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Condensation reactions of guanidines with bis-electrophiles: formation of highly nitrogenous heterocycles☆

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ABSTRACT

2-Amino-1,4-dihydropyrimidines were reacted with bis-electrophiles to produce novel fused bipyrimidine, pyrimidoaminotriazine, and pyrimidosulfonamide scaffolds. In addition, a quinazoline library was constructed using a guanidine Atwal–Biginelli reaction with 1-(quinazolin-2-yl)guanidines. The product heterocycles have novel constitutions with high nitrogen atom counts and represent valuable additions to screening libraries for the discovery of new modulators of biological targets.

1. Introduction

Diversity Oriented Synthesis (DOS) inspires chemists to design or apply chemical methodologies that result in the synthesis of structurally diverse, functionally rich and often architecturally complex small molecule scaffolds.[1,2] In many cases, new biological targets can be explored more effectively with DOS-derived probes and natural products than traditional aromatic 'drug-like' heterocycles.[3] Novel molecular scaffolds are therefore valuable additions to high throughput screening libraries and improve the odds of identifying lead compounds in drug discovery initiatives.[4,5]

As a continuation of our efforts in the preparation of rare heterocyclic scaffolds,[6] we became interested in developing a convergent synthetic route to 4*H*-pyrimido[1,2-*a*]pyrimidines. While there is evidence in the literature demonstrating melanin-concentrating hormone receptor (MCH1R) antagonistic effects,[7] protein kinase inhibition,[8] treatment of atherosclerosis and restenosis,[9] antiviral activities,[10] inhibition of platelet aggregation,[11] and anti-MRSA dihydrofolate reductase activity[12] of 4*H*-pyrimido[1,2-*a*]pyrimidines **1**, their synthesis and application is strikingly rare compared to the structurally and pharmacologically related ring-contracted imidazo[1,2-*a*]pyridines **2** (Fig. 1). The latter

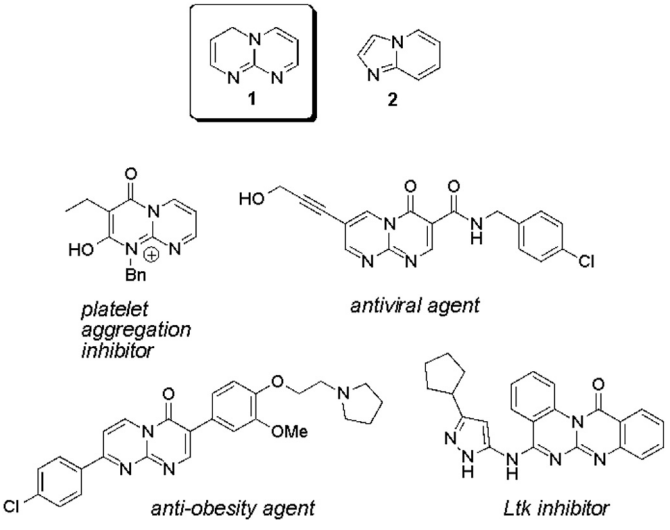

Fig. 1. The 4*H*-pyrimido[1,2-*a*]pyrimidine and imidazo[1,2-*a*]pyridine scaffolds **1** and **2**, and selected biologically active derivatives.

heterocycle is an abundant pharmacophore in medicinal chemistry and has been used in antiviral, antibacterial, anti-inflammatory, analgesic, antipyretic, and anxioselective indications. Derivatives of **2** are β-amyloid formation inhibitors and constitute a novel class of orally active nonpeptide bradykinin B2 receptor antagonists.[13] Several imidazo[1,2-*a*]pyridines are already clinically used,

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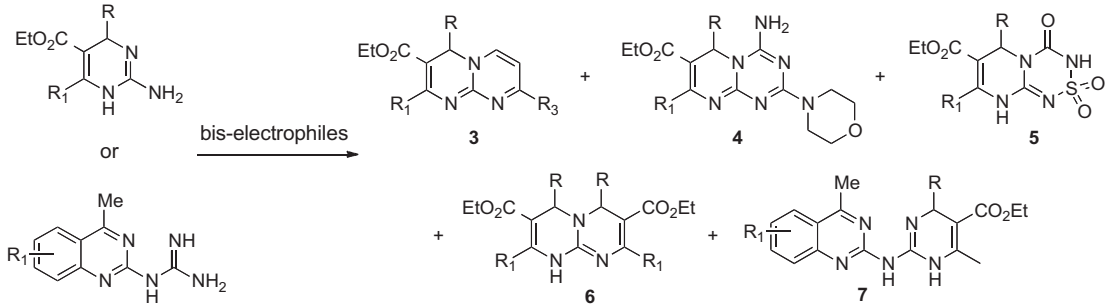
including zolimidine (an anti-ulcer drug), zolpidem (a hypnotic drug), and alpidem (a nonsedative anxiolytic). Imidazo[1,2-*a*]pyrimidine moieties are also important as benzodiazepine receptor agonists, antiviral agents, antibacterials, antifungal agents, and calcium channel blockers.[13]

Using a variant of the Biginelli three-component reaction for the preparation of cyclic guanidines,[14,15] we were able to develop efficient strategies for a tandem condensation with bis-electrophiles to give bipyrimidines **3**, pyrimidoaminotriazines **4**, cyclic pyrimidosulfonamides **5**, and pyrimidopyrimidines **6** (Scheme 1). In addition, a small sub-library of quinazoline-containing heterocycles **7** was assembled using Atwal–Biginelli conditions.[16,17]

Table 1
Conversion of thioureas (**8a**, R=CH_3; **8b**, R=$(CH_2)_2Ph$; **8c**, R=$CH(CH_3)_2$) to thioimidates **9a–c** and 2-aminopyrimidines **10a–c** according to Scheme 2

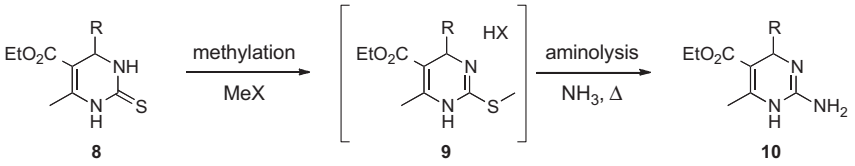
Entry	**8**/Conditions	**9**/Additive/time	**10**/Yield[a] %
1	**8a**/MeOTf, THF, 1.5 h	**9a**/NH_4OAc/20 h	**10a**/77
2	**8a**/MeOTf, $ClCH_2CH_2Cl$, 0.75 h	**9a**/NH_4OAc/15 h	**10a**/30
3	**8a**/MeOTf, PhCl, 3.5 h	**9a**/NH_4OAc/17 h	**10a**/61
4	**8a**/MeOTf, PhCl, 15 h	**9a**/NH_4Cl/21 h	**10a**/51
5	**8a**/$(MeO)_2SO_2$, THF, 60 h	**9a**/NH_4OAc/17 h	**10a**/57
6	**8b**/MeOTf, PhCl, 3.5 h	**9b**/NH_4OAc/17 h	**10b**/39
7	**8c**/MeOTf, PhCl, 3.5 h	**9c**/NH_4OAc/20 h	**10c**/33

[a] Isolated yield of purified product.



Scheme 1. Overview of heterocycles obtained by condensation of guanidines with bis-electrophiles.

New strategies for accessing structurally diverse guanidine-based Biginelli products have previously been reported by the Overman group.[18] Specifically, triazone-protected guanidines were found to endure the harsh acidic conditions frequently used for the Biginelli cyclization.[18] In order to access C-4 alkyl-substituted cyclic guanidines **10**, we first envisioned using thioureas **8** as starting materials followed by an aminolysis of the corresponding methylthioureas **9**, in a manner similar to that reported by Kappe (Scheme 2).[19]



Scheme 2. Thiourea methylation followed by aminolysis of the thioimidate provides access to 2-aminodihydropyrimidines.

2. Results and discussion

Thioureas **8** with R=methyl, phenethyl, and isopropyl were prepared through Biginelli multicomponent condensations from β-ketoesters, aldehydes, and thiourea under standard acid-catalyzed conditions.[20] The reaction parameters for the one-pot methylation/aminolysis were optimized on substrate **8a** (R=Me) (Table 1, entries 1–5). Initial investigations using methyl iodide resulted in dealkylation of the newly formed methylthiourea **9a**, most likely due to the presence of nucleophilic iodide ions in the vigorously heated aminolysis reaction mixture.[21] Accordingly, methyl triflate was used as an alternative electrophile for the *S*-alkylation and proved effective for the formation of the desired guanidine **10a** in good isolated yields. The use of dimethyl sulfate also provided **10a** in 57% yield but required prolonged reaction times (entry 5). High yields of product **10a** were achieved when THF was used as the reaction solvent. However, the methylation step was problematic due to the propensity of methyl triflate to polymerize THF.[22] The optimal solvent for this two-step reaction sequence was found to be chlorobenzene (PhCl), which was both inert to the reaction conditions and could safely be heated to 95–100 °C under sealed tube conditions (Table 1, entry 3). The aminolysis step was found to proceed smoothly on multigram scale (2.5 g) with ammonium acetate or ammonium chloride as additives in the presence of ammonia. Following this one-pot reaction, the hydrochloride salts of **10a–c** were prepared and subsequently used as substrates for further cyclization reactions (vide infra).

The 4-arylated 2-aminopyrimidine **13**·**TFA** was obtained in a two-step sequence starting from PMB–guanidine **11** (Scheme 3).[23] Treatment of a solution of **11** in hexafluoroisopropanol with enone **12** and sodium bicarbonate at 90 °C provided the PMB-protected **13** in 42% yield. Deprotection of the PMB group was accomplished in 70% yield in TFA buffered with water, triethylsilane, and thioanisole.[24] A three-component Biginelli reaction with guanidine hydrochloride **14**·**HCl**, ethyl 3-oxo-3-phenylpropanoate **15**, and aldehydes **16** and **17** was performed to access heterocycles **18**, **19**, and the hydrochloride salt **18**·**HCl** (Scheme 4).

Cyclization reactions of guanidines with the bis-electrophile 1,1,3,3-tetramethoxypropane (**20**) were explored under microwave conditions (Scheme 5 and Table 2).[25,26] We found that these reactions proceeded smoothly in 42–76% yield when the hydrochloride salts of **10a–c** or **18** were combined with **20** in a microwave vial and heated to 160 °C in trifluoroethanol (**21**) (entries 1–4). The use of the hydrochloride salts was essential since the corresponding reactions with free amines did not afford the cyclocondensation products. We also briefly explored the reaction of **18** with 4-methoxybut-3-enone **26** to give 8-methyl 4*H*-pyrimido[1,2-*a*]pyrimidine **27** in 64% yield (Table 2, entry 5).

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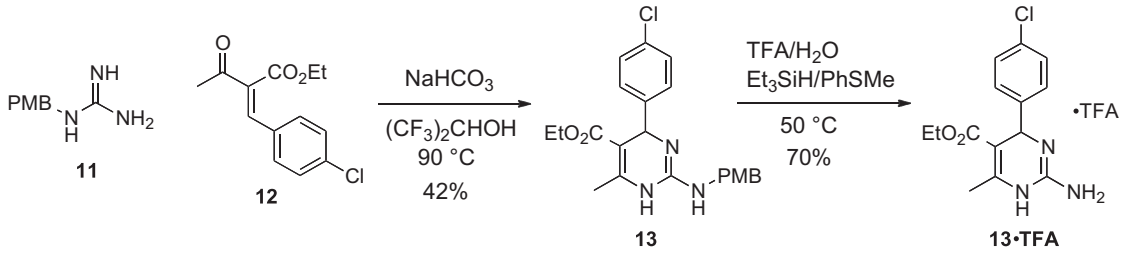
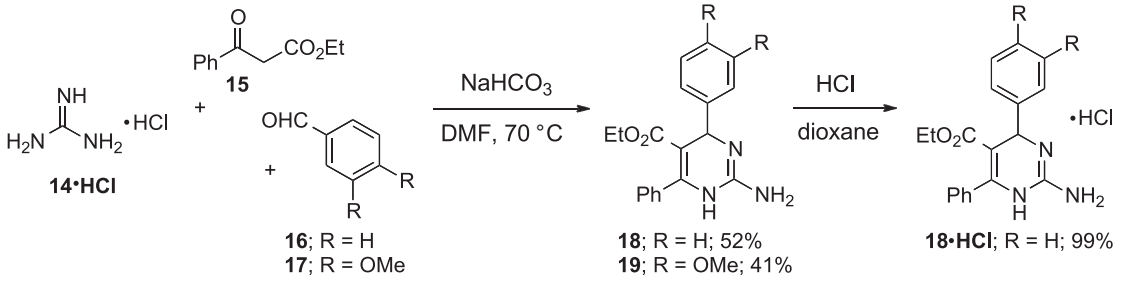
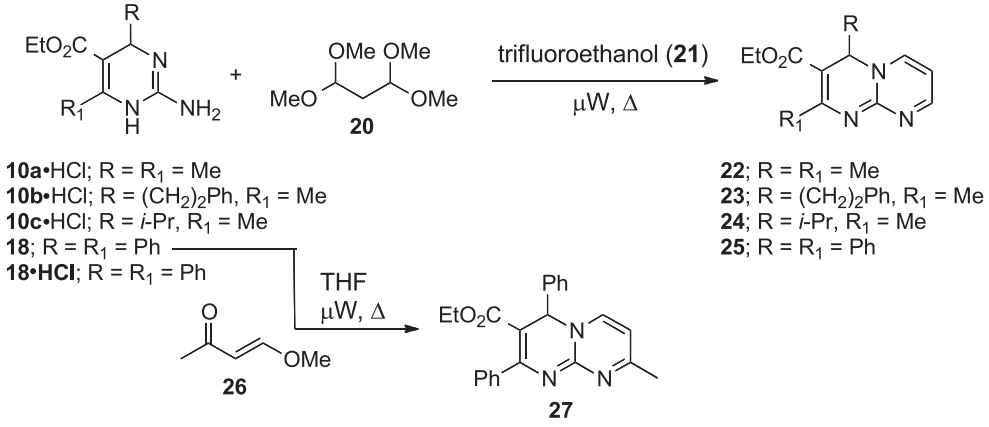


Scheme 3. Two-step preparation of 2-aminopyrimidine **13** from PMB-protected guanidine **11**.



Scheme 4. Preparation of 2-aminopyrimidines from guanidine hydrochloride.



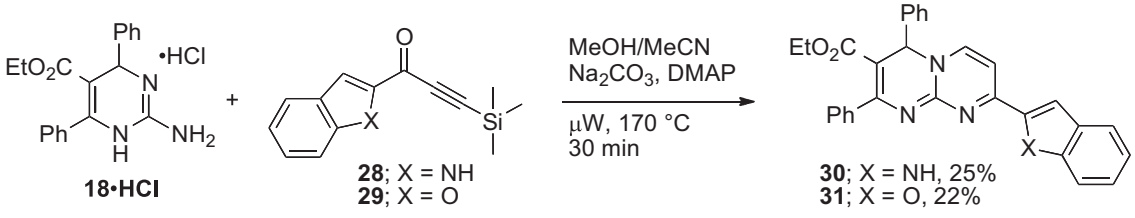
Scheme 5. Synthesis of 4*H*-pyrimido[1,2-*a*]pyrimidine-3-carboxylates.

Table 2
Cyclocondensation reactions of guanidines with bis-electrophiles **20** and **26** according to Scheme 5

Entry	Reactants	Solvent/temperature/time	Product/yield[a] %
1	**10a**·**HCl** and **20**	**21**/160 °C/1 h	**22**/76
2	**10b**·**HCl** and **20**	**21**/160 °C/2 h	**23**/71
3	**10c**·**HCl** and **20**	**21**/160 °C/2 h	**24**/71
4	**18**·**HCl** and **20**	**21**/160 °C/1.5 h	**25**/42
5	**18** and **26**	THF/150 °C/0.25 h	**27**/64

[a] Isolated yield of purified product.

Additional substituents on pyrimido[1,2-*a*]pyrimidines could be introduced by cyclocondensations of **18**·**HCl** with heterocyclic TMS-alkynones (Scheme 6).[27] In the presence of sodium carbonate and catalytic amounts of DMAP, microwave heating at 170 °C for 30 min provided the 8-heteroaryl substituted pyrimidopyridines **30** and **31** in modest yields. In order to further improve the synthesis of these interesting derivatives, we developed a one-pot Sonogashira coupling/cyclocondensation approach (Scheme 7). Room temperature conversion of acid chlorides **32**–**34** and trimethylsilyl acetylene in the presence of Pd(0)-catalysts led to ynones **35**–**37**, which were condensed with pyrimidines **18** and **19** under microwave irradiation to give pyrimidopyridines **38a**–**d** in improved



Scheme 6. Synthesis of 8-heteroaryl-4*H*-pyrimido[1,2-*a*]pyrimidine-3-carboxylates.

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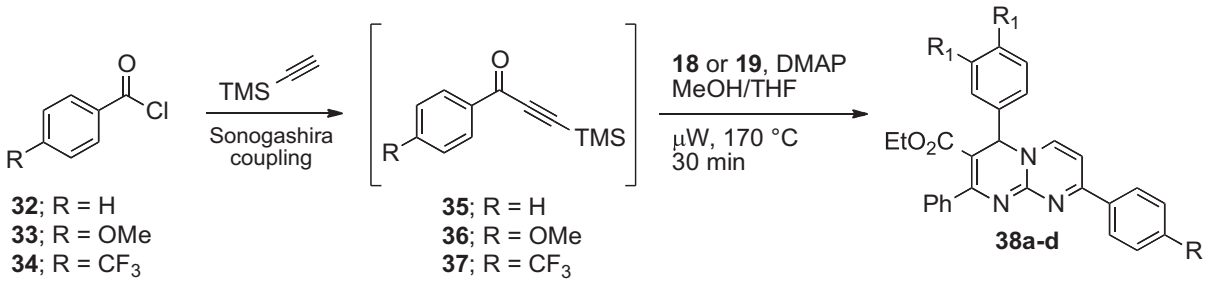


Scheme 7. One-pot Sonogashira coupling–cyclocondensation for the synthesis of 8-aryl-4*H*-pyrimido[1,2-*a*]pyrimidine-3-carboxylates.

overall yields of 28–60% (Table 3). A modest preference for NCy_2Me over Et_3N in the Sonogashira coupling was noted for acid chloride **32** (entries 1, 2, 5, and 6), whereas the yield of the electron-rich acyl chloride **33** was almost unchanged (entries 3 and 7). The efficiency of the conversion of the electron-deficient acyl chloride **34** decreased in the presence of NCy_2Me (entries 4 and 8). Copper- and solvent-free reaction conditions[28] also lowered yields (entries 9 and 10).

Table 3
Sonogashira couplings–cyclocondensations according to Scheme 7

Entry	Reactants	Sonogashira coupling conditions	Product/R/R_1/yield[a] %
1	**32** and **18**	$Pd(PPh_3)_2Cl_2$ (2 mol %); CuI (4 mol %), NEt_3, THF, rt	**38a**/H/H/54
2	**32** and **19**	$Pd(PPh_3)_2Cl_2$ (2 mol %); CuI (4 mol %), NEt_3, THF, rt	**38b**/H/OMe/39
3	**33** and **18**	$Pd(PPh_3)_2Cl_2$ (2 mol %); CuI (4 mol %), NEt_3, THF, rt	**38c**/OMe/H/32
4	**34** and **18**	$Pd(PPh_3)_2Cl_2$ (2 mol %); CuI (4 mol %), NEt_3, THF, rt	**38d**/CF_3/H/55
5	**32** and **18**	$Pd(PPh_3)_2Cl_2$ (2 mol %); CuI (4 mol %), NCy_2Me, THF, rt	**38a**/H/H/60
6	**32** and **19**	$Pd(PPh_3)_2Cl_2$ (2 mol %); CuI (4 mol %), NCy_2Me, THF, rt	**38b**/H/OMe/51
7	**33** and **18**	$Pd(PPh_3)_2Cl_2$ (2 mol %); CuI (4 mol %), NCy_2Me, THF, rt	**38c**/OMe/H/28
8	**34** and **18**	$Pd(PPh_3)_2Cl_2$ (2 mol %); CuI (4 mol %), NCy_2Me, THF, rt	**38d**/CF_3/H/29
9	**32** and **18**	$Pd(OAc)_2$ (1 mol %); NCy_2Me, 40 °C	**38a**/H/H/30
10	**34** and **18**	$Pd(OAc)_2$ (1 mol %), NCy_2Me, 40 °C	**38d**/CF_3/H/44

[a] Isolated yield of purified product.

Pyrimidopyridines **27**, **30**, **31**, and **38a–d** were isolated as single regioisomers, and their assignment was supported by an X-ray analysis of **38d** (Fig. 2). The regiochemical preference for substitution at C-8 can be explained by a destabilizing steric hindrance exerted between the pseudoaxial 4-aryl group and a *peri*-substituent at the 6-position.

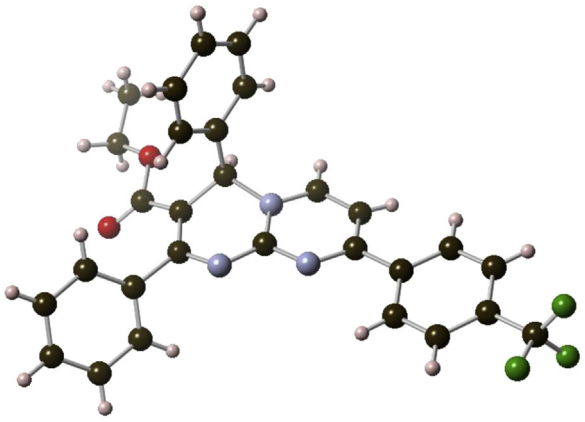


Fig. 2. X-ray structure of **38d** (CCDC 932463).

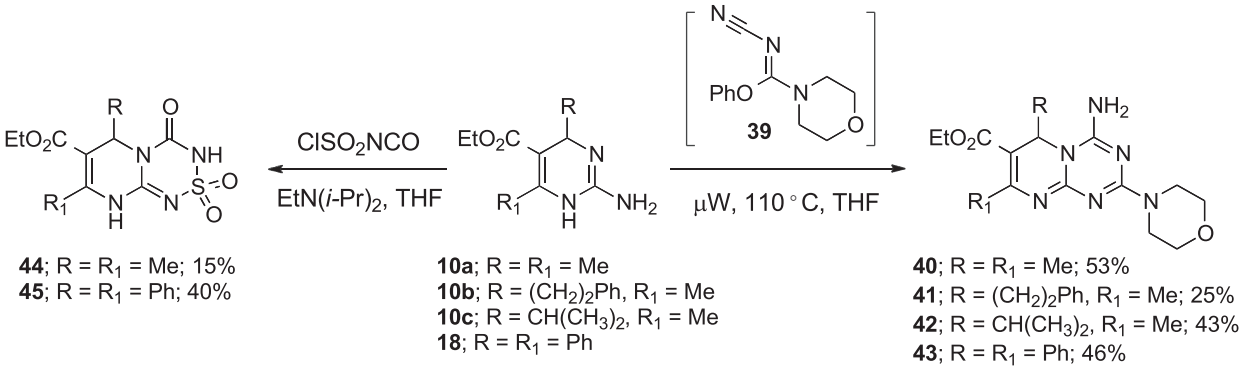
Starting with 2-aminopyrimidines **10a–c** and **18**, we were able to access two additional novel heterocyclic scaffolds, the 2-morpholino-6*H*-pyrimido[1,2-*a*][1,3,5]triazine-7-carboxylates **40–43**, and the 4-oxo-3,4,6,9-tetrahydropyrimido[2,1-*c*][1,2,4,6]thiatriazine-7-carboxylate 2,2-dioxides **44** and **45** (Scheme 8). Condensation of pyrimidines **10a–c** and **18** with in situ generated cyanoimine **39** furnished the pyrimidotriazines in 25–53% yield under microwave irradiation conditions. A similar transformation has been reported for the synthesis of aminotriazine-based anti-HIV agents.[29] Alternatively, treatment of **10a** and **18** with chlorosulfonyl isocyanate afforded the cyclic sulfamides **44** and **45** in 15% and 40% yield, respectively. We were able to obtain an X-ray structure of **44** that confirmed the assignment (Fig. 3).

Heterocycles **40–43** and **44–45** are representative examples for target scaffolds **4** and **5** shown in Scheme 1. We were also interested in further extending our conversions of 2-aminopyrimidines and guanidinoquinazolines to the structural variants **6** and **7**, which are only featured in very few reported examples in the literature.[30,31] In particular, we wanted to determine if aminopyrimidine **13**·**TFA** could be used as a substrate for a second Atwal–Biginelli condensation reaction. Although prolonged reaction times were required, we were pleased to find that the expected fused bicycle **46** was indeed formed as a 4:1 mixture of *anti*–*syn*-isomers in 57% yield (Scheme 9). The major *anti*-isomer was assigned based on literature precedence[30] as well as ab initio HF-6-311G* calculations (Fig. 4).[32] The latter provided a 5.8 kcal/mol gas-phase energy difference in favor of *anti*-**46**, suggesting that the reaction was not under complete thermodynamic control. Indeed, upon heating a sample of the product mixture for 26 h in the presence of deuterated acetic acid at 90 °C in DMSO-d_6, the signals characteristic for *syn*-**46** at 7.00–6.92 and 5.35 ppm disappeared in the ^{1}H NMR.

In an analogous synthetic sequence, guanidinoquinazolines **47a–d** were converted in moderate to high yields to the amine-linked pyrimidyl-quinazolines **49a–i** upon heating with **12** and **48a–d** in hexafluoroisopropanol (Scheme 10 and Table 4). The cyclocondensation worked particularly well for the morpholine-substituted enone **48d** (entry 8), whereas the yield for the dimethylamino-substituted enone **48a** was consistently low (entries 4 and 9). Quinazolines **47a–d** were prepared in a three-step sequence from the corresponding anilines.[33]

3. Conclusion

Cyclocondensations of heterocyclic guanidines with bis-electrophiles provide a rapid access to previously unexplored or sparsely documented heterocyclic scaffolds. Specifically, we were able to devise concise routes to new bipyrimidines, pyrimidoaminotriazines, pyrimidosulfonamides, pyrimidopyrimidines, and amine-linked pyrimidoquinazolines. Several



Scheme 8. Synthesis of 2-morpholino-6*H*-pyrimido[1,2-*a*][1,3,5]triazine-7-carboxylates **40**–**43** and 4-oxo-3,4,6,9-tetrahydropyrimido[2,1-*c*][1,2,4,6]thiatriazine-7-carboxylate 2,2-dioxides **44**–**45**.

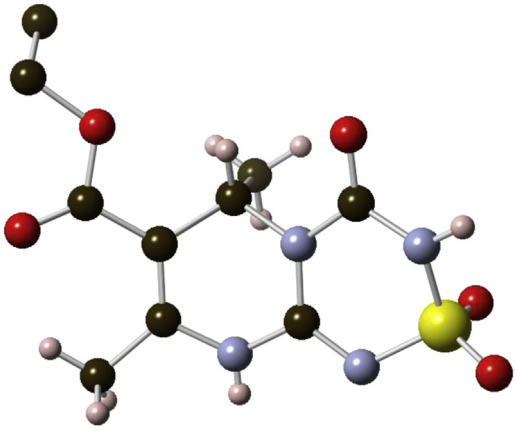


Fig. 3. X-ray structure of **44** (CCDC 935121). Due to static disorder in the ethyl ester group, the five ethyl hydrogen positions are uncertain and are therefore not shown.

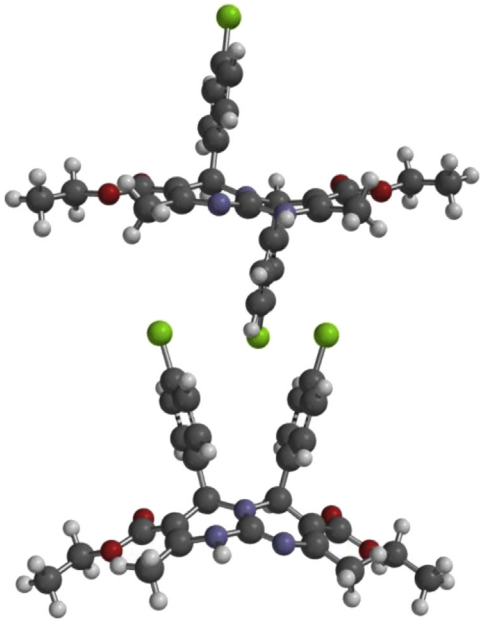


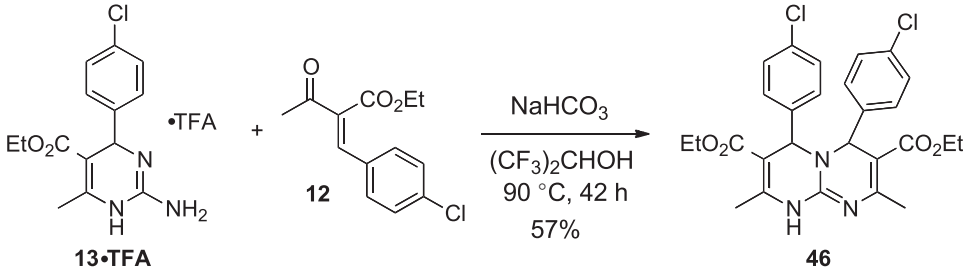
Fig. 4. HF-6-311G* structures of *anti*- (top) and *syn*- (bottom) **46**.

versatile methodologies were explored in this work: (a) a one-pot methylation/aminolysis sequence for the preparation of 2-aminodihydropyrimidine intermediates (Scheme 2); (b) an alternative Atwal–Biginelli cyclization of a PMB-protected guanidine for the construction of 2-aminodihydropyrimidines (Scheme 3); (c) a one-pot tandem Sonogashira coupling–alkynone cyclization to produce fused bipyrimidines (Scheme 7); (d) diverse cyclocondensation strategies, including consecutive Atwal–Biginelli reactions, to afford pyrimidopyrimidines, pyrimidotriazines, and pyrimidothiatriazines (Schemes 5, 8, and 9). Finally, quinazoline–dihydropyrimidine amines were prepared by extending Atwal–Biginelli conditions to quinazoline guanidines (Scheme 10). We are currently exploring the activity profile of these new heterocycles in a variety of biological screens.

4. Experimental section

4.1. General experimental procedures

All moisture-sensitive reactions were performed under an atmosphere of dry nitrogen and all glassware was either dried in an oven at 140 °C or flame dried under high vacuum prior to use. THF and Et_2O were dried by distillation over Na/benzophenone, and CH_2Cl_2 and toluene were purified using an alumina filtration system. Reactions were monitored by either ^1H NMR at 300 MHz in DMSO-



Scheme 9. A second Atwal–Biginelli cyclocondensation reaction converts 2-aminopyrimidine **13**·**TFA** into pyrimidopyrimidine **46**.

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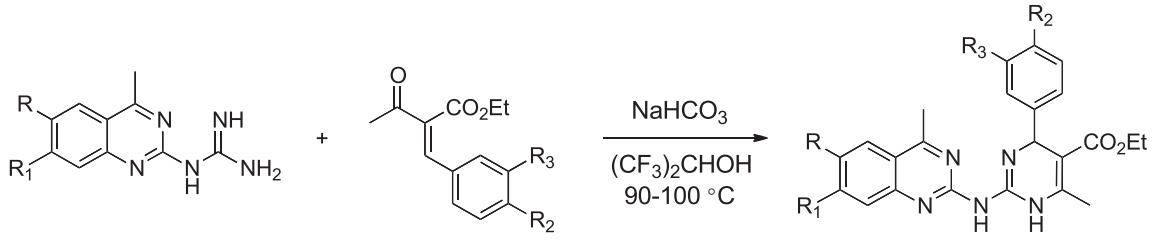

47a; R = Cl, R_1 = H
47b; R = Me, R_1 = H
47c; R = F, R_1 = H
47d; R, R_1 = OCH_2O

12; R_2 = Cl, R_3 = H
48a; R_2 = NMe_2, R_3 = H
48b; R_2 = H, R_3 = NO_2
48c; R_2 = Br, R_3 = H
48d; R_2 = N($(CH_2CH_2)_2O$), R_3 = H

49a-i

Scheme 10. Atwal–Biginelli cyclocondensation reactions with guanidine–quinazolines **47a–d**.

Table 4
Atwal–Biginelli reactions according to Scheme 10

Entry	Reactants	Substituents $R/R_1/R_2/R_3$	Product/yield[a] %
1	**47a** and **12**	Cl/H/Cl/H	**49a**/56
2	**47b** and **12**	Me/H/Cl/H	**49b**/62
3	**47c** and **12**	F/H/Cl/H	**49c**/52
4	**47c** and **48a**	F/H/NMe_2/H	**49d**/40
5	**47b** and **48b**	Me/H/H/NO_2	**49e**/67
6	**47d** and **12**	$-OCH_2O-$/Cl/H	**49f**/41
7	**47d** and **48c**	$-OCH_2O-$/Br/H	**49g**/57
8	**47d** and **48d**	$-OCH_2O-$/N($(CH_2CH_2)_2O$)/H	**49h**/81
9	**47d** and **48a**	$-OCH_2O-$/NMe_2/H	**49i**/45

[a] Isolated yield of purified product.

d_6, high resolution LC/MS (Thermo Scientific Exactive spectrometer), or TLC analysis (EM Science pre-coated silica gel 60 F_{254} plates). Visualization of TLCs was accomplished with a 254 nm UV light and by staining with a *p*-anisaldehyde solution (2.5 mL of *p*-anisaldehyde, 2 mL of AcOH, and 3.5 mL of concd H_2SO_4 in 100 mL of 95% EtOH) or a $KMnO_4$ solution (1.5 g of $KMnO_4$ and 1.5 g of K_2CO_3 in 100 mL of a 0.1% NaOH solution). Flash chromatography was performed on 40–63 μm silica gel (Silicycle) or on a Teledyne ISCO CombiFlash R_f. Melting points were determined using a Laboratory Devices Mel-Temp II and are not corrected. Infrared spectra were obtained on either a Nicolet Avatar 360, a Smiths Detection IdentifyIR FT-IR spectrometer, or Perkin Elmer ATR IR. Mass spectra were obtained on either a Micromass Autospec double focusing instrument or High Res LC/MS instrument (Thermo Scientific Exactive spectrometer). Purities were determined using an Agilent Technologies 385-ELSD. Microwave reactions were performed in a Biotage Initiator 2.0 Microwave reactor. ^1H and ^{13}C NMR spectra were obtained on a Bruker Avance 300, 400, 500, or 700 MHz instrument at room temperature unless otherwise noted. Chemical shifts (δ) are reported in parts per million (ppm) with the residual solvent peak used as an internal standard ($CHCl_3$ δ 7.26 ppm for ^1H and 77.00 ppm for ^{13}C, DMSO δ 2.50 ppm for ^1H and 40.45 ppm for ^{13}C). ^1H NMR spectra are tabulated as follows: chemical shift, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad), integration, and coupling constant(s) (J) in Hertz (Hz). ^{13}C NMR spectra were recorded using a proton-decoupled pulse sequence with a d_1 of 5 s, and are tabulated by the chemical shifts of the observed peaks. X-ray crystallographic data for **38d** (deposition number CCDC 932463) and **44** (CCDC 935121) were deposited with the Cambridge Crystallographic Data Center.

4.2. Ethyl 4,6-dimethyl-2-thioxo-1,3,6-trihydropyrimidine-5-carboxylate (8a).[20] General procedure A

A suspension of ethyl 3-oxobutanoate (2.50 mL, 19.7 mmol), thiourea (2.20 g, 28.9 mmol), ethanal (1.10 mL, 19.7 mmol), and benzyltriethylammonium chloride (0.386 g, 1.97 mmol) was heated in a sealed tube at 75 °C for 15 min. The reaction mixture turned light yellow in color and was heated at 100–105 °C for 20 h, allowed to cool to room temperature, diluted with water (20 mL), and stirred for 1 h. The resulting solid residue was isolated by vacuum filtration, washed with water (70 mL), recrystallized from boiling EtOH/H_2O (3:1, 50 mL), washed with EtOH/H_2O (1:1), followed by water, and dried in vacuo to afford **8a** (1.81 g, 43%) as pale yellow crystals: ^1H NMR (300 MHz, DMSO-d_6) δ 10.12 (s, 1H), 9.19 (s, 1H), 4.15–4.03 (m, 3H), 2.19 (s, 3H), 1.19 (t, 3H, J=6.9 Hz), 1.09 (d, 3H, J=6.3 Hz). The spectral data are consistent with the literature values.[20]

4.3. Ethyl 4-methyl-6-(2-phenylethyl)-2-thioxo-1,3,6-trihydropyrimidine-5-carboxylate (8b)[34]

According to general procedure A, a suspension of thiourea (1.72 g, 22.4 mmol), benzyltriethylammonium chloride (0.29 g, 1.50 mmol), hydrocinnamaldehyde (2.08 mL, 15.0 mmol), and ethyl 3-oxobutanoate (2.50 mL, 15.0 mmol) was heated at 120 °C for 3 h. The viscous orange reaction mixture was allowed to cool to room temperature, diluted with EtOAc (150 mL), and washed with water (3×100 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude light orange residue was recrystallized from hexanes/EtOAc (2:1), isolated by vacuum filtration, washed with hexanes, and dried in vacuo to afford **8b** as a pale yellow solid (2.24 g, 49%, ~90% pure): ^1H NMR (300 MHz, DMSO-d_6) 10.19 (s, 1H), 9.45 (s, 1H), 7.30–7.18 (m, 5H), 4.18–4.16 (m, 1H), 4.07–4.02 (m, 2H), 2.63–2.51 (m, 2H), 2.22 (s, 3H), 1.78–1.66 (m, 2H), 1.13 (t, 3H, J=7.2 Hz). The spectral data are consistent with the literature values.[34]

4.4. Ethyl 4-methyl-6-(methylethyl)-2-thioxo-1,3,6-trihydropyrimidine-5-carboxylate (8c)[20]

According to general procedure A, a suspension of thiourea (2.75 g, 35.9 mmol), citric acid (2.30 g, 12.0 mmol), isobutyraldehyde (2.22 mL, 23.9 mmol), and ethyl 3-oxobutanoate (4.0 mL, 23.2 mmol) was heated at 120 °C for 15 h. The viscous yellow/orange reaction mixture was allowed to cool to room temperature, diluted with EtOAc (300 mL), and washed with water (3×200 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The resulting light orange residue was slowly triturated with EtOAc (30 mL) and hexanes (60 mL) at room temperature. The suspension was cooled to −20 °C for 24 h and the resulting off-white precipitate was isolated by vacuum filtration, washed with hexanes/EtOAc (3:1, 100 mL), followed by hexanes (30 mL), and dried in vacuo to afford **8c** as an off-white solid (2.13 g, 33%, ~90% pure): ^1H NMR (300 MHz, DMSO-d_6)

10.09 (s, 1H), 9.23 (s, 1H), 4.15–4.02 (m, 2H), 4.00–3.97 (m, 1H), 2.23 (s, 3H), 1.71–1.65 (m, 1H), 1.20 (t, 3H, J=7.2 Hz), 0.82 (d, 3H, J=6.0 Hz), 0.76 (d, 3H, J=6.0 Hz). The spectral data are consistent with the literature values.[20]

4.5. Ethyl 2-amino-4,6-dimethyl-1,4-dihydropyrimidine-5-carboxylate (10a). General procedure B

To a light yellow suspension of **8a** (1.50 g, 7.00 mmol) in chlorobenzene (40 mL) at 0 °C was added methyl trifluoromethanesulfonate (0.91 mL, 7.7 mmol) in one portion. The reaction mixture was allowed to warm to room temperature and stirred for 3.5 h. Ammonium acetate (5.4 g, 70 mmol) was added and ammonia gas was bubbled through the cold (0 °C) reaction mixture for 10 min. The reaction tube was sealed and heated at 95–100 °C for 17 h. The reaction mixture was cooled to room temperature, diluted with saturated Na_2CO_3 (250 mL) and water (250 mL), extracted with EtOAc (3×400 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude residue was recrystallized from hexanes/EtOAc (1:1, 150 mL), isolated by vacuum filtration, washed with hexanes, and dried in vacuo to afford **10a** as a colorless solid (0.84 g, 61%, ELSD purity 97.3%): mp 196–198 °C; IR (ATR) 3390, 3303, 3088, 2975, 1661, 1584, 1493, 1370, 1329, 1303, 1226, 1154, 1092, 1066 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 6.81 (br s, 1H), 6.12 (br s, 2H), 4.18 (q, 1H, J=6.3 Hz), 4.05–3.95 (m, 2H), 2.10 (s, 3H), 1.16 (t, 3H, J=7.2 Hz), 0.97 (d, 3H, J=6.3 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 166.5, 160.8, 156.0, 98.6, 58.4, 45.5, 23.9, 15.0; HRMS (TOF ES$^+$) m/z calcd for $C_9H_{16}N_3O_2$ 198.1243, found 198.1242.

4.6. Ethyl 2-amino-6-methyl-4-(2-phenethyl)-1,4-dihydropyrimidine-5-carboxylate (10b)

According to general procedure B, a mixture of **8b** (2.50 g, 8.21 mmol) and methyl trifluoromethanesulfonate (1.1 mL, 9.0 mmol) in chlorobenzene (80 mL) was treated with ammonium acetate (6.3 g, 82 mmol) and ammonia gas to give the crude product, which was dissolved in CH_2Cl_2 (20 mL) and triturated with hexanes to yield a tan oil. This oil was isolated by decantation and again dissolved in CH_2Cl_2 (20 mL), triturated with hexanes (30 mL), and cooled to −20 °C to afford **10b** as a pale yellow solid (0.92 g, 39%, ELSD purity 97.3%): mp 129–134 °C; IR (ATR) 3390, 3348, 2975, 1650, 1584, 1465, 1374, 1238, 1172, 1206, 1146, 1077, 1029 cm^{-1}; ^1H NMR (300 MHz; DMSO-d_6) δ 7.29–7.15 (m, 6H), 6.87 (br s, 2H), 4.14 (m, 1H), 3.98–3.88 (m, 2H), 2.71–2.59 (m, 1H), 2.54–2.44 (m, 1H), 2.13 (s, 3H), 1.66–1.56 (m, 2H), 1.10 (t, 3H, J=6.9 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 165.8, 158.9, 155.1, 141.7, 128.3 (2C), 128.2 (2C), 125.6, 97.8, 58.2, 48.5, 38.2, 29.7, 22.6, 14.4; HRMS (TOF ES$^+$) m/z calcd for $C_{16}H_{22}N_3O_2$ 288.1712, found 288.1720.

4.7. Ethyl 2-amino-4-(methylethyl)-6-methyl-1,4-dihydropyrimidine-5-carboxylate (10c)

According to general procedure B, a mixture of **8c** (1.80 g, 7.42 mmol) and methyl trifluoromethanesulfonate (0.96 mL, 8.2 mmol) in chlorobenzene (70 mL) was treated with ammonium acetate (6.0 g, 78 mmol) and ammonia gas to give the crude product, which was purified by chromatography through a plug of SiO_2 (EtOAc–EtOH). The product slowly eluted with EtOH and was recrystallized from boiling CH_2Cl_2/hexanes (1:1, 40 mL) to afford **10c** as a white crystalline solid (0.581 g, 33%, ELSD purity 100.0%): mp 171–173 °C; IR (ATR) 3497, 3353, 2951, 2869, 1653, 1596, 1489, 1377, 1225, 1154, 1068, 995, 816 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 6.87 (br s, 1H), 6.07 (br s, 2H), 4.04–3.92 (m, 3H), 2.12 (s, 3H), 1.61–1.54 (m, 1H), 1.15 (t, 3H, J=7.2 Hz), 0.78 (d, 3H, J=6.9 Hz), 0.71 (d, 3H, J=6.9 Hz); ^{13}C NMR (75 MHz; DMSO-d_6) δ 166.5, 161.1, 156.2, 95.7, 57.9, 54.4, 34.6, 23.5, 18.1, 15.9, 14.4; HRMS (TOF ES$^+$) m/z calcd for $C_{11}H_{20}N_3O_2$ 226.1556, found 226.1569.

4.8. Ethyl 2-imino-4,6-dimethyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate hydrochloride (10a·HCl). General procedure C

To a suspension of **10a** (0.500 g, 2.54 mmol) in MeOH (5.0 mL) was added a solution of HCl in dioxane (1.5 mL, 3.0 mmol, 2.0 M) dropwise at room temperature. After 10 min, the solution was clear and the solvents were removed under reduced pressure. The resulting oil was triturated with ether (2×10 mL), isolated by vacuum filtration, and dried in vacuo to afford **10a·HCl** as a colorless foam (0.54 g, 91%): IR (ATR) 3361, 3236, 3055, 2975, 2869, 1681, 1551, 1241, 1096, 1070 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 10.90 (s, 1H), 9.06 (s, 1H), 7.89 (br s, 2H), 4.38–4.36 (m, 1H), 4.19–4.08 (m, 2H), 2.26 (s, 3H), 1.22 (t, 3H, J=7.2 Hz), 1.16 (d, 3H, J=6.3 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 164.9, 151.8, 144.1, 104.5, 60.5, 45.4, 22.9, 17.9, 14.6. For additional characterization data, see **10a**.

4.9. Ethyl 2-imino-6-methyl-4-(2-phenethyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate hydrochloride (10b·HCl)

According to general procedure C, **10b** (0.150 g, 0.522 mmol) was combined with a solution of HCl in ether (0.31 mL, 0.63 mmol, 2.0 M) and MeOH (1.0 mL) at room temperature to afford **10b·HCl** as a pale yellow solid (0.143 g, 85%): ^1H NMR (300 MHz, DMSO-d_6) δ 10.59 (br s, 1H), 9.18 (br s, 1H), 7.76 (br s, 2H), 7.31–7.16 (m, 5H), 4.33–4.30 (m, 1H), 4.14–4.02 (m, 2H), 2.73–2.49 (m, 2H), 2.26 (s, 3H), 1.78–1.09 (m, 2H), 1.15 (t, 3H, J=6.9 Hz). For additional characterization data, see **10b**.

4.10. Ethyl 2-imino-4-(methylethyl)-6-methyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate hydrochloride (10c·HCl)

According to general procedure C, **10c** (0.150 g, 0.666 mmol) was combined with a solution of HCl in ether (0.40 mL, 0.80 mmol, 2.0 M) in MeOH (1.5 mL) at room temperature to afford **10c·HCl** as a pale yellow solid (0.121 g, 69%): ^1H NMR (300 MHz, DMSO-d_6) δ 10.77 (br s, 1H), 9.14 (br s, 1H), 7.84 (br s, 2H), 4.19–4.07 (m, 3H), 2.28 (s, 3H), 1.78–1.72 (m, 1H), 1.21 (t, 3H, J=7.2 Hz), 0.87 (d, 3H, J=6.9 Hz), 0.77 (d, 3H, J=6.9 Hz). For additional characterization data, see **10c**.

4.11. 1-(4-(4-Chlorophenyl)-2-(4-methoxybenzylamino)-6-methyl-1,4-dihydropyrimidin-5yl)butan-1-one (13). General procedure D

A microwave vial was charged with **11**[23] (0.63 g, 2.8 mmol) and $(CF_3)_2CHOH$ (5.0 mL). To this homogeneous solution was added **12**[36,37] (1.4 g, 5.5 mmol) and $NaHCO_3$ (0.26 g, 3.0 mmol). The vial was sealed and immersed into a pre-heated oil bath at 90 °C and heated for 16 h. The solution was allowed to cool to room temperature, filtered through a small plug of Celite, and rinsed with CH_2Cl_2. The filtrate was concentrated under reduced pressure and purified by chromatography on SiO_2 (ISCO-R_f, 0–10%MeOH/CH_2Cl_2) to afford **13** as an orange crystalline solid (0.485 g, 42%, ELSD purity 99.7%): mp 60–64 °C; IR (neat) 3311, 2929, 2830, 1661, 1574, 1512, 1212, 1088, 818 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.22–7.11 (m, 6H), 6.78 (d, 2H, J=8.4 Hz), 5.29 (s, 1H), 4.33 (d, 1H, J=15.3 Hz), 4.25 (d, 1H, J=15.0 Hz), 4.03 (q, 2H, J=7.2 Hz), 3.78 (s, 3H), 2.38 (s, 3H), 1.14 (t, 3H, J=7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 159.2, 153.0, 143.2, 133.2 (2C), 128.9, 128.6 (2C), 128.3 (2C), 127.9 (2C), 114.2 (2C), 100.0, 59.5, 55.2, 53.7, 44.6, 22.4, 14.2; HRMS (ESI$^+$) m/z calcd for $C_{22}H_{25}O_3N_3Cl$ (M+H) 414.1579, found 414.1562.

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4.12. Ethyl 2-amino-4-(4-chlorophenyl)-6-methyl-1,4-dihydroprimidine-5-carboxylate 2,2,2-trifluoroacetate (13·TFA)

A solution of **13** (0.420 g, 1.01 mmol) in a mixture of TFA/Et_3SiH/thioanisole/H_2O (92.5:2.5:2.5:2.5, 23 mL) was stirred at 50 °C for 22 h, allowed to cool to room temperature, and concentrated under reduced pressure. The crude orange residue was purified by trituration with *tert*-butyl methyl ether, isolated by vacuum filtration, and dried in vacuo to give trifluoroacetate salt **13·TFA** (0.29 g, 70%, ELSD purity 99.9%) as a white solid: mp 207–218 °C (dec); IR (neat) 3241, 3205, 3084, 2963, 2901, 1709, 1666, 1239, 1200, 1186, 1139, 1096, 848, 828, 800, 771, 726 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$:MeOD, 1:1) δ 7.03 (d, 2H, J=8.4 Hz), 6.94 (d, 2H, J=8.4 Hz), 5.14 (s, 1H), 3.80 (q, 2H, J=7.2 Hz), 2.13 (s, 3H), 0.87 (t, 3H, J=7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$:MeOD, 1:1) δ 164.0, 150.3, 143.1, 139.7, 133.7, 128.3 (2C), 127.5 (2C), 103.1, 60.1, 52.1, 16.4, 12.8; HRMS (EI^+) m/z calcd for $C_{14}H_{17}O_2N_3Cl$ (M+H) 294.1004, found 294.0999.

4.13. Ethyl 2-amino-4,6-diphenyl-1,4-dihydropyrimidine-5-carboxylate (18).[30] General procedure E

To a solution of benzaldehyde (**16**, 2.0 mL, 20 mmol), urea **14·HCl** (3.32 g, 35.0 mmol), and $NaHCO_3$ (6.72 g, 80.0 mmol) in DMF (40 mL) was added ethyl 3-oxo-3-phenylpropanoate (**15**, 3.80 mL, 22.5 mmol) at room temperature. The reaction mixture was heated to 70 °C for 17 h, cooled to room temperature, and slowly diluted with water (100 mL). The aqueous mixture was stirred at room temperature for 1 h and the resulting solid was separated by decanting and vacuum filtration. The crude product was purified by heating in hexanes/EtOAc (1:1, 100 mL) for 30 min, separated by vacuum filtration, and dried in vacuo to afford **18** as a white solid (3.35 g, 52%): ^1H NMR (300 MHz, DMSO-d_6) δ 7.48 (s, 1H), 7.39–7.31 (m, 4H), 7.27–7.21 (m, 6H), 6.29 (s, 2H), 5.30 (s, 1H), 3.67 (q, 2H, J=7.2 Hz), 0.73 (t, 3H, J=7.2 Hz); MS (EI^+) m/z 321 (M^+, 43), 292 (38), 274 (32), 248 (52), 244 (100), 104 (37), 76 (42); HRMS (EI^+) m/z calcd for $C_{19}H_{19}N_3O_4$ 321.1477, found 321.1476. The spectral data are consistent with the literature values.[18]

4.14. Ethyl 2-imino-4,6-diphenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate hydrochloride (18·HCl)

According to general procedure C, **18** (1.28 g, 3.97 mmol) and a solution of HCl in dioxane (1.25 mL, 5.00 mmol, 4.0 M) and methanol (5.0 mL) afforded **18·HCl** as a white crystalline solid (1.42 g, 99%): ^1H NMR (300 MHz, DMSO-d_6) δ 10.86 (s, 1H), 9.75 (s, 1H), 8.09 (br s, 2H), 7.51–7.33 (m, 10H), 5.55 (d, 1H, J=3.6 Hz), 3.78 (q, 2H, J=6.9 Hz), 0.74 (t, 3H, J=6.9 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 164.6, 151.7, 144.6, 142.2, 133.7, 130.3, 129.4 (2C), 129.1 (2C), 128.8, 128.6 (2C), 127.1 (2C), 104.2, 60.4, 52.8, 13.7. For additional characterization data, see **18**.

4.15. Ethyl 2-amino-4-(3,4-dimethoxyphenyl)-6-phenyl-1,4-dihydropyrimidine-5-carboxylate (19)

According to general procedure E, ethyl 3-oxo-3-phenylpropanoate (**15**, 3.80 mL, 22.5 mmol), 3,4-dimethoxybenzaldehyde (**17**, 3.32 g, 20.0 mmol), urea **14·HCl** (2.31 g, 24.0 mmol), and $NaHCO_3$ (6.33 g, 75.4 mmol) in DMF (40 mL) provided the crude product, which was recrystallized from EtOAc/hexanes (2:1, 150 mL), isolated by vacuum filtration, washed with hexanes (50 mL), and dried in vacuo to afford **19** as a white crystalline solid (3.11 g, 41%, ELSD purity 100.0%): mp 261–263 °C (dec); IR (ATR) 3403, 3340, 2974, 1655, 1627, 1565, 1372, 1232, 1135, 1100, 1027 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 7.44 (s, 1H), 7.25–7.21 (m, 5H), 6.98 (s, 1H), 6.93–6.86 (m, 2H), 6.28 (br s, 2H), 5.23 (s, 1H), 3.72 (s, 6H), 3.67 (q, 2H, J=7.2 Hz), 0.75 (t, 3H, J=7.2 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 166.7, 161.6, 155.9, 149.0, 148.4, 143.2, 139.3, 128.5 (2C), 127.4, 127.3 (2C), 118.7, 112.2, 110.8, 98.0, 58.5, 56.0, 55.8, 52.9, 14.2; MS (EI^+) m/z 381 (M^+, 36), 352 (31), 308 (86), 244 (100), 198 (35), 77 (56); HRMS (EI^+) m/z calcd for $C_{21}H_{23}N_3O_4$ 381.1688, found 381.1687.

4.16. Ethyl 2,4-dimethyl-4*H*-pyrimido[1,2-*a*]pyrimidine-3-carboxylate (22). General procedure F

A suspension of **10a·HCl** (0.100 g, 0.428 mmol) and 1,1,3,3-tetramethoxypropane (**20**, 0.09 mL, 0.5 mmol) in trifluoroethanol (**21**, 1.5 mL) was heated in a microwave reactor at 160 °C for 1 h. The resulting mixture was dissolved in EtOAc (50 mL), washed with saturated sodium carbonate (50 mL), and extracted with EtOAc (2×50 mL). The organic layers were combined, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The resulting red/orange oil was purified via chromatography on neutral Al_2O_3 (0–2% MeOH/CH_2Cl_2) to afford **22** as a red/orange solid (0.076 g, 76%): mp 151–152 °C; IR (ATR) 3076, 2970, 1657, 1622, 1585, 1491, 1437, 1396, 1273, 1245, 1206, 1109, 1070, 990 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 8.51 (dd, 1H, J=2.4, 1.8 Hz), 8.24 (dd, 1H, J=2.1, 6.3 Hz), 6.70 (dd, 1H, J=3.9, 6.3 Hz), 5.26 (q, 1H, J=6.6 Hz), 4.18–4.03 (m, 2H), 2.25 (s, 3H), 1.23 (t, 3H, J=7.2 Hz), 1.16 (d, 3H, J=6.6 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 165.1, 163.4, 157.6, 151.5, 147.2, 110.3, 100.3, 59.5, 56.8, 23.4, 22.2, 14.8; HRMS (EI^+) m/z calcd for $C_{12}H_{16}N_3O_2$ 234.1243, found 234.1243.

4.17. Ethyl 2-methyl-4-phenethyl-4*H*-pyrimido[1,2-*a*]pyrimidine-3-carboxylate (23)

According to general procedure F, a mixture of **10b·HCl** (0.138 g, 0.426 mmol) and 1,1,3,3-tetramethoxypropane (**20**, 0.09 mL, 0.5 mmol) in trifluoroethanol (**21**, 2.0 mL) was heated in a microwave reactor at 160 °C for 2 h. The crude red/orange oil was purified by chromatography on neutral Al_2O_3 (EtOAc to 5% MeOH/CH_2Cl_2) to afford **23** as a yellow/brown oil (0.098 g, 71%, ELSD purity 99.5%): IR (ATR) 2981, 2925, 1665, 1618, 1579, 1491, 1430, 1393, 1275, 1238, 1202, 1096, 1063, 774, 697 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 8.52 (dd, 1H, J=3.9, 2.1 Hz), 8.18 (dd, 1H, J=6.6, 2.1 Hz), 7.26–7.08 (m, 5H), 6.70 (dd, 1H, J=3.9, 6.3 Hz), 5.21 (t, 1H, J=5.1 Hz), 4.20–4.07 (m, 2H), 2.46–2.37 (m, 2H), 2.28 (s, 3H), 1.86–1.76 (m, 2H), 1.19 (t, 3H, J=7.2 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 164.7, 162.6, 158.0, 151.3, 147.0, 140.5, 128.4 (2C), 128.0 (2C), 125.9, 109.2, 99.0, 59.8, 59.1, 36.3, 30.3, 23.1, 14.4; HRMS (TOF ESI^+) m/z calcd for $C_{19}H_{22}N_3O_2$ 324.1712, found 324.1707.

4.18. Ethyl 4-isopropyl-2-methyl-4*H*-pyrimido[1,2-*a*]pyrimidine-3-carboxylate (24)

According to general procedure F, a mixture of **10c·HCl** (0.113 g, 0.432 mmol) and 1,1,3,3-tetramethoxypropane (**20**, 0.076 mL, 0.45 mmol) in trifluoroethanol (**21**, 1.5 mL) was heated in a microwave reactor at 160 °C for 2 h. The crude red/orange oil was purified by chromatography on neutral Al_2O_3 (0–2% MeOH/CH_2Cl_2) to afford **24** as a dark red oil (0.080 g, 71%, ELSD purity 98.4%): IR (ATR) 3064, 2964, 1670, 1620, 1579, 1491, 1432, 1378, 1294, 1234, 1204, 1094, 1063, 999, 774 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.52 (dd, 1H, J=4.0, 2.4 Hz), 8.21 (dd, 1H, J=6.4, 2.0 Hz), 6.70 (dd, 1H, J=6.4, 4.0 Hz), 4.94 (d, 1H, J=6.4 Hz), 4.18–4.04 (m, 2H), 2.28 (s, 3H), 1.79–1.74 (m, 1H), 1.22 (t, 3H, J=7.2 Hz), 0.77 (d, 3H, J=6.8 Hz), 0.63 (d, 3H, J=6.8 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.4, 162.3, 157.6, 151.5, 147.4, 108.7, 98.3, 64.6, 59.0, 34.1, 23.1, 18.0, 17.4, 14.4; HRMS (TOF ESI^+) m/z calcd for $C_{14}H_{20}N_3O_2$ 262.1556, found 262.1558.

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4.19. Ethyl 2,4-diphenyl-4*H*-pyrimido[1,2-*a*]pyrimidine-3-carboxylate (25)

According to general procedure F, a solution of **18·HCl** (0.100 g, 0.311 mmol) and 1,1,3,3-tetramethoxypropane (**20**, 0.055 mL, 0.33 mmol) in trifluoroethanol (**21**, 1.5 mL) was heated in a microwave reactor at 150 °C for 1.5 h. The crude red/orange oil was purified by chromatography on SiO_2 (EtOAc) to afford **25** as a red/orange solid containing ~5–6% EtOAc (0.047 g, 42%, ELSD purity 100.0%): mp 185–186.5 °C; IR (ATR) 3070, 2982, 2869, 1694, 1612, 1689, 1558, 1493, 1476, 1441, 1277, 1232, 1189, 1074 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.55–8.54 (m, 2H), 7.42–7.30 (m, 10H), 6.78 (dd, 1H, J=4.8. 5.6 Hz), 6.45 (s, 1H), 3.80 (q, 2H, J=7.2 Hz), 0.80 (t, 3H, J=7.2 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.6, 163.5, 158.5, 151.7, 147.5, 141.5, 141.2, 129.5 (2C), 129.1 (2C), 128.5, 127.7 (2C), 126.7 (2C), 110.7, 98.7, 63.1, 59.6, 14.0; HRMS (TOF ESI$^+$) m/z calcd for $C_{22}H_{20}N_3O_2$ 358.1556, found 358.1556.

4.20. Ethyl 8-methyl-2,4-diphenyl-4*H*-pyrimido[1,2-*a*]pyrimidine-3-carboxylate (27)

A suspension of **18** (0.161 g, 0.500 mmol) and **26** (0.051 mL, 0.500 mmol) in distilled THF (1.0 mL) was heated in a microwave reactor for 15 min at 150 °C. The crude reaction mixture was recrystallized from hexanes/EtOAc (4:1, 20 mL), isolated by vacuum filtration, washed with hexanes, and dried in vacuo to afford **27** as a yellow-orange solid (0.12 g, 64%, ELSD purity 99.5%): mp 185–187 °C; IR (ATR) 3068, 2969, 1705, 1625, 1511, 1448, 1241, 1196, 1085 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 8.38 (d, 1H, J=6.9 Hz), 7.42–7.32 (m, 10H), 6.72 (d, 1H, J=6.6 Hz), 6.38 (s, 1H), 3.79 (q, 2H, J=7.2 Hz), 2.32 (s, 3H), 0.79 (t, 3H, J=7.2 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 173.3, 165.7, 159.1, 151.4, 146.2, 141.8, 141.4, 129.4 (2C), 129.1, 129.0 (2C), 128.5, 127.6 (2C), 126.7 (2C), 111.2, 98.1, 62.8, 59.5, 25.1, 14.0; MS (EI$^+$) m/z 371 (M$^+$, 43), 342 (51), 298 (100), 278 (63), 93 (69), 66 (52); HRMS (EI$^+$) m/z calcd for $C_{23}H_{21}N_3O_2$ 371.1634, found 371.1618.

4.21. Ethyl 8-(1*H*-indol-2-yl)-2,4-diphenyl-4*H*-pyrimido[1,2-*a*]pyrimidine-3-carboxylate (30). General procedure G

A suspension of **18·HCl** (0.150 g, 0.419 mmol), **28** (0.111 g, 0.461 mmol), sodium carbonate (0.067 g, 0.63 mmol), and DMAP (0.013 g, 0.10 mmol) in MeOH (0.34 mL, 8.4 mmol) and acetonitrile (2.5 mL) was heated in a microwave reactor at 170 °C for 30 min. The dark red/orange reaction mixture was concentrated under reduced pressure and purified by chromatography on SiO_2 (1:1, EtOAc/hexanes). The resulting product was recrystallized from boiling hexanes/EtOAc (6:1), isolated by vacuum filtration, washed with hexanes, and dried under high vacuum to afford **30** as a red solid (0.050 g, 25%, ELSD purity 99.6%): mp 170–172 °C; IR (ATR) 3202, 3057, 2975, 1666, 1610, 1472, 1435, 1277, 1251, 1221, 1195, 1092, 753 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 12.01 (s, 1H), 8.49 (d, 1H, J=6.8 Hz), 7.63 (d, 1H, J=8.0 Hz), 7.50–7.32 (m, 13H), 7.22 (t, 1H, J=7.2 Hz), 7.05 (t, 1H, J=7.2 Hz), 6.42 (s, 1H), 3.83 (q, 2H, J=7.2 Hz), 0.83 (t, 3H, J=7.2 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.3, 160.2, 158.7, 151.3, 146.2, 141.5, 140.8, 138.6, 133.7, 129.0 (2C), 128.8 (2C), 128.5, 128.1, 127.7, 127.1 (2C), 126.2 (2C), 124.9, 121.7, 120.2, 112.7, 108.1, 106.6, 97.8, 62.2, 59.0, 13.6; HRMS (TOF ES$^+$) m/z calcd for $C_{30}H_{25}N_4O_2$ 473.1978, found 473.1993.

4.22. Ethyl 8-(benzofuran-2-yl)-2,4-diphenyl-4*H*-pyrimido[1,2-*a*]pyrimidine-3-carboxylate (31)

According to general procedure G, a suspension of **18·HCl** (0.150 g, 0.419 mmol), **29** (0.112 g, 0.461 mmol), sodium carbonate (0.067 g, 0.63 mmol), and DMAP (0.013 g, 0.10 mmol) in MeOH (0.34 mL, 8.4 mmol) and acetonitrile (2.5 mL) provided a crude product, which was purified by chromatography on SiO_2 (1:1, EtOAc/hexanes). The resulting product was recrystallized (1:15, EtOAc/hexanes, 16 mL), isolated by vacuum filtration, washed with hexanes (5 mL), and dried in vacuo to afford **31** as a red/orange solid containing ~5% EtOAc (0.044 g, 22%, ELSD purity 99.1%): mp 195–196 °C; IR (ATR) 3064, 2975, 1614, 1586, 1504, 1474, 1446, 1430, 1374, 1305, 1281, 1247, 1224, 1206, 1165, 1146, 1092, 761 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 8.68 (d, 1H, J=6.6 Hz), 7.98 (s, 1H), 7.82 (d, 1H, J=7.8 Hz), 7.71 (d, 1H, J=8.4 Hz), 7.53–7.33 (m, 13H), 6.51 (s, 1H), 3.83 (q, 2H, J=6.9 Hz), 0.82 (t, 3H, J=6.9 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 165.5, 159.0, 157.6, 156.1, 151.7, 151.2, 148.3, 141.3, 140.3, 129.6 (2C), 129.2 (3C), 128.8, 128.4, 128.1, 127.8 (2C), 126.9 (2C), 124.6, 123.6, 113.0, 112.4, 107.2, 99.3, 63.0, 59.8, 14.0; HRMS (TOF ES$^+$) m/z calcd for $C_{30}H_{24}N_3O_3$ 474.1818, found 474.1802.

4.23. 1-Phenyl-3-(trimethylsilyl)prop-2-yn-1-one (35)[27,35]

To a suspension of bis(triphenylphosphine)palladium(II) chloride (0.035 g, 0.050 mmol) and copper iodide (0.019 g, 0.10 mmol) in freshly distilled THF (10 mL) were added sequentially Et_3N (0.35 mL, 2.5 mmol), benzoyl chloride (0.29 mL, 2.5 mmol), and TMS-acetylene (0.35 mL, 2.5 mmol). The reaction mixture turned from dark orange to pale yellow forming the $Et_3N·HCl$ precipitate over a 1 h period. TLC analysis (10:1, hexanes/EtOAc, product R_f=0.59) showed full conversion after 1 h. The $Et_3N·HCl$ salt was filtered off and the filtrate was concentrated under reduced pressure. The crude product was purified by chromatography on SiO_2 (10:1:0.1, hexanes/EtOAc/Et_3N) to afford **35** as a pale orange oil (0.48 g, 95%): R_f 0.59 (10:1, hexanes/EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 8.18–8.14 (m, 2H), 7.63–7.60 (m, 1H), 7.53–7.48 (m, 2H), 0.33 (s, 9H); MS (EI$^+$) m/z 202 (M$^+$, 43), 187 (100), 159 (38), 105 (24), 76 (31); HRMS (EI) m/z calcd for $C_{12}H_{14}OSi$ 202.0814, found 202.0814. The spectral data are consistent with the literature values.[27,35]

4.24. Ethyl 2,4,8-triphenyl-4*H*-pyrimido[1,2-*a*]pyrimidine-3-carboxylate (38a). General procedure H

To a suspension of bis(triphenylphosphine)palladium(II) chloride (0.007 g, 0.01 mmol) and copper iodide (0.004 g, 0.02 mmol) in freshly distilled THF (0.75 mL) was added sequentially *N*,*N*-dicyclohexylmethylamine (0.11 mL, 0.50 mmol), benzoyl chloride (0.058 mL, 0.50 mmol), and TMS-acetylene (0.071 mL, 0.50 mmol). The reaction mixture turned from dark orange to pale yellow forming the $Cy_2MeN·HCl$ precipitate over a 1.5 h period. TLC analysis (10:1 hexanes/EtOAc; R_f=0.62) showed a quantitative formation of **35** after 1.5 h. The mixture was diluted to 0.15 M with THF (2.3 mL), and **18** (0.13 g, 0.40 mmol), DMAP (0.012 g, 0.10 mmol), and MeOH (0.40 mL) were added. The solution was heated in a microwave reactor at 170 °C for 30 min. The dark red-black reaction mixture was diluted with CH_2Cl_2 (30 mL) and washed with saturated $NaHCO_3$ (1×30 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The resulting dark red oil was purified by chromatography on SiO_2 (1:1, hexanes/EtOAc) to afford **38a** as a red solid (0.11 g, 60%, ELSD purity 100%): mp 210–211 °C; IR (ATR) 3068, 2995, 1705, 1616, 1502, 1446, 1210, 1075 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 8.63 (d, 1H, J=6.9 Hz), 8.16 (d, 2H, J=6.9 Hz), 7.60–7.32 (m, 14H), 6.49 (s, 1H), 3.81 (q, 2H, J=6.9 Hz), 0.80 (t, 3H, J=6.9 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.9, 165.2, 158.5, 151.1, 147.4, 141.3, 140.9, 134.9, 132.4, 129.0 (4C), 128.6 (3C), 128.0, 127.8 (2C), 127.2 (2C), 126.3 (2C), 106.7, 98.2, 62.3, 59.1, 13.6; HRMS (TOF MS ES) m/z calcd for $C_{28}H_{24}N_3O_2$ (M+H) 434.1869, found 434.1882.

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4.25. Synthesis of 38a under copper- and solvent-free conditions

A mixture of palladium(II) acetate (0.001 g, 0.005 mmol), benzoyl chloride (0.058 mL, 0.50 mmol), TMS-acetylene (0.078 mL, 0.55 mmol), and *N*,*N*-dicyclohexylmethylamine (0.11 mL, 0.50 mmol) was heated in a sealed tube at 40 °C for 2 h. The reaction mixture turned heterogeneous and dark brown. After 2 h, TLC analysis (10:1, hexanes/EtOAc; R_f=0.63) showed a nearly quantitative formation of **35**. The reaction mixture was diluted to a concentration of 0.15 M with THF (3.0 mL) and **18** (0.129 g, 0.400 mmol), DMAP (0.012 g, 0.10 mmol), and MeOH (0.40 mL) were added. The solution was heated in a microwave reactor at 170 °C for 30 min. The resulting dark red reaction mixture was diluted with CH_2Cl_2 (30 mL) and washed with saturated $NaHCO_3$ solution (1×30 mL). The organic layer was dried (Na_2SO_4), concentrated under reduced pressure, and the crude residue was purified by chromatography on SiO_2 (2:1 to 1:1, hexanes/EtOAc). The resulting red solid was dissolved in EtOAc (1.0 mL) and crystallized by slowly adding hexanes (20 mL) at 0 °C. The solid was isolated by vacuum filtration, washed with hexanes, and dried in vacuo to afford **38a** (0.053 g, 30%). The spectral data are consistent with the values obtained in Section 4.24.

4.26. Ethyl 4-(3,4-dimethoxyphenyl)-2,8-diphenyl-4*H*-pyrimido[1,2-*a*]pyrimidine-3-carboxylate (38b)

According to general procedure H, a solution of bis(triphenylphosphine)palladium(II) chloride (0.007 g, 0.01 mmol), copper iodide (0.004 g, 0.02 mmol), benzoyl chloride (0.058 mL, 0.50 mmol), TMS-acetylene (0.071 mL, 0.50 mmol), and *N*,*N*-dicyclohexylmethylamine (0.11 mL, 0.50 mmol) in freshly distilled THF (0.75 mL) provided **35**. After addition of THF (2.3 mL), treatment with **19** (0.15 g, 0.40 mmol), DMAP (0.012 g, 0.10 mmol), and MeOH (0.40 mL) provided the crude product, which was purified by chromatography on SiO_2 (1:1 to 2:1, EtOAc/hexanes). The resulting solid was dissolved in EtOAc (1.0 mL) and crystallized by slowly adding hexanes (20 mL) at 0 °C. The precipitated solid was isolated by vacuum filtration, washed with hexanes, and dried in vacuo to afford **38b** as an orange solid (0.10 g, 51%, ELSD purity 99.9%): R_f 0.21 (2:1, EtOAc/hexanes); mp 95–96 °C; IR (ATR) 3086, 2987, 2932, 1662, 1618, 1517, 1435, 1215, 1075, 1027 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 8.66 (d, 1H, J=6.9 Hz), 8.14 (d, 2H, J=7.2 Hz), 7.60–7.51 (m, 3H), 7.46–7.36 (m, 6H), 7.14 (s, 1H), 7.00–6.94 (m, 2H), 6.39 (s, 1H), 3.79 (q, 2H, J=7.2 Hz), 3.73 (s, 3H), 3.71 (s, 3H), 0.81 (t, 3H, J=7.2 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 166.8, 165.2, 158.3, 150.9, 149.0, 148.8, 147.3, 141.1, 134.9, 133.7, 132.3, 129.0 (2C), 128.5 (2C), 127.9, 127.8 (2C), 127.2 (2C), 118.9, 112.0, 110.2, 106.6, 98.3, 62.3, 59.0, 55.5 (2C), 13.6; MS (EI$^+$) m/z 493 (M^+, 29), 420 (100), 338 (34), 155 (21); HRMS (EI$^+$) m/z calcd for $C_{30}H_{27}N_3O_4$ 493.2001, found 493.1977.

4.27. Ethyl 8-(4-methoxyphenyl)-2,4-diphenyl-4*H*-pyrimido[1,2-*a*]pyrimidine-3-carboxylate (38c)

According to general procedure H, a solution of bis(triphenylphosphine)palladium(II) chloride (0.007 g, 0.009 mmol), copper iodide (0.004 g, 0.02 mmol), *p*-anisoyl chloride (0.099 g, 0.58 mmol), TMS-acetylene (0.083 mL, 0.58 mmol), and *N*,*N*-dicyclohexylmethylamine (0.12 mL, 0.58 mmol) in freshly distilled THF (0.75 mL) led to **36** (R_f=0.17; 20:1, hexanes/EtOAc), which was dissolved in THF (2.3 mL) and treated with **18** (0.150 g, 0.467 mmol), DMAP (0.012 g, 0.093 mmol), and MeOH (0.4 mL) to provide a crude product, which was purified by chromatography on SiO_2 (1:1, hexanes/EtOAc). The resulting red/orange solid was dissolved in CH_2Cl_2 (1.0 mL) and crystallized by slowly adding hexanes (5.0 mL) and cooling to −20 °C. The crystalline solid was isolated by vacuum filtration, washed with hexanes, and dried in vacuo to afford **38c** as a red/orange solid (0.060 g, 28%, ELSD purity 99.8%): R_f 0.31 (1:1, hexanes/EtOAc); mp 210–212 °C; IR (ATR) 2969, 1700, 1594, 1493, 1439, 1297, 1241, 1212, 1169, 1075, 1023, 697 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 8.54 (d, 1H, J=6.9 Hz), 8.15 (d, 2H, J=9.0 Hz), 7.48–7.29 (m, 11H), 7.08 (d, 2H, J=8.7 Hz), 6.44 (s, 1H), 3.84 (s, 3H), 3.77 (q, 2H, J=7.2 Hz), 0.80 (t, 3H, J=7.2 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 166.2, 165.2, 162.8, 158.8, 151.2, 146.8, 141.4, 141.0, 129.8 (2C), 129.0 (2C), 128.6 (3C), 127.9, 127.1 (3C), 126.3 (2C), 114.4 (2C), 106.2, 97.9, 62.2, 59.0, 55.5, 13.5; HRMS (TOF ES$^+$) m/z calcd for $C_{29}H_{26}N_3O_3$ 464.1974, found 464.1975.

4.28. Ethyl 2,4-diphenyl-8-(4-(trifluoromethyl)phenyl)-4*H*-pyrimido[1,2-*a*]pyrimidine-3-carboxylate (38d)

According to general procedure H, a solution of bis(triphenylphosphine)palladium(II) chloride (0.007 g, 0.01 mmol), copper iodide (0.004 g, 0.02 mmol), 4-(trifluoromethyl)benzoyl chloride (0.074 mL, 0.50 mmol), TMS-acetylene (0.071 mL, 0.50 mmol), and Et_3N (0.071 mL, 0.50 mmol) in freshly distilled THF (3.0 mL) led to **37** (R_f=0.64; 10:1, hexanes/EtOAc), which was treated with **18** (0.129 g, 0.400 mmol), DMAP (0.012 g, 0.10 mmol), and MeOH (0.40 mL) to give a crude product, which was purified by chromatography on SiO_2 (2:1 to 1:1, EtOAc/hexanes) to afford **38d** as a red crystalline solid (0.11 g, 55%, ELSD purity 100.0%): R_f 0.31 (1:1, EtOAc/hexanes); mp 206–208 °C; IR (ATR) 3068, 2974, 1705, 1618, 1506, 1456, 1323, 1114, 1066 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 8.70 (d, 1H, J=6.9 Hz), 8.35 (d, 2H, J=8.1 Hz), 7.91 (d, 2H, J=8.4 Hz), 7.54–7.30 (m, 11H), 6.52 (s, 1H), 3.81 (q, 2H, J=6.9 Hz), 0.80 (t, 3H, J=7.2 Hz); ^{13}C NMR (150 MHz, DMSO-d_6) δ 165.6, 165.2, 158.2, 150.9, 148.0, 141.1, 140.7, 138.7, 131.7 (q, J_{CF}=33.0 Hz), 129.1 (2C), 128.7, 128.6 (4C), 128.1, 127.2 (2C), 126.4 (2C), 125.8 (q, 2C, J_{CF}=4.5 Hz), 123.9 (q, J_{CF}=271.5 Hz), 107.0, 98.5, 62.3, 59.1, 13.5; MS (EI) m/z 501 (M^+, 11), 428 (100), 278 (14), 223 (17); HRMS (EI) m/z calcd for $C_{29}H_{22}N_3O_2F_3$ 501.1664, found 501.1658. X-ray crystallographic data for **38d** were deposited with the Cambridge Crystallographic Data Center (deposition number CCDC 932463).

4.29. Ethyl 4-amino-6,8-dimethyl-2-morpholino-6*H*-pyrimido[1,2-*a*][1,3,5]triazine-7-carboxylate (40). General procedure I

To a solution of 3,3-diphenoxy-2-azaprop-2-enenitrile (0.133 g, 0.558 mmol) in THF (1.0 mL) was added morpholine (0.049 mL, 0.56 mmol) in one portion at room temperature. The homogeneous colorless reaction mixture was stirred at room temperature for 2 h to form **39** (R_f=0.33; 1:1, hexanes/EtOAc). To the reaction mixture was added **10a** (0.100 g, 0.507 mmol) and the resulting suspension was heated in a microwave reactor at 110 °C for 45 min. The mixture was purified by chromatography on SiO_2 (EtOH) to afford **40** as a white foam (0.090 g, 53%, ELSD purity 99.8%): R_f 0.17 (EtOH); IR (ATR) 3327, 2969, 2906, 2855, 1651, 1584, 1551, 1482, 1420, 1264, 1232, 1107, 1059, 1023, 885, 775 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 7.89 (br s, 2H), 5.15 (q, 1H, J=6.0 Hz), 4.14–4.01 (m, 2H), 3.65–3.58 (m, 8H), 2.16 (s, 3H), 1.22 (t, 3H, J=7.2 Hz), 1.08 (d, 3H, J=6.0 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 165.2, 160.8, 158.4, 156.2, 152.1, 100.3, 65.9 (2C), 58.8, 47.7, 43.5 (2C), 23.2, 19.4, 14.4; HRMS (TOF ESI$^+$) m/z calcd for $C_{15}H_{23}N_6O_3$ 335.1832, found 335.1825.

4.30. Ethyl 4-amino-8-methyl-2-morpholino-6-phenethyl-6*H*-pyrimido[1,2-*a*][1,3,5]triazine-7-carboxylate (41)

According to general procedure I, a solution of 3,3-diphenoxy-2-azaprop-2-enenitrile (0.091 g, 0.38 mmol) and morpholine (0.034 mL, 0.38 mmol) in THF (1.0 mL) led to **39**, which was treated

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with **10b** (0.100 g, 0.348 mmol). The reaction mixture was purified by chromatography on SiO_2 (EtOH) to afford **41** as a pale yellow foam (0.037 g, 25%): R_f 0.82 (EtOH); IR (ATR) 3308, 2913, 2850, 1638, 1581, 1551, 1482, 1424, 1266, 1232, 1096, 1059, 1023, 889, 781 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 7.90 (br s, 2H), 7.25–7.06 (m, 5H), 5.31 (t, 1H, J=5.4 Hz), 4.17–4.02 (m, 2H), 3.65–3.59 (m, 8H), 2.58–2.40 (m, 2H), 2.20 (s, 3H), 1.86–1.73 (m, 2H), 1.23 (t, 3H, J=7.2 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 165.4, 160.6, 159.4, 156.3, 152.6, 141.3, 128.3 (2C), 127.9 (2C), 125.7, 98.6, 65.9 (2C), 58.8, 51.3, 43.6 (2C), 35.6, 29.6, 23.1, 14.4; HRMS (TOF ESI$^+$) m/z calcd for $C_{22}H_{29}N_6O_3$ 425.2301, found 425.2301.

4.31. Ethyl 4-amino-6-isopropyl-8-methyl-2-morpholino-6*H*-pyrimido[1,2-*a*][1,3,5]triazine-7-carboxylate (42)

According to general procedure I, a solution of 3,3-diphenoxy-2-azaprop-2-enenitrile (0.116 g, 0.488 mmol) and morpholine (0.043 mL, 0.49 mmol) in THF (1.0 mL) led to **39**, which was treated with **10c** (0.100 g, 0.444 mmol). The reaction mixture was purified by chromatography on SiO_2 (EtOH) to afford **42** as a pale yellow foam (0.070 g, 43%, ELSD purity 99.7%): R_f 0.80 (EtOH); IR (ATR) 3341, 3152, 2964, 1655, 1577, 1547, 1480, 1424, 1275, 1227, 1111, 1079, 1022, 893, 787 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 7.86 (br s, 2H), 5.09 (d, 1H, J=5.4 Hz), 4.16–4.00 (m, 2H), 3.65–3.50 (m, 8H), 2.19 (s, 3H), 1.86–1.77 (m, 1H), 1.23 (t, 3H, J=6.9 Hz), 0.75 (d, 3H, J=6.9 Hz), 0.72 (d, 3H, J=6.9 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 166.0, 160.5, 158.6, 156.7, 152.7, 98.0, 65.9 (2C), 58.7, 55.4, 43.6 (2C), 34.1, 23.0, 17.8, 17.6, 14.4; HRMS (TOF ESI$^+$) m/z calcd for $C_{17}H_{27}N_6O_3$ 363.2145, found 363.2136.

4.32. Ethyl 4-amino-2-morpholino-6,8-diphenyl-6*H*-pyrimido[1,2-*a*][1,3,5]triazine-7-carboxylate (43)

According to general procedure I, a solution of 3,3-diphenoxy-2-azaprop-2-enenitrile (0.163 g, 0.685 mmol) and morpholine (0.060 mL, 0.68 mmol) in THF (1.0 mL) led to **39**, which was treated with **18** (0.200 g, 0.622 mmol). The reaction mixture was cooled to room temperature, diluted with ether (1.5 mL), and cooled to −20 °C for 1 h. The resulting precipitate was isolated by vacuum filtration and washed with ether (15 mL). The crude precipitate was recrystallized from boiling hexanes/EtOAc (4:1, 35 mL), isolated by vacuum filtration, washed with hexanes, and dried in vacuo to afford **43** as a yellow/green foam (0.130 g, 46%, ELSD purity 99.9%): IR (ATR) 3334, 3165, 2975, 2855, 1646, 1549, 1476, 1418, 1271, 1230, 1105, 1087, 1021, 995, 764, 695 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 8.04 (s, 2H), 7.47–7.44 (m, 2H), 7.37–7.27 (m, 8H), 6.30 (s, 1H), 3.79–3.69 (m, 4H), 3.58 (s, 6H), 0.77 (t, 3H, J=7.2 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 165.5, 160.6, 159.0, 156.3, 152.5, 141.7, 141.5, 128.6 (2C), 128.2 (2C), 128.1, 127.5, 127.0 (2C), 126.5 (2C), 100.4, 65.9 (2C), 58.7, 54.6, 43.6, 43.4, 13.5; HRMS (TOF ESI$^+$) m/z calcd for $C_{25}H_{27}N_6O_3$ 459.2145, found 459.2135.

4.33. Ethyl 6,8-dimethyl-4-oxo-3,4,6,9-tetrahydropyrimido[2,1-*c*][1,2,4,6]thiatriazine-7-carboxylate 2,2-dioxide (44). General procedure J

To a suspension of **10a** (0.100 g, 0.507 mmol) and DIPEA (0.13 mL, 0.76 mmol) in THF (2.5 mL) at 0 °C was added chlorosulfonyl isocyanate (0.068 mL, 0.76 mmol) in one portion. The reaction mixture became homogeneous within 5 min after the addition of the isocyanate. The solution was stirred for 3 h at 0 °C and warmed to room temperature for 14 h. ^1H NMR analysis indicated a 47% conversion, and therefore the mixture was treated at 0 °C with additional DIPEA (0.084 mL, 0.51 mmol) and chlorosulfonyl isocyanate (0.045 mL, 0.51 mmol). The reaction mixture was stirred at 0 °C for 2 h, allowed to warm to room temperature, and stirred for an additional 4 h. The resulting clear pale yellow solution was diluted with EtOAc (30 mL) and concentrated under reduced pressure after addition of SiO_2 (1.0 g). The resulting mixture was added directly to the top of a pre-flushed column and purified by chromatography on SiO_2 (1:1, hexanes/EtOAc to EtOAc). The resulting product was recrystallized from boiling CH_2Cl_2/hexanes (1:1.5, 2.5 mL), isolated by vacuum filtration, washed with hexanes, and dried in vacuo to afford **44** as a white solid (0.024 g, 15%): mp 219–220 °C; IR (ATR) 3308, 3239, 3184, 2988, 1707, 1609, 1471, 1329, 1294, 1253, 1189, 1161, 1083, 902, 753, 738, 662 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 10.89 (s, 1H), 5.45 (q, 1H, J=6.3 Hz), 4.25–4.08 (m, 2H), 2.27 (s, 3H), 1.24 (t, 3H, J=6.9 Hz), 1.17 (d, 3H, J=6.3 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 168.0, 151.9, 151.1, 149.2, 108.5, 64.1, 49.9, 23.8, 21.0, 18.1; HRMS (TOF ESI$^+$) m/z calcd for $C_{10}H_{15}N_4O_5S$ 303.0763, found 303.0755. X-ray crystallographic data for **44** were deposited with the Cambridge Crystallographic Data Center (deposition number CCDC 935121).

4.34. Ethyl 4-oxo-6,8-diphenyl-3,4,6,9-tetrahydropyrimido[2,1-*c*][1,2,4,6]thiatriazine-7-carboxylate 2,2-dioxide (45)

According to general procedure J, a solution of **18** (0.250 g, 0.778 mmol), DIPEA (0.19 mL, 1.2 mmol), and chlorosulfonyl isocyanate (0.10 mL, 1.2 mmol) in THF (2.5 mL) led to crude product, which was diluted with EtOAc (30 mL), concentrated under reduced pressure with SiO_2 (1.0 g), and purified by chromatography on SiO_2 (1:1, hexanes/EtOAc to EtOAc) to afford **45** as a white foam (0.132 g, 40%, ELSD purity 99.7%): IR (ATR) 3202, 3057, 2982, 1700, 1594, 1444, 1331, 1249, 1163, 1100, 979, 749, 693 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 11.18 (s, 1H), 7.47–7.37 (m, 11H), 6.66 (s, 1H), 3.84 (q, 2H, J=6.9 Hz), 0.78 (t, 3H, J=6.9 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 164.1, 148.5, 147.5, 146.4, 139.1, 132.9, 129.8, 129.1 (2C), 129.0 (2C), 128.7, 128.0 (2C), 126.2 (2C), 104.5, 60.2, 51.8, 13.4; HRMS (TOF ESI$^+$) m/z calcd for $C_{20}H_{19}N_4O_5S$ 427.1076, found 427.1077.

4.35. Diethyl 4,6-bis(4-chlorophenyl)-2,8-dimethyl-4,6-dihydro-1*H*-pyrimido[1,2-*a*]pyrimidine-3,7-dicarboxylate (46)

According to general procedure D, a solution of **13**·**TFA** (0.030 g, 0.074 mmol), **12** (0.074 g, 0.29 mmol), and $NaHCO_3$ (0.014 g, 0.016 mmol) in $(CF_3)_2CHOH$ (0.25 mL) was heated for 24 h. LC/MS analysis demonstrated an approximately 50% conversion of **13**, and two more equivalents of **12** (0.037 g, 0.15 mmol) were added. The reaction mixture was stirred at 90 °C for an additional 18 h after which complete consumption of the starting material was observed via LC/MS. Product **46** (0.022 g, 57%) was obtained as a yellow crystalline 4:1 mixture of *anti*–*syn*-isomers that could not be further separated: R_f 0.42 (MeOH/CH_2Cl_2, 0.2:10); mp 70–75 °C; IR (CH_2Cl_2) 2979, 2922, 1677, 1622, 1544, 1490, 1446, 1369, 1274, 1228, 1199, 1088, 1014, 830, 736 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 12.05 (s, 1H), 11.95 (s, 0.2H), 7.43–7.41 (d, 2H, J=8.4 Hz), 7.31–7.29 (d, 2× 2H, J=8.4 Hz), 6.97–6.94 (d, 2× 0.5H, J=8.8 Hz), 5.38 (s, 2× 0.25H), 5.18 (s, 2× 1H), 4.10–4.01 (m, 2× 4H), 2.49 (s, 2× 3H), 1.17–1.13 (t, 2× 3H, J=7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3, 164.0 (2C), 148.2, 145.6, 144.7, 138.6, 137.7, 135.3, 134.4, 129.5 (2C), 129.1, 128.9 (2C), 128.3, 105.1, 103.4, 64.8, 62.3, 60.8, 56.6, 19.3, 14.0; HRMS (ESI$^+$) m/z calcd for $C_{27}H_{28}O_4N_3Cl_2$ (M+H) 528.1451, found 528.1441.

4.36. Ethyl 2-(4-morpholinobenzylidene)-3-oxobutanoate (48d)[36]

A solution of L-proline (1.21 g, 10.5 mmol) in DMSO (10 mL) was treated with 4-morpholinebenzaldehyde (1.12 g, 5.86 mmol) at room temperature. After 10 min, ethyl acetoacetate (0.80 mL, 6.3 mmol) was added and the mixture was stirred for 17 h. The

yellow solution was treated with EtOAc, followed by water, and the organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated. The resulting oil was purified by chromatography on SiO_2 (ISCO-R_f, 20–100% EtOAc/hexanes, 15 min gradient) to give **48d** as a sticky yellow 4.4:1 mixture of inseparable *Z*/*E* isomers (0.713 g, 40%): mp 94–96 °C; IR (neat) 2974, 1713, 1588, 1514, 1260, 1163, 982 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.53 (s, 0.2 H), 7.43 (s, 1H), 7.35 (d, 2H, *J*=7.8 Hz), 7.28 (d, 0.4H, *J*=8.8 Hz), 6.82–6.78 (overlap d, 2.4H), 4.33 (q, 2H, *J*=7.2 Hz), 4.23 (q, 0.4H, *J*=7.2 Hz), 3.80–3.78 (m, 5H), 3.24–3.21 (m, 5H), 2.37 (s, 0.6H), 2.34 (s, 3H), 1.31–1.28 (2 overlapping t, 3.7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.0, 194.5, 168.4, 164.6, 152.4, 152.1, 141.1, 140.3, 131.5, 131.4, 130.6, 129.7, 122.9, 122.6, 114.0, 113.9, 66.2, 61.2, 60.9, 47.3, 47.2, 31.0, 26.0, 14.0, 13.8; HRMS (ESI^+) *m*/*z* calcd for $C_{17}H_{22}NO_4$ (M+H) 304.1543, found 304.1535.

4.37. Ethyl 2-(6-chloro-4-methylquinazolin-2-ylamino)-4-(4-chlorophenyl)-6-methyl-1,4-dihydropyrimidine-5-carboxylate (49a)

According to general procedure D, a solution of **47a** (0.029 g, 0.12 mmol), **12**[36,37] (0.23 g, 0.90 mmol), and $NaHCO_3$ (0.026 g, 0.31 mmol) in $(CF_3)_2CHOH$ (0.40 mL) afforded **49a** as a light yellow solid (0.053 g, 56%, ELSD purity 95.4%): mp >200 °C; IR (neat) 3059, 2975, 1650, 1575, 1461, 1420, 1305, 1215, 1094, 838 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 10.87 (br s, 1H), 10.43 (br s, 1H), 8.11 (d, 1H, *J*=1.6 Hz), 7.85–7.79 (m, 2H), 7.39 (d, 2H, *J*=8.8 Hz), 7.36 (d, 2H, *J*=8.8 Hz), 5.70 (s, 1H), 4.07 (q, 2H, *J*=7.2 Hz), 2.77 (s, 3H), 2.39 (s, 3H), 1.17 (t, 3H, *J*=7.2 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.3, 165.6, 161.8, 151.8, 149.0, 148.8, 144.0, 134.3, 132.5, 128.9, 128.7, 128.5, 124.9, 120.8, 100.4, 59.8, 52.7, 21.9, 18.9, 14.6; HRMS (ESI^+) *m*/*z* calcd for $C_{23}H_{22}N_5O_2Cl_2$ (M+H) 470.1145, found 470.1146.

4.38. Ethyl 4-(4-chlorophenyl)-2-(4,6-dimethylquinazolin-2-ylamino)-6-methyl-1,4-dihydropyrimidine-5-carboxylate (49b)

According to general procedure D, a solution of **47b** (0.055 g, 0.26 mmol), **12**[36,37] (0.28 g, 1.09 mmol), and $NaHCO_3$ (0.049 g, 0.58 mmol) in $(CF_3)_2CHOH$ (0.40 mL) afforded **49b** as a light yellow solid (0.073 g, 62%, ELSD purity 98.4%): mp >200 °C; IR (neat) 3058, 2975, 1655, 1535, 1450, 1420, 1316, 1215, 1077, 839 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 10.72 (br s, 2H), 7.83 (s, 1H), 7.70 (d, 1H, *J*=8.4 Hz), 7.63 (d, 1H, *J*=8.4 Hz), 7.38 (app s, 4H), 5.71 (s, 1H), 4.06 (q, 2H, *J*=6.4 Hz), 2.75 (s, 3H), 2.45 (s, 3H), 2.39 (s, 3H), 1.16 (t, 3H, *J*=6.8 Hz); ^{13}C NMR (100 MHz, DMSO-d_6, 100 °C) δ 168.1, 164.8, 159.3, 150.4, 149.1, 147.4, 143.3, 135.0, 133.2, 131.4, 127.8, 127.5, 125.4, 123.6, 119.3, 99.3, 58.6, 51.9, 20.7, 20.3, 18.4, 13.5; HRMS (ESI^+) *m*/*z* calcd for $C_{24}H_{25}N_5O_2Cl$ (M+H) 450.1691, found 450.1680.

4.39. Ethyl 4-(4-chlorophenyl)-2-(6-fluoro-4-methylquinazolin-2-ylamino)-6-methyl-1,4-dihydropyrimidine-5-carboxylate (49c)

According to general procedure D, a solution of **47c** (0.048 g, 0.22 mmol), **12** (0.22 g, 0.86 mmol), and $NaHCO_3$ (0.043 g, 0.51 mmol) in $(CF_3)_2CHOH$ (0.40 mL) afforded **49c** as a yellow solid (0.051 g, 52%, ELSD purity 90%): mp >200 °C; IR (neat) 3059, 2975, 1663, 1536, 1450, 1420, 1310, 1215, 1077, 826 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 10.71 (br s, 2H), 7.93–7.83 (m, 2H), 7.72 (ddd, 1H, *J*=2.4, 8.8, 8.8 Hz), 7.39–7.35 (m, 4H), 5.70 (s, 1H), 4.07 (q, 2H, *J*=7.2 Hz), 2.75 (s, 3H), 2.39 (s, 3H), 1.16 (t, 3H, *J*=7.2 Hz); ^{13}C NMR (100 MHz, DMSO-d_6, 100 °C) δ 168.5, 164.7, 159.9, 157.6 (d, J_{CF}=243.5 Hz), 150.5, 148.2, 146.3, 143.0, 131.5, 128.2 (d, J_{CF}=8.1 Hz), 127.9, 127.7, 127.5, 122.7 (d, J_{CF}=25.2 Hz), 119.3 (d, J_{CF}=8.1 Hz), 108.6 (d, J_{CF}=22.1 Hz), 99.5, 58.7, 51.9, 20.9, 18.1, 13.5; HRMS (ESI^+) *m*/*z* calcd for $C_{23}H_{22}N_5O_2ClF$ (M+H) 454.1441, found 454.1435.

4.40. Ethyl 4-(4-dimethylaminophenyl)-2-(6-fluoro-4-methylquinazolin-2-ylamino)-6-methyl-1,4-dihydropyrimidine-5-carboxylate (49d)

According to general procedure D, a solution of **47c** (0.032 g, 0.15 mmol), **48a**[36,37] (0.15 g, 0.59 mmol), and $NaHCO_3$ (0.027 g, 0.32 mmol) in $(CF_3)_2CHOH$ (0.60 mL) gave **49d** as an orange solid (0.027 g, 40%, ELSD purity 99.4%): mp >220 °C; IR (neat) 3059, 2974, 1655, 1543, 1420, 1307, 1215, 1077, 838 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 10.57 (br s, 2H), 7.84–7.81 (m, 2H), 7.71–7.67 (m, 1H), 7.15 (d, 2H, *J*=8.4 Hz), 6.63 (d, 2H, *J*=8.4 Hz), 5.57 (s, 1H), 4.06 (q, 2H, *J*=6.8 Hz), 2.82 (s, 6H), 2.74 (s, 3H), 2.38 (s, 3H); 1.19 (t, 3H, *J*=6.8 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.9 (d, J_{CF}=4.0 Hz), 165.3, 161.3, 157.8 (d, J_{CF}=242.5 Hz), 151.6, 149.7, 147.4, 146.5, 132.2, 128.6 (d, J_{CF}=8.1 Hz), 126.7, 123.1 (d, J_{CF}=25.2 Hz), 119.5 (d, J_{CF}=9.1 Hz), 112.3, 109.3 (d, J_{CF}=22.1 Hz), 100.2, 59.2, 51.8, 40.1, 21.8, 18.2, 14.2; HRMS (ESI^+) *m*/*z* calcd for $C_{25}H_{28}N_6O_2F$ (M+H) 463.2252, found 463.2248.

4.41. Ethyl 2-(4.6-dimethylquinazolin-2-ylamino)-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyrimidine-5-carboxylate (49e)

According to general procedure D, a solution of **47b** (0.043 g, 0.20 mmol), **48b**[36,38] (0.16 g, 0.60 mmol), and $NaHCO_3$ (0.057 g, 0.68 mmol) in $(CF_3)_2CHOH$ (0.60 mL) gave **49e** as a light yellow solid (0.062 g, 67%, ELSD purity 90.4%): mp >200 °C; IR (neat) 3059, 2974, 1668, 1525, 1450, 1420, 1340, 1215, 1077, 734, 692 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 10.94 (br s, 1H), 10.53 (br s, 1H), 8.23 (app t, 1H, *J*=1.6 Hz), 8.12–8.09 (m, 1H), 7.85 (s, 1H), 7.80 (d, 1H, *J*=7.6 Hz), 7.73 (d, 1H, *J*=8.4 Hz), 7.67–7.63 (m, 2H), 5.85 (s, 1H), 4.08 (q, 2H, *J*=7.2 Hz), 2.77 (s, 3H), 2.47 (s, 3H), 2.40 (s, 3H), 1.17 (t, 3H, *J*=7.2 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 169.0, 165.1, 159.8, 151.1, 147.8, 147.5, 147.0, 135.6, 133.8, 132.8, 130.3, 126.0, 124.3, 122.3, 121.0, 119.6, 98.7, 59.4, 51.9, 21.6, 21.0, 19.0, 14.1; HRMS (ESI^+) *m*/*z* calcd for $C_{24}H_{25}N_6O_4$ (M+H) 461.1932, found 461.1913.

4.42. Ethyl 4-(4-chlorophenyl)-6-methyl-2-(8-methyl-[1,3]dioxolo[4,5-*g*]quinazolin-6-ylamino)-1,4-dihydropyrimidine-5-carboxylate (49f)

According to general procedure D, a solution of **47d** (0.029 g, 0.12 mmol), **12**[36,37] (0.035 g, 0.14 mmol), and $NaHCO_3$ (0.026 g, 0.31 mmol) in $(CF_3)_2CHOH$ (0.40 mL) afforded **49f** as a light yellow solid (0.024 g, 41%, ELSD purity 98.2%): mp >200 °C; IR (neat) 3059, 2974, 1649, 1450, 1420, 1215, 1094, 1077, 768 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 10.76 (br s, 2H), 7.43 (s, 1H), 7.38 (d, 2H, *J*=8.8 Hz), 7.34 (d, 2H, *J*=8.7 Hz), 7.26 (s, 1H), 6.19 (br s, 2H), 5.65 (s, 1H), 4.06 (q, 2H, *J*=7.2 Hz), 2.65 (s, 3H), 2.37 (s, 3H), 1.16 (t, 3H, *J*=7.2 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 166.7, 165.2, 159.6, 153.3, 150.9, 148.5, 145.8, 143.7, 131.8, 128.5, 127.9, 115.6, 102.9, 102.1, 101.0, 99.0, 59.2, 51.6, 21.8, 18.9, 14.2; HRMS (ESI^+) *m*/*z* calcd for $C_{24}H_{23}N_5O_4Cl$ (M+H) 480.1433, found 480.1431.

4.43. Ethyl 4-(4-bromophenyl)-6-methyl-2-(8-methyl-[1,3]dioxolo[4,5-*g*]quinazolin-6-ylamino)-1,4-dihydropyrimidine-5-carboxylate (49g)

According to general procedure D, a solution of **47d** (0.041 g, 0.17 mmol), **48c**,[36,37] and $NaHCO_3$ (0.031 g, 0.37 mmol) in $(CF_3)_2CHOH$ (0.40 mL) afforded **49g** as a yellow solid (0.039 g, 57%, ELSD purity 98.2%): mp >200 °C; IR (neat) 3059, 2974, 1700, 1629, 1536, 1420, 1192, 1077, 1028, 839 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 10.61 (br s, 2H), 7.51 (d, 2H, *J*=8.4 Hz), 7.41 (s, 1H), 7.29 (d, 2H,

J=8.4 Hz), 7.25 (s, 1H), 6.20 (br s, 2H), 5.66 (s, 1H), 4.06 (q, 2H, J=7.2 Hz), 2.66 (s, 3H), 2.38 (s, 3H), 1.16 (t, 3H, J=7.2 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.6, 165.2, 159.7, 153.2, 151.0, 148.5, 145.8, 144.1, 131.4, 128.3, 120.3, 115.5, 102.9, 102.1, 101.0, 98.9, 59.2, 51.7, 21.8, 19.0, 14.2; HRMS (ESI$^+$) m/z calcd for $C_{24}H_{23}N_5O_4Br$ (M+H) 524.0928, found 524.0915.

4.44. Ethyl 6-methyl-2-(8-methyl-[1,3]dioxolo[4,5-*g*]quinazolin-6-ylamino)-4-(4-morpholinophenyl)-1,4-dihydropyrimidine-5-carboxylate (49h)

According to general procedure D, a solution of **47d** (0.046 g, 0.17 mmol), **48d** (0.21 g, 0.70 mmol), and $NaHCO_3$ (0.032 g, 0.38 mmol) in CF_3CHOH (0.40 mL) gave **49h** as a yellow solid (0.073 g, 81%, ELSD purity 99.7%): mp >220 °C; IR (neat) 3058, 2816, 1655, 1543, 1450, 1420, 1316, 1215, 1077, 1028, 956 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.56 (br s, 2H), 7.41 (s, 1H), 7.24 (s, 1H), 7.19 (d, 2H, J=8.0 Hz), 6.86 (d, 2H, J=8.0 Hz), 6.19 (br s, 2H), 5.58 (s, 1H), 4.06 (app t, 2H, J=6.0 Hz), 3.68 (br s, 4H), 3.03 (br s, 4H), 2.65 (s, 3H), 2.37 (s, 3H), 1.17 (t, 3H, J=6.8 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.5, 165.4, 160.1, 153.2, 151.2, 150.2, 148.6, 145.7, 135.4, 126.7, 115.4, 115.0, 102.9, 102.1, 101.0, 99.8, 66.0, 59.1, 51.6, 48.3, 21.9, 18.7, 14.2; HRMS (ESI$^+$) m/z calcd for $C_{28}H_{31}N_6O_2$ (M+H) 531.2350, found 531.2338.

4.45. Ethyl 4-(4-(dimethylamino)phenyl)-6-methyl-2-(8-methyl-[1,3]dioxolo[4,5-*g*]quinazolin-6-ylamino)-1,4-dihydropyrimidine-5-carboxylate (49i)

According to general procedure D, a solution of **47d** (0.043 g, 0.17 mmol), **48a**[36,37] (0.18 g, 0.69 mmol), and $NaHCO_3$ (0.031 g, 0.37 mmol) in $(CF_3)_2CHOH$ (0.60 mL) gave **49i** as an off-white solid (0.038 g, 45%, ELSD purity 100%): mp >220 °C; IR (neat) 3059, 2934, 1663, 1549, 1450, 1420, 1215, 1077, 1029, 839 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.61 (br s, 2H), 7.42 (s, 1H), 7.24 (s, 1H), 7.14 (d, 2H, J=8.4 Hz), 6.64 (d, 2H, J=8.8 Hz), 6.19 (br s, 2H), 5.54 (s, 1H), 4.06 (q, 2H, J=6.8 Hz), 2.82 (s, 6H), 2.66 (s, 3H), 2.37 (s, 3H), 1.18 (t, 3H, J=6.8 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.4, 165.4, 160.1, 153.1, 151.1, 149.7, 148.6, 145.6, 132.4, 126.7, 115.4, 112.3, 102.9, 102.1, 101.0, 100.0, 59.1, 51.6, 40.1, 21.8, 18.7, 14.2; HRMS (ESI$^+$) m/z calcd for $C_{26}H_{29}N_6O_4$ (M+H) 489.2245, found 489.2237.

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.04.127.

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