctionalized pyrimidine template for diversity-oriented synthesis.

4. Experimental section

4.1. General information

Commercially available reagents were used without further purification. Solvents were treated prior to use according to the standard methods. Column chromatography was performed on silica gel (300–400 mesh). Melting points were determined on an XT-4 electrothermal micromelting point apparatus and are uncorrected. NMR spectra were recorded at 400 (^{1}H) and 100 (^{13}C) MHz, respectively, on a Varian Mercury plus-400 instrument using $CDCl_3$ as solvent and TMS as an internal standard. Mass spectra were obtained on a Bruker Daltonics APEXII 47e FT-ICR spectrometer. The Biginelli DHPM **1** and their dehydrogenated compounds **2** were readily prepared according to the procedures by Fu et al.[11] and Yamamoto et al.[9]

4.2. General procedure for the synthesis of *C*2-functionalized pyrimidines

At 0 °C, DIAD (1.5 mmol) was dissolved in THF (3 mL), followed by the addition of TPP (1.5 mmol) with the forming of a suspension, then 2-hydroxy pyrimidine (1.0 mmol) and nucleophile (1.5 mmol) were added. The mixture was warmed to rt and stirred for further 2–6 h. After completion of the reaction monitored by thin layer chromatography (TLC), the solvent was evaporated under reduced pressure, and then the crude product was purified by column chromatography over silica gel with ethyl acetate and petroleum ether as the eluent, to give target product **4**, **6** or **8**.

*4.2.1. Ethyl 4-methyl-6-phenyl-2-(piperidin-1-yl)pyrimidine-5-carboxylate (**4a**).* Obtained 273 mg, yield 84%, white solid, mp 69–70 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.37–7.58 (m, 5H), 4.02 (q, *J*=6.8 Hz, 2H), 3.89 (t, *J*=5.6 Hz, 4H), 2.49 (s, 3H), 1.62 (m, 6H), 0.93 (t, *J*=7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ=169.2, 166.9, 165.7, 160.1, 139.7, 129.2, 128.0, 113.1, 60.7, 44.6, 25.8, 24.8, 23.2, 13.5. ESI-MS: *m*/*z* 326 ([M+H$^+$]).

*4.2.2. Ethyl 4-(4-methoxyphenyl)-6-methyl-2-(piperidin-1-yl)pyrimidine-5-carboxylate (**4b**).* Obtained 287 mg, yield 81%, white solid, mp 87–88 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.56 (d, *J*=8.8 Hz, 2H), 6.91 (d, *J*=8.8 Hz, 2H), 4.11 (q, *J*=7.6 Hz, 2H), 3.88 (t, *J*=5.2 Hz, 4H), 3.84 (s, 3H), 2.47 (s, 3H), 1.60–1.68 (m, 6H), 1.03 (t, *J*=7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ=169.5, 166.5, 164.7, 160.7, 132.0, 129.7, 113.5, 60.8, 55.3, 44.6, 25.8, 24.8, 23.1, 13.7. ESI-MS: *m*/*z* 356 ([M+H$^+$]).

*4.2.3. Ethyl 4-methyl-2-(piperidin-1-yl)-6-p-tolylpyrimidine-5-carboxylate (**4c**).* Obtained 281 mg, yield 83%, white solid, mp 68–69 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.47 (d, *J*=8.0 Hz, 2H), 7.19 (d, *J*=8.0 Hz, 2H), 4.08 (q, *J*=6.8 Hz, 2H), 3.88 (t, *J*=5.2 Hz, 4H), 2.47 (s, 3H), 2.38 (s, 3H), 1.59–1.67 (m, 6H), 0.99 (t, *J*=7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ=169.4, 166.6, 165.5, 139.3, 136.8, 128.7, 128.0, 60.7, 44.6, 25.8, 24.8, 23.1, 21.3, 13.6. ESI-MS: *m*/*z* 340 ([M+H$^+$]).

*4.2.4. Ethyl 4-(4-chlorophenyl)-6-methyl-2-(piperidin-1-yl)pyrimidine-5-carboxylate (**4d**).* Obtained 280 mg, yield 78%, white solid, mp 54–55 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.50 (d, *J*=8.4 Hz, 2H), 7.36 (d, *J*=8.4 Hz, 2H), 4.07 (m, *J*=6.8 Hz, 2H), 3.88 (t, *J*=5.2 Hz, 4H), 2.48 (s, 3H), 1.60–1.68 (m, 6H), 1.01 (t, *J*=7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ=169.4, 166.6, 165.5, 139.3, 136.8, 128.7, 128.0, 113.1, 60.7, 44.6, 25.8, 24.8, 23.1. ESI-MS: *m*/*z* 360 ([M+H+]).

*4.2.5. Ethyl 4-(4-bromophenyl)-6-methyl-2-(piperidin-1-yl)pyrimidine-5-carboxylate (**4e**).* Obtained 342 mg, yield 85%, white solid, mp 61–62 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.52 (d, *J*=8.4 Hz, 2H), 7.43 (d, *J*=8.0 Hz, 2H), 4.05 (q, *J*=7.2 Hz, 2H), 3.88 (t, *J*=5.2 Hz, 4H), 2.49 (s, 3H), 1.60–1.68 (m, 6H), 1.00 (t, *J*=7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ=168.8, 167.2, 164.5, 160.0, 138.7, 131.2, 129.7, 123.6, 60.8, 44.6, 25.8, 24.8, 23.2, 13.6. ESI-MS: *m*/*z* 404 ([M+H$^+$]).

*4.2.6. Ethyl 4-(4-fluorophenyl)-6-methyl-2-(piperidin-1-yl)pyrimidine-5-carboxylate (**4f**).* Obtained 295 mg, yield 86%, white solid, mp 51–52 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.06–7.59 (m, 4H), 4.06 (q, *J*=6.8 Hz, 2H), 3.88 (t, *J*=5.6 Hz, 4H), 2.48 (s, 3H), 1.61 (m, 6H), 1.00 (t, *J*=6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ=169.3, 167.3, 165.0, 164.7, 162.5, 160.3, 136.0, 130.4, 130.2, 115.4, 115.1, 113.2, 61.1, 44.9, 26.1, 25.0, 23.4, 13.8. ESI-MS: *m*/*z* 344 ([M+H$^+$]).

*4.2.7. Methyl 4-(4-fluorophenyl)-6-isopropyl-2-(piperidin-1-yl)pyrimidine-5-carboxylate (**4g**).* Obtained 286 mg, yield 80%, white solid, mp 96–97 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.06–7.60 (m, 4H), 3.89 (t, *J*=5.2 Hz, 4H), 3.59 (s, 3H), 3.19 (m, 1H), 1.58–1.68 (m, 6H), 1.24 (d, *J*=6.4 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ=174.4, 170.0, 164.7, 163.8, 162.2, 160.5, 135.7, 129.9, 115.2, 115.0, 112.4, 51.9, 44.7, 32.7, 25.7, 24.8, 21.7. ESI-MS: *m*/*z* 358 ([M+H$^+$]).

*4.2.8. Ethyl 4-methyl-2-morpholino-6-phenylpyrimidine-5-carboxylate (**4h**).* Obtained 268 mg, yield 82%, white solid, mp 118–119 °C. ^{1}H

NMR (400 MHz, $CDCl_3$) δ=7.40–7.58 (m, 5H), 4.04 (q, J=7.2 Hz, 2H), 3.76 (t, J=4.8 Hz, 4H), 2.50 (s, 3H), 0.95 (t, J=7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ=168.9, 167.0, 165.7, 160.2, 139.3, 129.5, 128.2, 128.1, 114.5, 66.9, 60.9, 44.1, 23.1, 13.5. ESI-MS: m/z 328 ([M+H$^+$]).

*4.2.9. Ethyl 4-(4-methoxyphenyl)-6-methyl-2-morpholinopyrimidine-5-carboxylate (**4i**).* Obtained 286 mg, yield 80%, white solid, mp 72–74 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.58(d, J=9.2 Hz, 2H), 6.93 (d, J=8.4 Hz, 2H), 4.13 (q, J=6.8 Hz, 2H), 3.84 (s, J=4.8 Hz, 3H), 3.75 (t, J=4.8 Hz, 4H), 2.47 (s, 3H), 1.05 (t, J=7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ=169.3, 166.6, 164.7, 160.9, 160.2, 131.5, 129.7, 114.2, 113.6, 66.9, 61.0, 55.3, 55.3, 44.1, 23.1, 13.7. ESI-MS: m/z 358 ([M+H$^+$]).

*4.2.10. Ethyl 4-methyl-2-morpholino-6-p-tolylpyrimidine-5-carboxylate (**4j**).* Obtained 273 mg, yield 80%, white solid, mp 68–70 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.49 (d, J=8.0 Hz, 2H), 7.22 (d, J=8.0 Hz, 2H), 4.10 (q, J=7.2 Hz, 2H), 3.92 (t, J=4.4 Hz, 4H), 3.75 (t, J=4.4 Hz, 4H), 2.48 (s, 4H), 2.38 (s, 3H), 1.01 (t, J=6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ=169.2, 166.7, 165.4, 160.2, 139.6, 136.4, 128.9, 128.1, 128.0, 114.5, 66.9, 60.9, 44.1, 23.0, 21.3, 13.6. ESI-MS: m/z 342 ([M+H$^+$]).

*4.2.11. Ethyl 4-(4-chlorophenyl)-6-methyl-2-morpholinopyrimidine-5-carboxylate (**4k**).* Obtained 299 mg, yield 83%, white solid, mp 80–83 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.37–7.52 (m, 4H), 4.10 (m, J=7.2 Hz, 2H), 3.92 (t, J=5.6 Hz, 4H), 3.76 (t, J=5.2 Hz, 4H), 2.50 (s, 3H), 1.02 (t, J=7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ=168.7, 167.2, 164.5, 160.0, 137.7, 135.7, 129.5, 128.4, 114.3, 66.8, 61.1, 44.1, 23.2, 13.7. ESI-MS: m/z 362 ([M+H$^+$]).

*4.2.12. Ethyl 4-(4-bromophenyl)-6-methyl-2-morpholinopyrimidine-5-carboxylate (**4l**).* Obtained 324 mg, yield 80%, white solid, mp 92–93 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.43–7.55 (m, 4H), 4.08 (q, J=7.2 Hz, 2H), 3.91 (t, J=4.4 Hz, 4H), 3.75 (t, J=4.8 Hz, 4H), 2.49 (s, 3H), 1.02 (t, J=6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ=168.7, 167.3, 164.5, 160.1, 138.3, 131.4, 129.8, 123.9, 114.3, 66.8, 61.1, 44.2, 23.2, 13.7. ESI-MS: m/z 406 ([M+H$^+$]).

*4.2.13. Ethyl 4-(4-fluorophenyl)-6-methyl-2-morpholinopyrimidine-5-carboxylate (**4m**).* Obtained 283 mg, yield 82%, white solid, mp 86–89 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.07–7.59 (m, 4H), 4.10 (q, J=7.2 Hz, 2H), 3.92 (t, J=4.8 Hz, 4H), 3.76 (t, J=4.8 Hz, 4H), 2.49 (s, 3H), 1.02 (t, J=7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ=168.8, 167.1, 164.9, 164.4, 162.4, 160.1, 135.3, 130.1, 130.1, 115.3, 115.1, 114.3, 66.8, 61.1, 44.1, 23.2, 13.7. ESI-MS: m/z 346 ([M+H$^+$]).

*4.2.14. Methyl 4-(4-fluorophenyl)-6-isopropyl-2-morpholinopyrimidine-5-carboxylate (**4n**).* Obtained 301 mg, yield 84%, white solid, mp 102–103 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.08–7.61 (m, 4H), 3.92 (t, J=4.4 Hz, 4H), 3.77 (t, J=5.2 Hz, 4H), 3.61 (s, 3H), 3.19 (m, 1H), 1.26 (d, J=6.4 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ=174.6, 169.7, 164.9, 163.9, 162.4, 160.6, 135.3, 130.0, 115.4, 115.2, 113.7, 66.8, 52.1, 44.2, 32.9, 21.7. ESI-MS: m/z 360 ([M+H$^+$]).

*4.2.15. Ethyl 2-(ethylamino)-4-methyl-6-phenylpyrimidine-5-carboxylate (**4o**).* Obtained 219 mg, yield 77%, white solid, mp 70–72 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.38–7.54 (m, 5H), 5.39 (s, 1H), 4.05 (q, J=6.8 Hz, 2H), 3.51 (m, 2H), 2.49 (s, 3H), 1.22 (t, J=7.6 Hz, 3H), 0.94 (t, J=7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ=168.8, 167.1, 166.1, 161.1, 139.2, 129.3, 128.1, 127.9, 115.0, 60.9, 36.2, 22.9, 14.8, 13.5. ESI-MS: m/z 286 ([M+H$^+$]).

*4.2.16. Ethyl 2-ethoxy-4-methyl-6-phenylpyrimidine-5-carboxylate (**6a**).* Obtained 271 mg, yield 95%, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.30–7.56 (m, 5H), 4.40 (m, 2H), 4.05 (m, 2H), 2.47 (s, 3H), 1.34 (t, J=6.8 Hz, 3H), 0.92 (t, J=7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ=168.4, 168.0, 166.2, 163.8, 137.6, 129.7, 128.1, 128.0, 119.4, 63.4, 61.3, 22.5, 14.2, 13.3. ESI-MS: m/z 287 ([M+H$^+$]).

*4.2.17. Ethyl 2-isopropoxy-4-methyl-6-phenylpyrimidine-5-carboxylate (**6b**).* Obtained 279 mg, yield 93%, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.38–7.65 (m, 5H), 5.41 (m, 1H), 4.14 (m, 2H), 2.55 (s, 3H), 1.38 (m, 6H), 1.06 (t, J=6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ=168.4, 168.1, 166.2, 163.5, 137.7, 129.7, 128.1, 128.0, 119.2, 61.3, 22.6, 22.5, 21.6, 21.3, 13.3. ESI-MS: m/z 301 ([M+H$^+$]).

*4.2.18. Ethyl 2-(benzyloxy)-4-methyl-6-phenylpyrimidine-5-carboxylate (**6c**).* Obtained 313 mg, yield 90%, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.30–7.63 (m, 10H), 5.51 (s, 2H), 4.15 (q, J=7.2 Hz, 2H), 2.58 (s, 3H), 1.02 (t, J=7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ=168.6, 168.1, 166.3, 163.7, 137.6, 136.2, 129.9, 128.4, 128.2, 128.2, 128.1, 127.9, 119.9, 69.2, 61.5, 22.6, 13.4. ESI-MS: m/z 349 ([M+H$^+$]).

*4.2.19. Ethyl 4-(4-chlorophenyl)-2-ethoxy-6-methylpyrimidine-5-carboxylate (**6d**).* Obtained 307 mg, yield 96%, pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.69 (dd, J=2 Hz, 6.4 Hz, 2H), 7.41 (dd, J=2 Hz, 6.0 Hz, 2H), 4.50 (q, J=6.8 Hz, 2H), 4.5018 (q, J=6.8 Hz, 2H), 2.57 (s, 3H), 1.45 (t, J=6.8 Hz, 3H), 1.10 (t, J=6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ=168.8, 168.0, 165.2, 164.0, 136.3, 136.3, 129.6, 128.5, 119.5, 63.7, 61.6, 22.7, 14.3, 13.6. ESI-MS: m/z 320 M$^+$, 322 [M+2]$^+$. Anal. Calcd for $C_{16}H_{17}ClN_2O_3$: C, 59.91; H, 5.34; N, 8.73. Found: C, 59.69; H, 5.31; N, 8.70.

*4.2.20. Ethyl 2-(4-nitrophenoxy)-4-methyl-6-phenylpyrimidine-5-carboxylate (**6e**).* Obtained 310 mg, yield 82%, white solid, mp 118–119 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ=8.33–8.29 (m, 2H), 7.60–7.50 (m, 2H), 7.49–7.27 (m, 5H), 4.23–4.18 (m, 2H), 2.59 (s, 3H), 1.09–1.06 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ=169.6, 167.6, 166.8, 162.9, 157.6, 144.8, 136.8, 130.6, 128.6, 128.3, 125.3, 122.1, 62.0, 22.7, 13.6. ESI-MS: m/z 379 M$^+$. Anal. Calcd for $C_{20}H_{17}N_3O_5$: C, 63.32; H, 4.52; N, 11.08. Found: C, 63.02; H, 4.50; N, 11.02.

*4.2.21. Ethyl 2-(4-nitrophenoxy)-4-(4-methoxyphenyl)-6-methylpyrimidine-5-carboxylate (**6f**).* Obtained 388 mg, yield 95%, white solid, mp 105–107 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ=8.30 (dd, J=2 Hz, 6.8 Hz, 2H), 7.59 (dd, J=2 Hz, 6.8 Hz, 2H), 7.41 (dd, J=2 Hz, 6.8 Hz, 2H), 6.93 (dd, J=2 Hz, 6.8 Hz, 2H), 4.27 (q, J=7.2 Hz, 2H), 3.85 (s, 3H), 2.57 (s, 3H), 1.17 (t, J=7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ=169.2, 168.1, 165.8, 162.8, 161.8, 157.7, 144.7, 130.1, 128.9, 125.3, 122.1, 121.4, 114.0, 62.0, 55.4, 22.6, 13.8. ESI-MS: m/z 409 M$^+$. Anal. Calcd for $C_{21}H_{19}N_3O_6$: C, 61.61; H, 4.68; N, 10.26. Found: C, 61.29; H, 4.65; N, 10.20.

*4.2.22. Ethyl 2-(4-nitrophenoxy)-4-(4-chlorophenyl)-6-methylpyrimidine-5-carboxylate (**6g**).* Obtained 355 mg, yield 86%, white solid, mp 121–123 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ=8.31 (dd, J=2 Hz, 6.8 Hz, 2H), 7.54 (dd, J=1.6 Hz, 6.8 Hz, 2H), 7.43–7.39 (m, 4H), 4.23 (q, J=7.2 Hz, 2H), 2.59 (s, 3H), 1.14 (t, J=7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ=169.8, 167.4, 165.5, 162.9, 157.5, 144.9, 137.1, 135.2, 129.7, 128.9, 125.4, 122.1, 121.9, 62.2, 22.8, 13.7. ESI-MS: m/z 413 M$^+$, 415 [M+2]$^+$. Anal. Calcd for $C_{20}H_{16}ClN_3O_5$: C, 58.05; H, 3.90; N, 10.15. Found: C, 58.28; H, 3.93; N, 10.20.

*4.2.23. Ethyl 2-(4-nitrophenoxy)-4-(4-fluorophenyl)-6-isopropylpyrimidine-5-carboxylate (**6h**).* Obtained 329 mg, yield 80%, colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ=8.34–8.30 (m, 2H), 7.65–7.60 (m, 2H), 7.45–7.42 (m, 2H), 7.28–7.10 (m, 2H), 3.74 (s, 3H), 3.22–3.15 (m, 1H), 1.32–1.14 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ=177.5, 168.3, 165.5, 163.4, 162.9, 157.6, 144.8, 132.9, 130.4, 125.2, 122.1, 120.9, 115.9, 115.7, 52.9, 33.5, 21.6. ESI-MS: m/z 411 M$^+$. Anal. Calcd for $C_{22}H_{20}FN_3O_5$: C, 62.11; H, 4.74; N, 9.88. Found: C, 62.36; H, 4.72; N, 9.83.

*4.2.24. Ethyl 2-(4-chlorophenoxy)-4-(4-chlorophenyl)-6-methylpyrimidine-5-carboxylate (**6i**).* Obtained 313 mg, yield 78%, white solid,

mp 97–99 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.55–7.52 (m, 2H), 7.41–7.35 (m, 4H), 7.18–7.16 (m, 2H), 4.24–4.19 (m, 2H), 2.56 (s, 3H), 1.15–1.11 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ=169.5, 167.7, 165.3, 163.7, 151.2, 136.8, 135.5, 130.6, 129.7, 129.5, 128.8, 122.9, 121.1, 62.0, 22.8, 13.7. ESI-MS: *m*/*z* 402 M^+, 404 $[M+2]^+$. Anal. Calcd for $C_{20}H_{16}Cl_2N_2O_3$: C, 59.57; H, 4.00; N, 6.95. Found: C, 59.82; H, 4.02; N, 6.98.

*4.2.25. Ethyl 2-(benzoyloxy)-4-methyl-6-phenylpyrimidine-5-carboxylate (**8a**).* Obtained 254 mg, yield 70%, white solid, mp 89–90 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ=8.25–8.23 (m, 2H), 7.69–7.63 (m, 3H), 7.51–7.43 (m, 5H), 4.23 (q, *J*=7.2 Hz, 2H), 2.67 (s, 3H), 1.09 (t, *J*=7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ=169.3, 167.4, 167.1, 164.1, 160.3, 136.7, 134.1, 130.6, 130.5, 128.6, 128.5, 128.4, 124.3, 62.1, 22.6, 13.6. ESI-MS: *m*/*z* 363 M^+. Anal. Calcd for $C_{21}H_{18}N_2O_4$: C, 69.60; H, 5.01; N, 7.73. Found: C, 69.86; H, 5.00; N, 7.76.

*4.2.26. Ethyl 2-(benzoyloxy)-4-(4-methoxyphenyl)-6-methylpyrimidine-5-carboxylate (**8b**).* Obtained 267 mg, yield 68%, colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ=8.25–8.23 (m, 2H), 7.72–7.66 (m, 2H), 7.64–7.62 (m, 1H), 7.52–7.49 (m, 2H), 6.98–6.95 (m, 2H), 4.28 (q, *J*=6.8 Hz, 2H), 3.84 (s, 3H), 2.65 (s, 3H), 1.18 (t, *J*=6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ=168.9, 167.8, 166.1, 164.1, 161.7, 160.2, 134.0, 130.5, 130.2, 128.9, 128.6, 128.5, 123.6, 114.0, 62.0, 55.3, 22.5, 13.7. ESI-MS: *m*/*z* 392 M^+. Anal. Calcd for $C_{22}H_{20}N_2O_5$: C, 67.34; H, 5.14; N, 7.14. Found: C, 67.04; H, 5.13; N, 7.17.

*4.2.27. Ethyl 2-(benzoyloxy)-4-(4-chlorophenyl)-6-methylpyrimidine-5-carboxylate (**8c**).* Obtained 273 mg, yield 69%, colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ=8.25–8.22 (m, 2H), 7.67–7.63 (m, 3H), 7.53–7.49 (m, 2H), 7.45–7.43 (m, 2H), 4.26 (q, *J*=6.8 Hz, 2H), 2.67 (s, 3H), 1.16 (t, *J*=6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ=169.6, 167.2, 165.6, 164.1, 160.3, 137.0, 135.1, 130.6, 129.9, 128.9, 128.6, 128.5, 124.1, 62.3, 22.6, 13.7. ESI-MS: *m*/*z* 396 M^+, 398 $[M+2]^+$. Anal. Calcd for $C_{21}H_{17}ClN_2O_4$: C, 63.56; H, 4.32; N, 7.06. Found: C, 63.86; H, 4.34; N, 7.08.

*4.2.28. Ethyl 2-(benzoyloxy)-4-(4-fluorophenyl)-6-isopropylpyrimidine-5-carboxylate (**8d**).* Obtained 248 mg, yield 63%, colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ=8.26–8.24 (m, 2H), 7.73–7.69 (m, 2H), 7.67–7.63 (m, 1H), 7.54–7.49 (m, 2H), 7.17–7.12 (m, 2H), 3.78 (s, 3H), 3.20 (t, *J*=7.2 Hz, 2H), 1.36 (s, 3H), 1.34 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ=177.4, 168.2, 165.5, 165.4, 164.0, 162.9, 160.9, 134.1, 132.9, 130.6, 130.5, 128.6, 128.5, 123.0, 115.9, 115.7, 52.9, 33.6, 21.6. ESI-MS: *m*/*z* 394 M^+, 396 $[M+2]^+$. Anal. Calcd for $C_{23}H_{21}FN_2O_4$: C, 67.64; H, 5.18; N, 6.86. Found: C, 67.89; H, 5.21; N, 6.89.

*4.2.29. Ethyl 2-(4-methoxybenzoyloxy)-4-(4-chlorophenyl)-6-methylpyrimidine-5-carboxylate (**8e**).* Obtained 307 mg, yield 72%, white solid, mp 99–100 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ=8.18 (dd, *J*=2 Hz, 6.8 Hz, 2H), 7.64 (dd, *J*=2 Hz, 4.8 Hz, 2H), 7.43 (dd, *J*=2 Hz, 4.8 Hz, 2H), 6.98 (dd, *J*=1.6 Hz, 7.2 Hz, 2H), 4.28–4.23 (m, 2H), 3.90 (s, 3H), 2.66 (s, 3H), 1.18–1.14 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ=169.5, 167.3, 165.6, 164.4, 160.5, 136.9, 135.1, 132.9, 129.9, 128.9, 123.9, 120.6, 113.9, 62.2, 55.5, 22.7, 13.7. ESI-MS: *m*/*z* 426 M^+, 428 $[M+2]^+$. Anal. Calcd for $C_{22}H_{19}ClN_2O_5$: C, 61.90; H, 4.49; N, 6.56. Found: C, 61.61; H, 4.45; N, 6.51.

*4.2.30. Ethyl 2-(4-nitrobenzoyloxy)-4-(4-chlorophenyl)-6-methylpyrimidine-5-carboxylate (**8f**).* Obtained 353 mg, yield 80%, pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ=8.43–8.36 (m, 4H), 7.65 (dd, *J*=2 Hz, 6.8 Hz, 2H), 7.45 (dd, *J*=2 Hz, 6.4 Hz, 2H), 4.28 (q, *J*=6.8 Hz, 2H), 2.69 (s, 3H), 1.17 (t, *J*=6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ=169.9, 166.9, 165.8, 162.2, 159.7, 151.2, 137.3, 134.8, 133.9, 131.7, 129.8, 129.0, 124.6, 123.8, 62.4, 22.7, 13.7.

ESI-MS: *m*/*z* 441 M^+, 443 $[M+2]^+$. Anal. Calcd for $C_{21}H_{16}ClN_3O_6$: C, 57.09; H, 3.65; N, 9.51. Found: C, 57.30; H, 3.67; N, 9.56.

*4.2.31. Ethyl 2-(4-chlorobenzoyloxy)-4-(4-chlorophenyl)-6-methylpyrimidine-5-carboxylate (**8g**).* Obtained 339 mg, yield 79%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ=8.16 (dd, *J*=2 Hz, 4.8 Hz, 2H), 7.63 (dd, *J*=1.6 Hz, 5.6 Hz, 2H), 7.49 (dd, *J*=2.4 Hz, 4.8 Hz, 2H), 7.44 (dd, *J*=2.0 Hz, 4.8 Hz, 2H), 4.29–4.21 (m, 2H), 2.67 (s, 3H), 1.18–1.08 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ=169.7, 167.1, 165.7, 163.2, 160.0, 140.8, 137.1, 134.9, 131.9, 129.8, 129.6, 129.0, 128.9, 128.6, 126.9, 124.3, 62.3, 22.6, 13.7. ESI-MS: *m*/*z* 430 M^+, 432 $[M+2]^+$. Anal. Calcd for $C_{21}H_{16}Cl_2N_2O_4$: C, 58.48; H, 3.74; N, 6.50. Found: C, 58.20; H, 3.71; N, 6.53.

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Supplementary data

Supplementary data related to this article can be found online at doi:10.1016/j.tet.2011.02.046. These data include MOL files and InChIKeys of the most important compounds described in this article.

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