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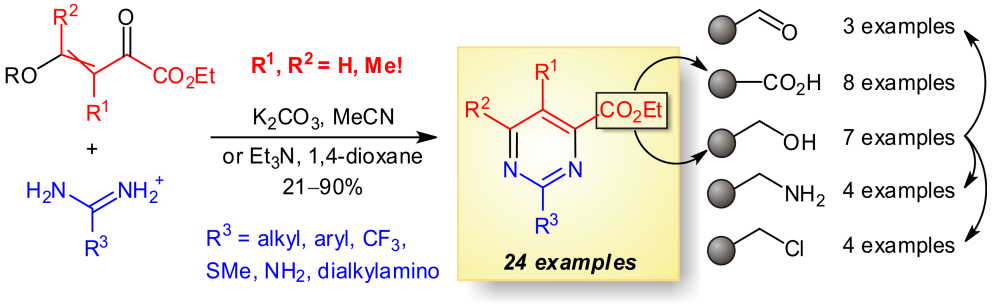

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Reaction of β-alkoxyvinyl α-ketoesters with acyclic *NCN* binucleophiles – scalable approach to novel functionalized pyrimidines

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ABSTRACT

Two protocols for synthesis of series of low-molecular-weight di- and tri-substituted pyrimidines bearing a functional group at the 4th position, which rely on a base-mediated condensation of amidines or guanidines with β-alkoxyvinyl α-keto esters, have been developed. This approach allowed for multigram preparation of novel pyrimidine-4-carboxylates in 21–90% yield. The synthetic utility of these compounds was demonstrated by some standard functional group transformations providing promising building blocks for organic synthesis and drug discovery.

1. Introduction

Pyrimidine is one of the most important heterocycles, which is an essential constituent of natural compounds such as nucleic acids and vitamins (thiamine, riboflavin and folic acid).[1,2] It is not surprising therefore that pyrimidine derivatives are extremely popular in drug discovery;[3] they are represented by numerous examples of marketed drugs with a broad range of pharmacological activities, *i.e.* anticancer,[4–10] antiviral,[11–14] anxiolytic,[15] antioxidant,[16–18] antifungal,[19] anticonvulsant,[20] and antibacterial agents.[5,21] Within just 2017–2018, several pyrimidine-containing drugs were approved by FDA.[19]

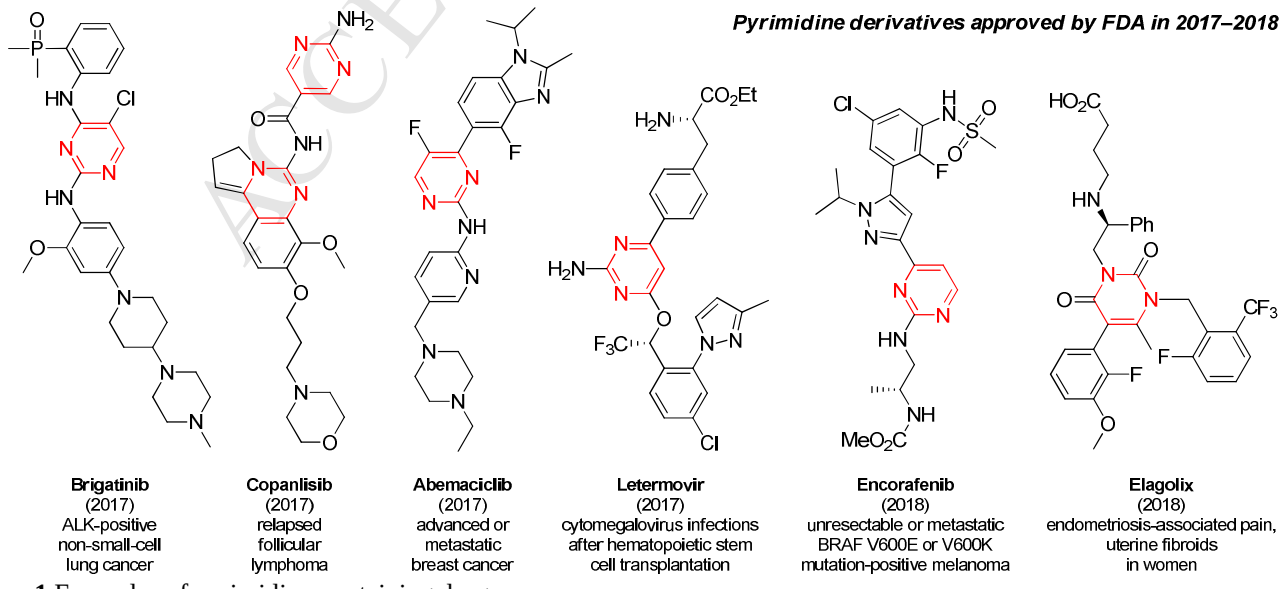
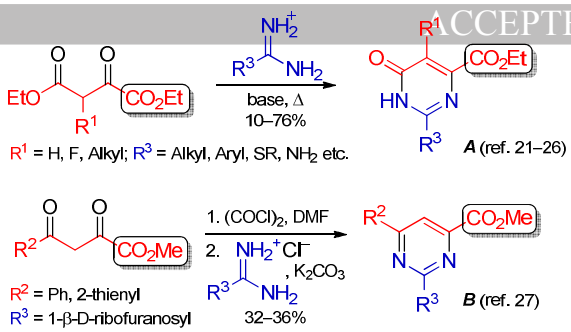


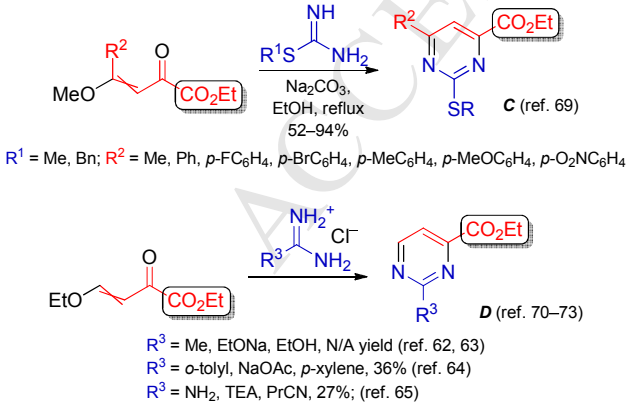
Figure 1 Examples of pyrimidine-containing drugs



Scheme 1 Synthesis of pyrimidine-4-carboxylates by reactions of 1,3-dicarbonyl compounds and *NCN* binucleophiles

A general approach to pyrimidine derivatives relies on the principal two-component condensation of *NCN* binucleophiles with *CCC* bis-electrophiles. 1,3-Dicarbonyl compounds are commonly used for that; however, this variation of the method have found limited application for the preparation of pyrimidine-4-carboxylates. Most reported examples referred to reactions of oxaloacetic acid esters with amidines, thiuronium salts or guanidine (Scheme 1, **A**).[22–27] In another work, benzoyl- or (2-thienoyl)pyruvate were first transformed into mixtures of the corresponding β-chlorovinylketones, which then reacted with 1-(β-d-ribofuranosyl)formamidine to give the corresponding pyrimidine derivatives in 32–36% overall yields (**B**).[28]

β-Alkoxyvinyl carbonyl compounds are renown synthetic equivalents of 1,3-dicarbonyl compounds which were widely used for the synthesis of numerous heterocyclic systems, including pyrimidines, and often led to better yields and purity of the target products.[29,30] Utility of these bis-electrophiles was demonstrated mainly by the preparation of substituted pyrimidines bearing alkyl, haloalkyl or aryl moiety at the C-4 position.[31–62] It should be noted that the related methods were reported in the patent literature.[63–67] Some published papers described synthesis of pyrimidine-5-carboxylates.[29,55,56,68] In the case of pyrimidine-4-carboxylates, only a few isolated examples were published, in particular, reactions of β-alkoxyvinyl α-ketoesters with only two specific substrates: 2-methylisothiourea or 2-benzylisothiourea (Scheme 2, ***C***).[69] In turn, the reaction of amidines or guanidine (***D***)[70–73] led to the corresponding pyrimidines in generally poor yields (up to 36%). Therefore, no optimized protocols were developed.



Scheme 2 Synthesis of pyrimidine-4-carboxylates by reactions of β-alkoxyvinyl carbonyl compounds and *NCN* binucleophiles

Furthermore, aryl-substituted binucleophiles were used predominantly - they are generally more convenient to handle and often have distinct reactivity as compared to their aliphatic counterparts. This is an example of recent finding by Churcher and co-authors,[74] who outlined that in many publications, the scope of the synthetic methods have been shown only for the most "convenient" substrates. Further application of such results by medicinal and industrial chemists often requires additional optimization of the protocols.

In this work, we have aimed at thorough and comprehensive studying of the lowest-molecular-weight β-alkoxyvinyl carbonyl compounds **1**–**3** as bis-electrophiles in the reactions with classical *NCN* binucleophiles, *i.e.* amidines (**4**–**10**) *S*-methylthiuronium salt (**11**), and guanidines (**12**–**15**) (Figure 2). These bis-electrophiles were scarcely studied in the pyrimidine synthesis to date; in fact, most of the resulting pyrimidine-4-carboxylates obtained in this work were not described in the literature so far. In addition to that, application of the resulting products for preparation of multipurpose building blocks relevant for drug discovery was envisaged. As a result of this, carboxylic acids (8 examples), alcohols (7 examples), aldehydes (3 examples), chlorides (4 examples) and amines (4 examples) were obtained on multigram scale; 43 out of 51 pyrimidines prepared were novel compounds. Nearly all compounds are functionalized low-molecular-weight building blocks highly compatible with stringent compound quality criteria which are still important to drug discovery.[75]

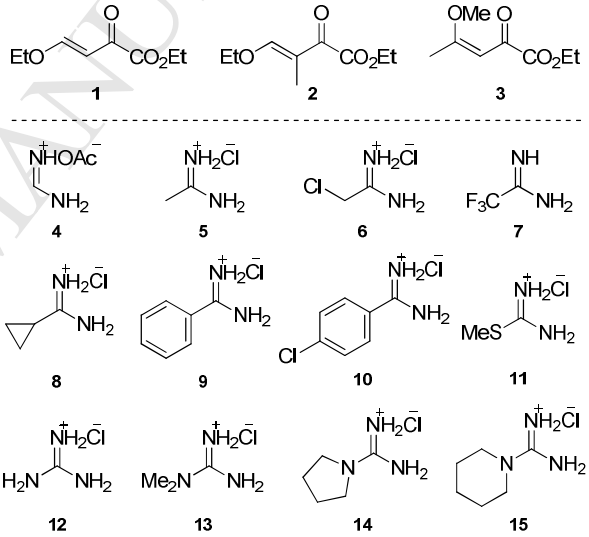


Figure 2 Substrates studied in this work

2. Results/Discussion

The compounds **1**–**3** were prepared according to the known literature method.[76] Typical procedure for the reaction of **1**–**3** with binucleophiles **4**–**15** included heating of the starting materials at 70 °C in the presence of K_2CO_3 in MeCN for 2 h (method **A**). The reaction proceeded smoothly only in the case of **3**, which appeared to be the most reactive bis-electrophile in the series studied, providing the target pyrimidines **16**{**3**,**4**–**10**} and **16**{**3**,**13**–**15**} in 67–90% yield (Table 1, Entries 16–26). Reaction of **3** with trifluoroacetamidine (**7**) did not require a base, providing 2-(trifluoromethyl)pyrimidine **16**{**3**,**7**}, which was used in the next step without isolation and purification (Entry 19).

It should be noted that the reaction of **3** and guanidines **13**–**15** was accompanied with trans-esterification of the CO_2Et moiety with MeOH formed, so that the corresponding pyrimidines bearing the dialkylamino moiety **16**{**3**,**13**–**15**} contained up to 33% of the corresponding methyl ester **17**{**3**,**13**–**15**}. Since formation of this side product was not a problem for further

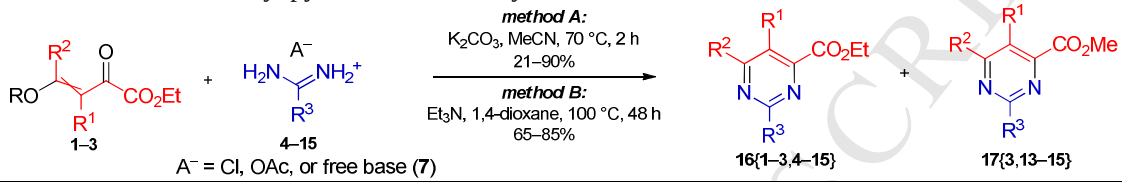
transformations, the resulting mixtures of **16**{**3**,**13**–**15**} and **17**{**3**,**13**–**15**} were used in the next steps without additional purification (Table 1, Entries 24–26).

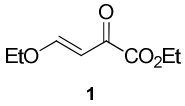
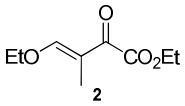
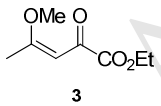
In the case of guanidine **12**, the reaction with **3** using method **A** appeared to be too slow; therefore, alternative reaction conditions were developed, *i.e.* heating of the starting compounds in the presence of Et_3N in 1,4-dioxane at 100 °C for 48 h (method **B**), which gave the target product **16**{**3**,**12**} in 82% yield (Table 1, Entry 23).

It was found that the method **B** was superior to the method **A** in the case of the less reactive 1,3-bis-electrophile **1** and amidines **5**, **8** or **10** (**A**: 39–57% yield; **B**: 65–80% yield; Table 1, Entries 2, 4 and 5). Lower yields and purity of the target products in the case of method **A** could be related to partial hydrolysis of the starting amidine with H_2O formed in the reaction; moreover, ammonia which was also released reacted with **1** to give the corresponding enaminone, thus complicating isolation of the target product. Therefore, the method **B** was used for less reactive *NCN* binucleophiles in the reaction with **1** (75–85% yield, Entries 6–8), as well as for all experiments with the compound **2** (71–86% yield, Entries 9–15), which appeared to be the least reactive among the 1,3-bis-electrophiles studied, possibly due to the steric hindrance around the ketone moiety.

Unfortunately, the method **B** was unfruitful in all experiments with formamidine acetate (**4**) (Entries 1, 9 and 16); meanwhile, the method **A** was applied for the preparation of the corresponding pyrimidines **16**{**1**,**4**} and **16**{**3**,**4**} more or less successfully (21% and 72% yield, respectively).

Table 1. Synthesis of substituted ethyl pyrimidine-4-carboxylates **16**{**1**–**3**,**4**–**15**}



#	β-Alkoxyvinyl α-ketoester	*NCN* binucleophile	Product	R^3	Yield, %	Method
1		**4**	**16**{**1**,**4**}	H	21 (**A**), 0 (**B**)[a]	**A/B**
2		**5**	**16**{**1**,**5**}	Me	39 (**A**), 65 (**B**)[a]	**A/B**
3		**6**	**16**{**1**,**6**}	CH_2Cl	69	**A**
4		**8**	**16**{**1**,**8**}	cyclopropyl	53 (**A**), 73 (**B**)[a]	**A/B**
5		**10**	**16**{**1**,**10**}	*p*-ClC_6H_4	57 (**A**), 80 (**B**)[a]	**A/B**
6		**11**	**16**{**1**,**11**}	SMe	75	**B**
7		**12**	**16**{**1**,**12**}	NH_2	76	**B**
8		**14**	**16**{**1**,**14**}	pyrrolidin-1-yl	85	**B**
9		**4**	**16**{**2**,**4**}	H	0	**A/B**
10		**5**	**16**{**2**,**5**}	Me	71	**B**
11		**8**	**16**{**2**,**8**}	cyclopropyl	76	**B**
12		**10**	**16**{**2**,**10**}	*p*-ClC_6H_4	83	**B**
13		**11**	**16**{**2**,**11**}	SMe	75	**B**
14		**12**	**16**{**2**,**12**}	NH_2	77	**B**
15		**14**	**16**{**2**,**14**}	pyrrolidin-1-yl	85	**B**
16		**4**	**16**{**3**,**4**}	H	72	**A**
17		**5**	**16**{**3**,**5**}	Me	78	**A**
18		**6**	**16**{**3**,**6**}	CH_2Cl	67	**A**
19		**7**	**16**{**3**,**7**}	CF_3	N/A[d]	**A**[c]
20		**8**	**16**{**3**,**8**}	cyclopropyl	74	**A**
21		**9**	**16**{**3**,**9**}	Ph	81	**A**
22		**10**	**16**{**3**,**10**}	*p*-ClC_6H_4	83	**A**
23		**12**	**16**{**3**,**12**}	NH_2	82	**B**
24		**13**	**16**{**3**,**13**}+**17**{**3**,**13**}	NMe_2	90 (**16**:**17** = 2.5:1)[b]	**A**
25		**14**	**16**{**3**,**14**}+**17**{**3**,**14**}	pyrrolidin-1-yl	90 (**16**:**17** = 2:1)[b]	**A**
26		**15**	**16**{**3**,**15**}+**17**{**3**,**15**}	piperidin-1-yl	89 (**16**:**17** = 2:1)[b]	**A**

[a]Both methods **A** and **B** were evaluated

[b]**16**:**17** ratio by ^{1}H NMR – the product was obtained as a mixture of **16** and **17** at the given ratio and was used in the next step without additional purification

[c]The reaction was performed without K_2CO_3

[d]The compound was used in the next step without isolation

The least reactive β-alkoxyvinyl α-ketoester **2** gave no target product **16**{**2**,**4**} under either reaction conditions. In the case of chloromethyl-substituted amidine **6** (Entries 3 and 18), the method **B** could not be used due to alkylation of Et_3N with **6**; nevertheless, the corresponding products **16**{**1**,**6**} and **16**{**3**,**6**} could be obtained using the method **A**.

It is important to outline that 20 of 24 synthesized pyrimidine ester derivatives **16**{**1**–**3**,**4**–**15**} are novel compounds which were not described in the literature to date.

To demonstrate utility of the target esters **16**, their transformations into building blocks **18**–**22** was performed *via* standard carboxylate group modifications. (Figure 3, see the Supporting Information for more details).

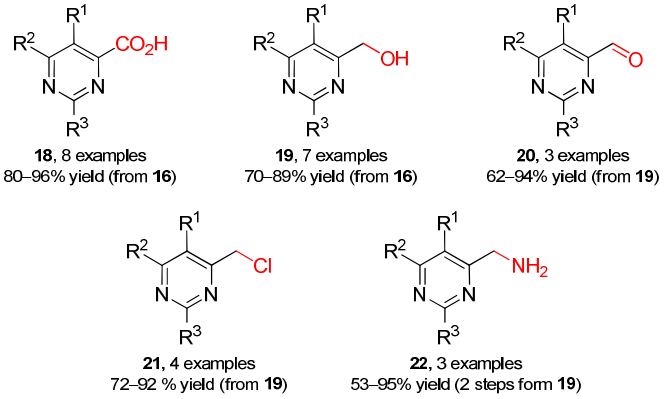


Figure 3. Pyrimidine-derived building blocks **18**–**22**

3. Conclusion

The reaction of β-alkoxyvinyl α-keto esters **1**–**3** with amidines **4**–**10**, *S*-methylthiuronium salt **11**, and guanidines **12**–**15** in the presence of K_2CO_3 in MeCN (method **A**, 21–90% yield) or upon treatment with Et_3N in 1,4-dioxane (method **B**, 65–85% yield) is an efficient approach to the preparation of 4-carboxylalkylpyrimidines **16**. The method **A** was fruitful for the most reactive substrates (*i.e.* 1,3-bis-electrophile **3** and amidines), whereas in most other cases, the method **B** was more expedient. Utility of these key intermediates was confirmed by some typical functional group transformations; 43 out of 51 products were novel compounds. Most of these functionalized pyrimidine derivatives are low-molecular-weight and hydrophilic; they were prepared on multigram scale and are therefore promising building blocks for organic synthesis, drug discovery and agrochemistry, which are readily available to scientific community and can significantly expand the currently accessible lead-like chemical space (Figure S1).

4. Experimental section

The solvents were purified according to the standard procedures.[77] The compounds **1**–**3**,[76] **4**,[78] **5**,[79] **6**,[80] **7**,[81] **8**,[82] **9** and **10**,[33] **11**,[83] **13**,[83] **14** and **15**[84] were prepared according to the literature methods. All other reagents and starting materials were obtained from commercial sources. Melting points were measured on MPA100 OptiMelt automated melting point system. Analytical TLC was performed using Polychrom SI F254 plates. Column chromatography was performed using silica gel (230–400 mesh) as the stationary phase. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 170 Avance 500 spectrometer (at 500 MHz for ^{1}H NMR, 126 MHz for ^{13}C NMR and 470 MHz for ^{19}F NMR) and Varian Unity Plus 400 spectrometer (at 400 MHz for ^{1}H NMR, 101 MHz for ^{13}C NMR and 376 MHz for ^{19}F NMR). NMR chemical shifts are reported in ppm (δ scale) downfield from TMS as an internal standard and are referenced using residual NMR solvent peaks at 7.26 and 77.16 ppm for ^{1}H and ^{13}C in $CDCl_3$, 2.50 and 39.52 ppm for ^{1}H and ^{13}C in DMSO-d_6. Coupling constants (*J*) are shown in Hz. Spectra are reported as follows: chemical shift (δ, ppm), multiplicity, integration, coupling constants (Hz). Elemental analyses were performed at the Laboratory of Organic Analysis, Department of Chemistry, National Taras Shevchenko University of Kyiv. Mass spectra were recorded on an Agilent 1100 LCMSD SL instrument (chemical ionization (CI)) and Agilent 5890 Series II 5972 GCMS instrument (electron impact ionization (EI)). Elemental analysis was performed using Elementar Vario MICRO Cube CHNS/O/Cl analyzer. Instant JChem v. 17.2.27.0 was used for the calculation of physico-chemical parameters, Chemaxon, Hungary, www.chemaxon.com

*4.1. General procedure for the preparation of esters **16** (Method **A**).*

K_2CO_3 (27.6 g. 0.180 mol) was added to a stirred solution of the corresponding β-alkoxyvinyl α-ketoester **1**–**3** (0.100 mol) in MeCN (300 mL) and the resulting mixture was heated to 70 °C. Then, the corresponding *NCN* binucleophile **4**–**15** (0.130 mol, or 0.180 mol in the case of **4**) was added in portions. The reaction mixture was refluxed for 2 h, then cooled to rt and evaporated in *vacuo*. The residue was diluted with H_2O (200 mL) and extracted with *t*-BuOMe (2×100 mL) (in the case of **16**{**1**,**8**}, **16**{**1**,**10**} and **16**{**3**,**9**–**10**}) or CH_2Cl_2 (2×100 mL) (in other cases). The organic phase was separated, washed with H_2O (50 mL), dried over Na_2SO_4, filtered through silica gel and evaporated in *vacuo*.

The products **16{3,13–15}** contained the corresponding methyl esters **17**{**3**,**13**–**15**} formed by trans-esterification upon the reaction with ethyl 4-methoxy-2-oxopent-3-enoate (**3**).

*Ethyl pyrimidine-4-carboxylate **16{1,4}**.*[85]

Yielg 3.19 g (21 %); yellow crystals; mp = 39–41 °C (hexanes) (lit.[85] 35–36 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.36 (d, *J* = 1.4 Hz, 1H), 8.94 (d, *J* = 5.0 Hz, 1H), 7.97 (dd, *J* = 5.0, 1.4 Hz, 1H), 4.45 (q, *J* = 7.1 Hz, 2H), 1.40 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.5, 158.8, 158.7, 154.5, 120.5, 62.3, 13.7. LC/MS (CI): *m/z* = 153 $[M+H]^+$. Anal. calcd. for $C_7H_8N_2O_2$: C, 55.26; H, 5.30; N, 18.41. Found: C, 55.37; H, 5.25; N, 18.78.

*Ethyl 2-(chloromethyl)pyrimidine-4-carboxylate **16{1,6}**.*

The compound was purified by distillation in *vacuo*. Yield 13.8 g (69%); brownish liquid; bp = 102–104 °C / 1 mmHg. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.97 (d, *J* = 4.9 Hz, 1H), 7.87 (d, *J* = 4.9 Hz, 1H), 4.80 (s, 2H), 4.45 (q, *J* = 7.1 Hz, 2H), 1.39 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.1, 163.2, 159.5, 155.3, 119.1, 62.4, 46.2, 13.7. GC/MS (EI): *m/z* = 156/158 $[M\text{-}OEt+H]^+$, 173/175 $[M\text{-}H_2C{=}CH(CH_3){+}H]^+$, 201/203 $[M+H]^+$. Anal. calcd. for $C_8H_9ClN_2O_2$: C, 47.90; H, 4.52; N, 13.96; Cl, 17.67. Found: C, 47.55; H, 4.75; N, 14.01; Cl, 17.71.

*Ethyl 6-methylpyrimidine-4-carboxylate **16{3,4}**.*

Yield 12.0 g (72%); colorless crystals, mp = 32–34 °C (hexanes) (bp = 86–88 °C / 1 mmHg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.22 (s, 1H), 7.85 (s, 1H), 4.46 (q, *J* = 7.2 Hz, 2H), 2.62 (s, 3H), 1.42 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.6, 164.3, 158.8, 154.6, 120.5, 62.6, 24.3, 14.1. LC/MS (CI): *m/z* = 139 $[M\text{-}H_2C{=}CH(CH_3){+}H]^+$, 167 $[M+H]^+$. Anal. calcd. for $C_8H_{10}N_2O_2$: C, 57.82; H, 6.07; N, 16.86. Found: C, 57.51; H, 6.43; N, 16.86.

Ethyl 2,6-dimethylpyrimidine-4-carboxylate ***16{3,5}***.

Yield 14.1 g (78%); colorless crystals, mp = 44–47 °C (hexanes) (bp = 94–96 °C / 1 mmHg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (s, 1H), 4.47 (q, *J* = 7.1 Hz, 2H), 2.79 (s, 3H), 2.59 (s, 3H), 1.42 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.4, 168.7, 164.6, 155.0, 117.4, 62.5, 26.1, 24.3, 14.2. LC/MS (CI): *m/z* = 181$[M+H]^+$. Anal. calcd. for $C_9H_{12}N_2O_2$: C, 59.99; H, 6.71; N, 15.55. Found: C, 59.91; H, 6.78; N, 15.34.

Ethyl 2-(chloromethyl)-6-methylpyrimidine-4-carboxylate ***16{3,6}***.

The compound was purified by distillation in *vacuo*. Yield 14.4 g (67%); yellow powder; mp = 36–38 °C; bp = 117–119 °C / 1 mmHg. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (s, 1H), 4.78 (s, 2H), 4.48 (q, *J* = 7.2 Hz, 2H), 2.65 (s, 3H), 1.42 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.7, 166.2, 164.0, 155.5, 119.2, 62.7, 46.8, 24.4, 14.2. GC/MS (EI): *m/z* = 155/157 $[M\text{-}OEt]^+$, 186/188 $[M\text{-}H_2C{=}CH(CH_3)]^+$, 214/216 $[M]^+$. Anal. calcd. for $C_9H_{11}ClN_2O_2$: C, 50.36; H, 5.17; N, 13.05; Cl, 16.52. Found: C, 50.25; H, 5.31; N, 12.73; Cl, 16.72.

Ethyl 2-cyclopropyl-6-methylpyrimidine-4-carboxylate ***16{3,8}***.

Yield 15.3 g (74%); yellowish liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (s, 1H), 4.42 (q, *J* = 7.1 Hz, 2H), 2.49 (s, 3H), 2.30 (tt, *J* = 8.2, 2.7 Hz, 1H), 1.39 (t, *J* = 7.1 Hz, 3H), 1.16 – 1.13 (m, 2H), 1.05 – 1.02 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.6, 169.1, 164.8, 154.5, 116.9, 62.2, 24.3, 18.3, 14.2, 11.0. LC/MS (CI): *m/z* = 207 $[M+H]^+$. Anal. calcd. for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84; N, 13.58. Found: C, 64.05; H, 6.92; N, 13.77.

Ethyl 6-methyl-2-phenylpyrimidine-4-carboxylate ***16{3,9}***.

Yield 19.6 g (81%); yellowish solid; mp = 95–97 °C (hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.54 (s, 2H), 7.72 (s, 1H), 7.52 – 7.47 (m, 3H), 4.51 (q, *J* = 6.7 Hz, 2H), 2.69 (s, 3H), 1.48 (t, *J* = 6.7 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.6, 165.0, 164.8, 155.4, 137.1, 130.9, 128.5, 128.5, 118.0, 62.3, 24.6, 14.2. LC/MS (CI): *m/z* = 213 $[M\text{-}Et]^-$, 243 $[M+H]^+$. Anal. calcd. for $C_{14}H_{14}N_2O_2$: C, 69.41; H, 5.82; N, 11.56. Found: C, 69.47; H, 5.97; N, 11.35.

Ethyl 2-(4-chlorophenyl)-6-methylpyrimidine-4-carboxylate ***16{3,10}***.

Yield 23.0 g (83%); colorless powder; mp = 107–109 (hexanes). °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.49 (d, *J* = 8.5 Hz, 2H), 7.73 (s, 1H), 7.47 (d, *J* = 8.5 Hz, 2H), 4.51 (q, *J* = 7.0 Hz, 2H), 2.68 (s, 3H), 1.48 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.7, 164.7, 164.0, 155.4, 137.2, 135.6, 129.9, 128.7, 118.1, 62.4, 24.6, 14.2. LC/MS (CI): *m/z* = 277/279 $[M+H]^+$. Anal. calcd. for $C_{14}H_{13}ClN_2O_2$: C,s 60.77; H, 4.74; N, 10.12; Cl, 12.81. Found: C, 60.55; H, 4.66; N, 10.01; Cl, 13.11.

Ethyl 2-(dimethylamino)-6-methylpyrimidine-4-carboxylate ***16{3,13}***.

The compound was obtained as a mixture with methyl 2-(dimethylamino)-6-methylpyrimidine-4-carboxylate **17**{**3**,**13**} (**16**:**17** = 2.5:1). Yield 18.8 g (90%); yellowish liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.84 (s, 1H), 4.28 (q, *J* = 7.1 Hz, 2H), 3.11 (s, 6H), 2.29 (s, 3H), 1.29 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.9, 164.9, 162.1, 154.6, 107.3, 52.2, 36.3, 23.9, 13.7. LC/MS (CI): *m/z* = 210 $[M+H]^+$.

Methyl 2-(dimethylamino)-6-methyl-pyrimidine-4-carboxylate ***17{3,13}*** *(spectral data)*.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.86 (s, 1H), 3.82 (s, 3H), 3.11 (s, 6H), 2.29 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.0, 165.4, 162.1, 154.9, 107.4, 61.2 36.4, 23.9. LC/MS (CI): *m/z* = 195 $[M+H]^+$.

Ethyl 6-methyl-2-(pyrrolidin-1-yl)pyrimidine-4-carboxylate ***16{3,14}***.

The compound was obtained as a mixture with methyl 6-methyl-2-(pyrrolidin-1-yl)pyrimidine-4-carboxylate **17**{**3**,**14**} (**16**:**17** = 2:1). Yield 21.2 (90%); yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.92 (s, 1H), 4.35 (q, *J* = 6.9 Hz, 2H), 3.62 – 3.54 (m, 4H), 2.36 (s, 3H), 1.95 – 1.91 (m, 4H), 1.35 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.4, 165.5, 160.9, 155.2, 107.9, 52.8, 46.6, 25.4, 24.4, 14.2. LC/MS (CI): *m/z* = 236 $[M+H]^+$.

Methyl 6-methyl-2-(pyrrolidin-1-yl)pyrimidine-4-carboxylate ***17{3,14}*** *(spectral data)*.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.94 (s, 1H), 3.89 (s, 3H), 3.62 – 3.54 (m, 4H), 2.36 (s, 3H), 1.99 – 1.93 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.6, 166.1, 161.2, 155.6, 108.0, 61.8, 46.7, 25.5, 24.5. LC/MS (CI): *m/z* = 222 $[M+H]^+$.

Ethyl 6-methyl-2-(piperidin-1-yl)pyrimidine-4-carboxylate ***16{3,15}***.

The compound was obtained as a mixture with methyl 6-methyl-2-(piperidin-1-yl)pyrimidine-4-carboxylate **17**{**3**,**15**} (**16**:**17** = 2:1). Yield 22.2 g (89%); yellowish oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.94 (s, 1H), 4.40 (q, *J* = 7.0 Hz, 2H), 3.85 (s, 4H), 2.39 (s, 3H), 1.68 – 1.60 (m, 6H), 1.41 (t, *J* = 7.0 Hz, 3H).^{13}C NMR (126 MHz, $CDCl_3$) δ 169.6, 165.5, 162.1, 155.6, 108.0, 61.8, 44.6, 25.8, 24.8, 24.5,14.2. LC/MS (CI): *m/z* = 250 $[M+H]^+$.

Methyl 6-methyl-2-(piperidin-1-yl)pyrimidine-4-carboxylate ***17{3,15}*** *(spectral data)*.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.96 (s, 1H), 3.94 (s, 3H), 3.87 – 3.86 (m, 4H), 2.39 (s, 3H), 1.68 – 1.60 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.6, 165.5, 162.1, 155.6, 108.1, 61.8, 44.7, 25.8, 24.8, 24.5. LC/MS (CI): *m/z* = 236 $[M+H]^+$.

4.2. General procedure for the preparation of esters ***16*** *(Method* ***B****).*

Et_3N (27.9 mL, 20.2 g, 0.200 mol) was added to a stirred mixture of β-alkoxyvinyl ester **1**–**3** (0.100 mol) and the corresponding amidine/guanidine **4**–**15** (0.120 mol) in 1,4-dioxane (200 mL). The resulting mixture was stirred at 100 °C for 48 h, then cooled to rt and evaporated in *vacuo*. The residue was diluted with H_2O (150 mL) and extracted with *t*-BuOMe (2×100 mL). The combined organic extracts were washed with water (50 mL), dried over Na_2SO_4, filtered through silica gel and evaporated in *vacuo.*

Ethyl 2-methylpyrimidine-4-carboxylate ***16{1,5}***.

Yield 10.8 g (65%; Method **A** – 39%); brownish liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 (d, *J* = 4.9 Hz, 1H), 7.74 (d, *J* = 4.9 Hz, 1H), 4.44 (q, *J* = 7.1 Hz, 2H), 2.80 (s, 3H), 1.38 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.1, 164.3, 159.0, 155.2, 117.7, 62.6, 26.2, 14.2. LC/MS (CI): *m/z* = 139 $[M\text{-}H_2C{=}CH(CH_3){+}H]^+$, 167 $[M+H]^+$. Anal. calcd. for $C_8H_{10}N_2O_2$: C, 57.82; H, 6.07; N, 16.86. Found: C, 57.94; H, 5.68; N, 17.19.

Ethyl 2-cyclopropylpyrimidine-4-carboxylate ***16{1,8}***.

Yield 14.0 g (73%; Method **A** – 53%); yellowish liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (d, *J* = 4.9 Hz, 1H), 7.63 (d, *J* = 4.9 Hz, 1H), 4.42 (q, *J* = 7.2 Hz, 2H), 2.38 – 2.30 (m, 1H), 1.38 (t, *J* = 7.2 Hz, 3H), 1.16 – 1.12 (m, 2H), 1.08 – 1.04 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.1, 164.4, 158.9, 154.8, 117.2,

62.4, 18.4, 14.1, 11.4. LC/MS (CI): *m/z* = 193 $[M+H]^+$. Anal. calcd. for $C_{10}H_{12}N_2O_2$: C, 62.49; H, 6.29; N, 14.57. Found: C, 62.22; H, 6.54; N, 14.96.

Ethyl 2-(4-chlorophenyl)pyrimidine-4-carboxylate ***16{1,10}***.

Yield 21.0 g (80%; Method A – 57%); colorless crystals; mp = 90–93 °C (hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.99 (d, *J* = 4.9 Hz, 1H), 8.46 (d, *J* = 8.7 Hz, 2H), 7.83 (d, *J* = 4.9 Hz, 1H), 7.46 (d, *J* = 8.7 Hz, 2H), 4.50 (q, *J* = 7.1 Hz, 2H), 1.47 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.9, 158.9, 155.2, 137.1, 134.9, 129.8, 129.5, 128.5, 118.1, 62.1, 13.8. LC/MS (CI): *m/z* = 263/265 $[M+H]^+$. Anal. calcd. for $C_{13}H_{11}ClN_2O_2$: C, 59.44; H, 4.22; N, 10.66; Cl, 13.49. Found: C, 59.56; H, 4.30; N, 10.86; Cl, 13.23.

Ethyl 2-(methylthio)pyrimidine-4-carboxylate ***{1,11}***.[86]

Yield 14.9 g (75%); yellowish liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.59 (d, *J* = 4.9 Hz, 1H), 7.45 (d, *J* = 4.9 Hz, 1H), 4.30 (q, *J* = 7.1 Hz, 2H), 2.45 (s, 3H), 1.26 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.3, 163.3, 158.6, 154.7, 115.0, 62.0, 13.7, 13.6. LC/MS (CI): *m/z* = 199 $[M+H]^+$. Anal. calcd. for $C_8H_{10}N_2O_2S$: C, 48.47; H, 5.08; N, 14.13; S, 16.17. Found: C, 48.85; H, 4.75; N, 14.35; S, 16.54.

Ethyl 2-(pyrrolidin-1-yl)pyrimidine-4-carboxylate ***16{1,14}***.

Yield 18.8 g (85%); yellowish crystals; mp = 54–57 °C (hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.45 (d, *J* = 4.7 Hz, 1H), 7.03 (d, *J* = 4.7 Hz, 1H), 4.38 (q, *J* = 7.2 Hz, 2H), 3.65 – 3.55 (m, 4H), 1.99 – 1.93 (m, 4H), 1.37 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.7, 160.2, 159.1, 155.5, 107.6, 61.5, 46.3, 25.0, 13.7. LC/MS (CI): *m/z* = 222 $[M+H]^+$. Anal. calcd. for $C_{11}H_{15}N_3O_2$: C, 59.71; H, 6.83; N, 18.99. Found: C, 59.76; H, 6.97; N, 19.18.

Ethyl 2,5-dimethylpyrimidine-4-carboxylate ***16{2,5}***.

Yield 13.0 g (71%); yellow liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.45 (s, 1H), 4.30 (q, *J* = 7.1 Hz, 2H), 2.58 (s, 3H), 2.28 (s, 3H), 1.26 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.4, 164.7, 160.1, 153.9, 126.3, 61.7, 25.0, 15.5, 13.6. LC/MS (CI): *m/z* = 181$[M+H]^+$. Anal. calcd. for $C_9H_{12}N_2O_2$: C, 59.99; H, 6.71; N, 15.55. Found: C, 60.17; H, 6.38; N, 15.45.

Ethyl 2-cyclopropyl-5-methylpyrimidine-4-carboxylate ***16{2,8}***.

Yield 15.7 g (76%); yellowish liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.50 (s, 1H), 4.44 (q, *J* = 7.1 Hz, 2H), 2.39 (s, 3H), 2.28 (tt, *J* = 8.3, 3.9 Hz, 1H), 1.41 (t, *J* = 7.1 Hz, 3H), 1.12 – 1.09 (m, 2H), 1.07 – 1.03 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.0, 165.4, 160.4, 154.3, 126.0, 62.0, 17.8, 15.8, 14.1, 10.8. LC/MS (CI): *m/z* = 135 $[M-CO_2-H_2C=CH(CH_3)+H]^+$, 179 $[M-H_2C=CH(CH_3)+H]^+$, 207 $[M+H]^+$. Anal. calcd. for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84; N, 13.58. Found: C, 63.95; H, 6.68; N, 13.96.

Ethyl 2-(4-chlorophenyl)-5-methylpyrimidine-4-carboxylate ***16{2,10}***.

Yield 23.0 g (83%); brownish liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (s, 1H), 8.37 (d, *J* = 8.4 Hz, 2H), 7.46 – 7.38 (m, 2H), 4.47 (q, *J* = 7.1 Hz, 2H), 2.48 (s, 3H), 1.44 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.3, 161.7, 160.8, 155.1, 137.0, 135.4, 129.5, 128.8, 127.7, 62.2, 16.1, 14.2. LC/MS (CI): *m/z* = 277/279 $[M+H]^+$. Anal. calcd. for $C_{14}H_{13}ClN_2O_2$: C, 60.77; H, 4.74; N, 10.12; Cl, 12.81. Found: C, 61.08; H, 4.50; N, 10.09; Cl, 13.04.

Ethyl 2-(methylthio)-5-methylpyrimidine-4-carboxylate ***16{2,11}***.

Yield 14.9 g (75%); brownish liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.38 (s, 1H), 4.33 (q, *J* = 7.1 Hz, 2H), 2.46 (s, 3H), 2.28 (s, 3H), 1.31 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.8, 164.4, 160.1, 154.5, 124.0, 61.6, 15.1, 13.7, 13.6. LC/MS (CI): *m/z* = 213 $[M+H]^+$. Anal. calcd. for $C_9H_{12}N_2O_2S$: C, 50.93; H, 5.70; N, 13.20; S, 15.10. Found: C, 50.55; H, 6.07; N, 13.51; S, 15.17.

Ethyl 5-methyl-2-(pyrrolidin-1-yl)pyrimidine-4-carboxylate ***16{2,14}***.

Yield 20.0 g (85%); yellowish crystals; mp = 40–41 (hexanes) °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (s, 1H), 4.37 (q, *J* = 7.1 Hz, 2H), 3.53 (s, 4H), 2.19 (s, 3H), 1.93 (s, 4H), 1.36 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.7, 160.5, 158.8, 155.3, 114.8, 61.2, 46.2, 25.1, 14.5, 13.7. LC/MS (CI): *m/z* = 236 $[M+H]^+$. Anal. calcd. for $C_{12}H_{17}N_3O_2$: C, 61.26; H, 7.28; N, 17.86. Found: C, 61.56; H, 7.20; N, 17.89.

Ethyl 2-aminopyrimidine-4-carboxylate ***16{1,12}***.[73]

After evaporation in *vacuo* of the reaction mixture, the residue was diluted with H_2O (100 mL) and *t*-BuOMe (30 mL). The precipitate formed was filtered, washed with H_2O (2×10 mL) and dried in *vacuo*. Yield 12.7 g (76%); beige powder; mp = 239–242 °C (EtOH). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.46 (dd, *J* = 4.9, 2.2 Hz, 1H), 7.05 (s, 2H), 7.04 (dd, *J* = 4.4, 1.5 Hz, 1H), 4.30 (q, *J* = 6.9 Hz, 2H), 1.29 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 164.9, 164.4, 161.0, 156.1, 109.4, 61.9, 14.5. LC/MS (CI): *m/z*= 122 $[M-OEt]^+$, 168 $[M+H]^+$. Anal. calcd. for $C_7H_9N_3O_2$: C, 50.29; H, 5.43; N, 25.14. Found: C, 50.05; H, 5.15; N, 25.10.

Ethyl 2-amino-5-methylpyrimidine-4-carboxylate ***16{2,12}***.

After evaporation in *vacuo* of the reaction mixture, the residue was diluted with H_2O (100 mL) and *t*-BuOMe (30 mL). The precipitate formed was filtered, washed with H_2O (2×10 mL) and dried in *vacuo*. Yield 13.8 g (75%); yellowish powder; mp = 195–199 °C (EtOH). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.27 (s, 1H), 6.67 (s, 2H), 4.31 (q, *J* = 7.1 Hz, 2H), 2.14 (s, 3H), 1.30 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 165.8, 162.5, 161.9, 155.9, 116.38, 61.7, 14.7, 14.5. LC/MS (CI): *m/z*= 182 $[M+H]^+$. Anal. calcd. for $C_8H_{11}N_3O_2$: C, 53.03; H, 6.12; N, 23.19. Found: C, 52.96; H, 6.44; N, 23.48.

Ethyl 2-amino-6-methylpyrimidine-4-carboxylate ***16{3,12}***.[87]

After evaporation in *vacuo* of the reaction mixture, the residue was diluted with H_2O (100 mL) and *t*-BuOMe (30 mL). The precipitate formed was filtered, washed with H_2O (2×10 mL) and dried in *vacuo*. Yield 14.9 g (82%); brownish powder; mp = 145–147 °C (EtOH) (lit.[87] 151 °C). ^{1}H NMR (500 MHz, DMSO-d_6) δ 6.96 (s, 1H), 6.90 (s, 2H), 4.29 (q, *J* = 7.0 Hz, 2H), 2.31 (s, 3H), 1.29 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 170.3, 165.1, 164.3, 156.0, 109.0, 61.8, 24.1, 14.5. LC/MS (CI): *m/z*= 182 $[M+H]^+$. Anal. calcd. for $C_8H_{11}N_3O_2$: C, 53.03; H, 6.12; N, 23.19. Found: C, 53.06; H, 6.43; N, 23.46.

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