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Synthesis of Fully Substituted Pyrimidines

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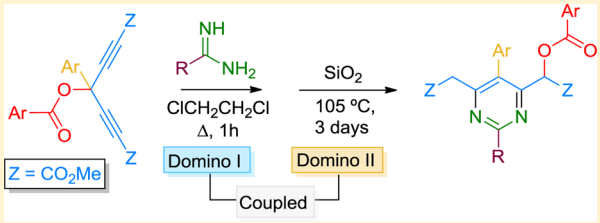
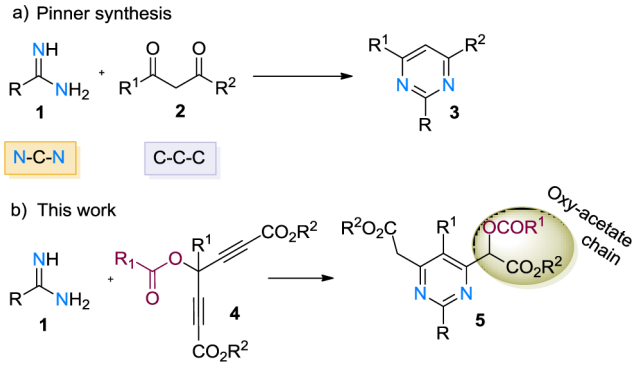
Supporting Information

ABSTRACT: A novel approach to the synthesis of fully substituted pyrimidine derivatives armed with an oxy-functionalized acetate chain at the ring is described. The manifold uses amidines as the nitrogen source and activated skipped diynes as the electrophilic reactive partners in a coupled domino strategy. In the first domino reaction, two consecutive aza-Michael additions assemble the six-membered ring heterocycle, while in the second domino process, a [H]-shift and a [3,3]-sigmatropic rearrangement lead to the aromatization of the product.



Pyrimidine is the most common of the three possible diazines (six-membered aromatic rings with two nitrogen atoms) and constitutes an important pharmacophore endowed with a wide range of pharmacological activities.[1] As such, pyrimidine derivatives have received a great deal of attention from the synthetic community.[2] The most common synthetic approach involves the addition of a N−C−N fragment to a compound possessing a reactive C−C−C connectivity. The most representative example of this type of reaction is the well-known Pinner pyrimidine synthesis which involves the condensation of amidines **1** with 1,3-dicarbonyl compounds **2** or their synthetic equivalents (Scheme 1a). Although the nature

Scheme 1. Manifolds for the Synthesis of Substituted Pyrimidines



and reactivity profile of these C−C−C units have been widely explored,[2] available methods incorporating an alkyne motive remains scarce,[3] and these are mainly related to the use of ethynyl ketone derivatives.[3b−f] Other important strategies involving alkynes rely on the [2 + 2 + 2]-intermolecular cycloaddition of one alkyne molecule and two nitrile molecules[3a,i] or the [4 + 2]-cycloaddition of 1,3-diazadienes with electron-deficient acetylenes to deliver the pyrimidine ring.[3g,h] Whereas the first one utilizes two identical nitrile blocks affording a reduced functional diversity decorating the ring (symmetric products, substituent redundancy), the second one requires the previous access to a reactive 1,3-azadiene unit featuring a convenient leaving group installed at the 3-position (the leaving group steers the final aromatization step).[3g] These limitations call for the development of new alkyne-based methodologies capable of providing these heterocyclic structures with multiple substitution patterns decorating the ring. In addition, these methodologies should also be able to construct pyrimidine-focused chemical libraries.[4]

As part of an ongoing project, we have developed efficient domino methodologies for the diversity-oriented access to bioactive aromatic scaffolds from simple and readily available tertiary 1,4-diynes blocks **4** (Scheme 1).[5] These units are conveniently synthesized in multigram scale by a four-component A_2BB' reaction involving acid chlorides and alkyl propiolates.[6] The multicomponent nature of this reaction allows these 1,4-diynes blocks to be obtained with a convenient grade of diversity at the tertiary position (R^1, R^1COO) and the ester groups (R^2) in a simple and fast manner. Herein, we report a simple, direct, and versatile methodology based on the use of these 1,4-diyne units for rapid access to fully substituted pyrimidines decorated with a convenient grade of functional diversity and bearing an oxy-functionalized side chain at the ring. The methodology is based on a novel domino manifold which uses amidines **1** as the nitrogen source (N−C−N block) and a tertiary skipped diyne unit **4** as the source of the C_3 block (Scheme 1b).

Recent reports from our laboratory have shown that 1,4-diynes **4** conveniently behave either as 1,3- or 1,4-dicarbonyl compounds when they are made to react with aza-nucleophiles such as primary amines,[5a] hydrazines,[5b] 1,*n*-diamines,[5c] or secondary amines.[5d] We therefore envisioned that amidines **1**

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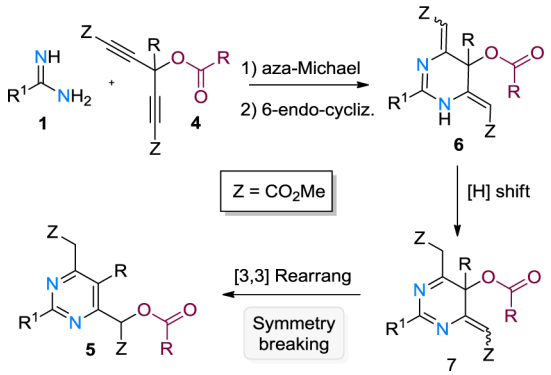
could react with these 1,4-diyne blocks to afford fully substituted pyrimidines **5** with complete atom economy and good functional diversity decorating the aromatic ring (Scheme 1b). Based on our previous experience, we anticipated that amidines **1** would react with the alkyne functionalities of **4** through two consecutive aza-Michael additions to afford the cyclic intermediates **6**. This would be followed by a [H]-shift to form a cyclic intermediate **7** with a new endocyclic unsaturation and, finally, a [3,3]-sigmatropic rearrangement to form the desired pyrimidines **5** via an irreversible aromatization-driven process (Scheme 2). This rearrangement would break the latent

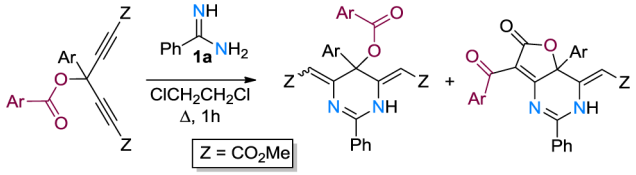
Scheme 2. Expected Domino Pathway Affording Pyrimidines 5



symmetry present in the two advanced intermediates **6** and **7** by the installation of two chemically differentiated acetate chains at the ring of the final pyrimidine product.

As a proof of the concept, we studied the reaction of commercially available benzamidine **1a** with skipped diyne **4a**. Although we were pleased to observe the consumption of the starting material **1a** by TLC analysis (in refluxing DCE, 1 h), we also noticed that the desired pyrimidine product was not observed among the mixture of reaction products which were isolated after flash column chromatography. Instead, the *E*/*Z* mixture of the cyclic intermediate **6aa** was identified as the main reaction product (73%) with compound **8aa** as a byproduct of the reaction (14%) coming from a different reaction pathway (Scheme 3).[7] Further attempts to obtain the

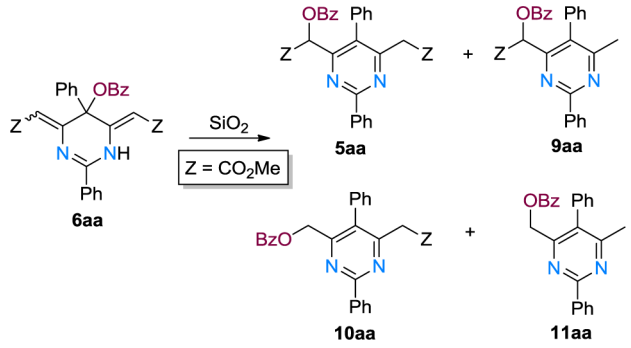
Scheme 3. Optimization of the Domino Manifold



aromatized product **5aa** from **1a** and **4a** by varying the solvent (EtOH, *t*-BuOH, DMF, toluene) and the reaction temperature were unsuccessful. To begin testing the generality of this process we carried out the reaction with other diynes obtaining similar results.

It soon became evident that we needed to concentrate our efforts in determining the best reaction conditions to allow intermediate **6aa** to progress toward the desired pyrimidine through the [H]-shift and the [3,3]-sigmatropic rearrangement. As a matter of fact, in the previous synthesis of pyrroles[5a] and pyrazoles[5b] from tertiary skipped diynes **4**, we had not encountered this difficulty in progressing past the first cyclic intermediate, although we found that the pyrazole ring formation required more energic conditions than the pyrrole ring (reaction differences mirror the aromatic differences!). After some experimentation, we quickly turned our attention to the use of silica gel as a mild acidic catalyst with the combination of heating to aid in the rearrangement. Hence, an *E*/*Z* mixture of **6aa** was adsorbed on silica gel and the opened vessel (round bottomed flask) was then heated in a domestic microwave oven (at 900 W) for different periods of time. While the reaction was incomplete at shorter reaction times, mixtures containing the desired pyrimidine and decarboxylated products **9aa**–**11aa** were obtained at longer reaction times without selectivity in the product distribution (Scheme 4) (see

Scheme 4. Thermally Driven Transformation of Intermediate 6aa into Pyrimidines 5aa and 9aa–11aa



Supporting Information). A similar scenario took place when the same aromatization reaction was attempted using a scientific microwave apparatus. Fortunately, with the use of conventional heating, with longer reaction times and the appropriate reaction temperature, good selectivity toward the desired pyrimidine **5aa** was obtained (3 days, 100–110 °C, 90% NMR yield).

Our next goal was to be able to implement both processes in the same reaction vessel by means of the so-called coupled domino reaction strategy[8] and, thus, avoid the isolation of the *E*/*Z* mixture of the cyclic products **6**. Fortunately, the protocol was straightforward and consisted of absorbing on silica gel the crude reaction mixture obtained in the first step (reaction of **1a** and **4a**) and subjecting it to the previously studied thermal conditions. In this manner, **5aa** was isolated in a 46% overall yield.

Once the reaction could be standardized, we next studied the scope of this coupled domino process with regard to the diyne and the amidine (Table 1). In general, the reaction displayed a wide scope with regard to both components. With regard to the 1,4-diyne component, the derivatives **4a**–**f**[6] were studied, which feature electronically different aromatic rings at the diyne tertiary position and on the ester functionality.

As it was expected, all of them expressed the same reactivity pattern with similar chemical efficiencies (entries 1–6). Other commercially available amidines **1a**–**e** were converted to the corresponding fully substituted pyrimidines **5a**–**e** with similar efficiencies.

The extension of this protocol to the aliphatic substituted tertiary 1,4-diynes proved to be more difficult than previously expected, and it resulted in a new reactivity profile for the

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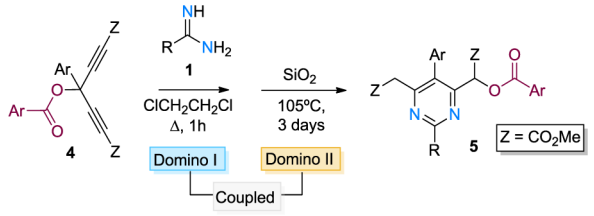
Table 1. Coupled Domino Reactions of Activated Skipped Diynes 4 and Amidines 1

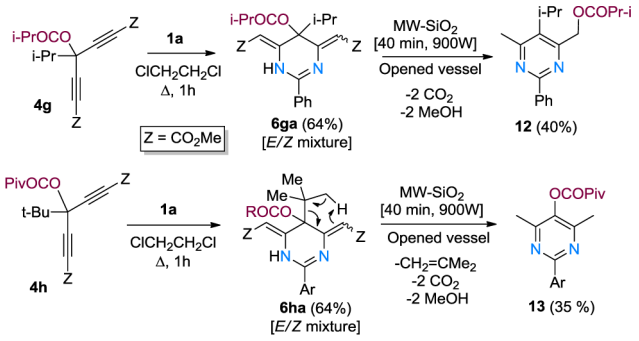


entry	Ar	4	R	1	5 (%)[a]
1	Ph	**a**	Ph	**a**	**5aa** (46)
2	4-ClC_6H_4	**b**	Ph	**a**	**5ba** (42)
3	3,5-di$OMeC_6H_3$	**c**	Ph	**a**	**5ca** (48)
4	4-MeC_6H_4	**d**	Ph	**a**	**5da** (52)
5	4-FC_6H_4	**e**	Ph	**a**	**5ea** (42)
6	3-ClC_6H_4	**f**	Ph	**a**	**5fa** (41)
9	Ph	**a**	3-$NO_2C_6H_4$	**b**	**5ab** (48)
10	Ph	**a**	4-ClC_6H_4	**c**	**5ac** (53)
11	Ph	**a**	4-MeC_6H_4	**d**	**5ad** (48)
12	Ph	**a**	Me	**e**	**5ae** (37)

[a]Yields of isolated products.

1,4,5,6-tetrahydropyrimidine intermediate **6** (Scheme 5). The multicomponent methodology for access to these 1,4-diynes

Scheme 5. Extension to the Aliphatic Series of Tertiary Skipped Diynes: A New Reactivity Pattern



required that the aliphatic substituent at the C-sp^3 position had to be necessarily branched.[9] With this structural constraint, we assayed the reaction of imidine **1a** with 1,4-diynes **4g** and **4h**, armed with an isopropyl and a *tert*-butyl group at the C-sp^3 position, respectively. Both substrates were smoothly transformed into the corresponding intermediates **6ga** and **6ha** (64% yield in each case), but reactions did not progress past these intermediates even after being submitted to the thermal conditions of the second reaction (e.g., after the third day of heating, the *E*/*Z* isomeric mixture of **6ga** was quantitatively transformed into a single isomer). Both intermediates showed a similarly high thermal barrier to aromatization. The aromatization could be finally achieved by microwave-assisted heating of these intermediates absorbed on silica gel [40 min, 900 W, opened vessel, domestic oven], but it was at the expense of the decarboxylative elimination of both methyl ester groups. Under these conditions, the intermediate **6ga** rearranged to the pyrimidine derivative **12** in 40% yield. Significantly, this reaction allowed us to install three differentiated aliphatic chains at the ring, one of them armed with a terminal acyloxy group as a convenient chemical handle. Surprisingly, under the same reaction conditions, the intermediate **6ha** rearranged to the symmetric 5-pivaloyloxy-pyrimidine derivative **13** in 35% yield (Scheme 5). Besides the expected decarboxylations, the reaction involved the loss of the original *tert*-butyl group without migration of the pivaloyloxy group. We believe that this different reaction pattern relies on the steric congestion imposed by the *tert*-butyl group at the C-sp^3 position which increases the energy for the [3,3]-sigmatropic rearrangement involving the ester group and it facilities the rearrangement involving the aliphatic substituent (retro-ene reaction) which is probably also aided by the gem-dimethyl effect exercised by the other two methyl groups of the substituent (see Scheme 5). The presence of an O-substituent at the pyrimidine ring of **13** is quite interesting because the 5-pyrimidinol derivatives have been shown to be suitable structural motifs for the rational design of novel air-stable radical scavengers and chain-breaking antioxidants that are more effective than phenols.[10]

In summary, we have developed a novel alkyne-based approach for the synthesis of fully substituted pyrimidine derivatives armed with a functionalized alkyl ester chain. The manifold uses amidines as the nitrogen source and activated skipped diynes as the electrophilic reactive partners and utilizes a coupled domino reaction strategy to perform the whole transformation. Whereas a sequence of two consecutive aza-Michael addition assembles the six-membered ring heterocycle (the 1,4,5,6-tetrahydropyrimidine core), a second domino process involving a [H]-shift and a [3,3]-sigmatropic rearrangement leads to the aromatization of the product. The novelty of this reaction and its simple experimental protocol make this process an excellent candidate for the fast construction of structure-focused libraries based on the pyrimidine unit decorated with an aryl, alkyl, or hydroxyl group at the C-5 position of the ring and different alkyl/aryl functionalities adorning the rest of the ring. Importantly, the protocol differentiates the otherwise identical alkyne chains of the starting 1,4-diyne and installs them as two differentiated side chains at the ring of the final pyrimidine ring. Last but not least, the three esters present in the 1,4-diyne precursor can be incorporated into the final pyrimidine structure to be used as convenient chemical handles for further reactivity generation.

EXPERIMENTAL SECTION

General Information. ^1H and ^{13}C NMR spectra of $CDCl_3$ solutions were recorded either at 400 and 100 MHz or at 500 and 125 MHz, respectively. Microwave reactions were conducted in sealed glass vessels (capacity 10 mL) using either a CEM Discover microwave reactor or a conventional microwave oven (Whirlpool MD 131), using silica gel (particle size 0.063−0.200 mm). In all cases, the reagents were first dissolved in dichloromethane, then mixed with silica gel, and then followed by removal of the solvent under reduced pressure. FT-IR spectra were measured in chloroform solutions using an FT-IR spectrophotometer. Mass spectra (low resolution) (EI/CI) and HRMS (EI/TOF) were obtained with a gas chromatograph/mass spectrometer. Analytical thin-layer chromatography plates used UV-active silica on aluminum. Flash column chromatography was carried out with silica gel with a particle size <0.020 mm, using appropriate mixtures of ethyl acetate and hexanes as eluents. All reactions were performed in oven-dried glassware. All materials were obtained from commercial suppliers and used as received unless otherwise noted. The free amidines **1b**, **1c**, and **1d** were obtained by treatment of solutions of the commercially available HCl or HI salts with 2.0 M aqueous KOH solutions. The aqueous layers were extracted with CH_2Cl_2 and dried over Mg_2SO_4. Free acetamidine **1e** was prepared as previously described.[11]

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General Procedure for the Synthesis of 6aa–6ca and 8aa–8ca. After skipped diyne **4a** (376 mg; 1.0 mmol) was dissolved in 1,2-dichloroethane (10 mL), benzamidine (**1a**) (1.20 mmol) was added and the reaction was heated to reflux for 1 h. After the mixture was cooled, the solvent was removed under reduced pressure. This was followed by isolation of the corresponding products by flash column chromatography (silica gel, *n*-hexane/EtOAc (80:20–60:40)).

***6aa** [(2E,/2Z) Mixture].* (362 mg; 73% yield). Two isomers, separated by flash chromatography (30% EtOc/Hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): (less polar isomer) δ 3.30 (s, 3H), 3.62 (s, 3H), 5.28 (s, 1H), 6.11 (s, 1H), 7.32 (tt, 1H, $^3J_{(H,H)}$ = 7.3 and 2.0 Hz), 7.39–7.43 (m, 2H), 7.48–7.65 (m, 8H), 8.16 (d, 2H, $^3J_{(H,H)}$ = 7.8 Hz), 8.20–8.22 (m, 2H), 12.03 (s, 1H) ppm; (more polar isomer) δ 3.65 (s, 3H), 3.68 (s, 3H), 5.28 (s, 1H), 5.56 (s, 1H), 7.31–7.35 (m, 1H), 7.37–7.41 (m, 2H), 7.51–7.60 (m, 7H), 7.64–7.67 (m, 1H), 8.16–8.18 (m, 2H), 8.23–8.25 (m, 2H), 12.1 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): (less polar isomer) δ 50.9, 51.2, 74.2, 91.4, 114.9, 124.0 (2C), 127.1 (2C), 128.0, 128.56 (2C), 128.58 (2C), 129.0 (2C), 129.4, 130.2 (2C), 132.0, 132.3, 133.6, 142.5, 148.3, 154.3, 156.6, 164.9, 165.1, 170.2 ppm; (more polar isomer) δ 51.2, 51.4, 75.0, 91.8, 109.5, 124.1 (2C), 127.6 (2C), 128.6, 128.8 (2C), 129.0 (2C), 129.1 (2C), 129.4, 130.0 (2C), 132.2, 132.4, 134.0, 142.7, 148.4, 155.37, 155.44, 164.2, 165.9, 170.0 ppm; FTIR ($CHCl_3$): (less polar isomer) ν = 1728.4, 1672.0, 1634.3, 1560.3, 1435.1, 1280.5, 1251.5 cm^{-1}; LRMS (70 eV): *m*/*z* (%): (less polar isomer) 496 (M$^+$, 63), 376 (37), 360 (22), 359 (87), 318 (20), 317 (31), 105 (100), 77 (54). Elemental analysis calcd (%) for $C_{29}H_{24}N_2O_6$: C, 70.15; H 4.87; N 5.64. Found: (less polar isomer) C, 69.83; H 5.10; N 5.48. Yellow amorphous solid.

***6ba** [(2E,/2Z) Mixture].* (379 mg; 67% yield). Two isomers, separated by flash chromatography (20% EtOc/Hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): (less polar isomer, major isomer) δ 3.35 (s, 3H), 3.64 (s, 3H), 5.22 (s, 1H), 6.10 (s, 1H), 7.36 (d, 2H, $^3J_{(H,H)}$ = 8.6 Hz), 7.47 (d, 2H, $^3J_{(H,H)}$ = 8.6 Hz), 7.53–7.59 (m, 5H), 8.12 (d, 2H, $^3J_{(H,H)}$ = 8.6 Hz), 8.13–8.15 (m, 2H), 12.04 (s, 1H) ppm; (more polar isomer, representative signals) δ 3.67 (s, 3H), 3.69 (s, 3H), 5.24 (s, 1H), 5.51 (s, 1H), 12.05 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): (less polar isomer) δ 51.0, 51.4, 73.9, 91.7, 115.1, 125.5 (2C), 127.1 (2C), 127.7, 128.9 (2C), 129.0 (2C), 129.1 (2C), 131.6 (2C), 132.0, 132.3, 134.1, 140.4, 140.8, 148.5, 154.1, 156.0, 164.0, 165.0, 170.12 ppm; LRMS (70 eV): *m*/*z* (%): (less polar isomer) 564 (M$^+$, 0.4), 305 (37), 247 (49), 158 (24), 156 (84), 141 (37), 130 (100), 111 (38), 104 (24), 103 (53), 75 (28); HRMS calculated for $C_{29}H_{22}Cl_2N_2O_6$: 564.0855, found 564.0853. Yellowish amorphous solid.

***6ca** [(2E,/2Z) Mixture].* (291 mg; 76% yield). Two isomers, separated by flash chromatography (30% EtOc/Hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): (less polar isomer) δ 3.38 (s, 3H), 3.63 (s, 3H), 3.78 (s, 6H), 3.83 (s, 6H), 5.29 (s, 1H), 6.10 (s, 1H), 6.40 (t, 1H, $^3J_{(H,H)}$ = 2.3 Hz), 6.69 (t, 1H, $^3J_{(H,H)}$= 2.3 Hz), 6.77 (d, 2H, $^3J_{(H,H)}$= 2.3 Hz), 7.34 (d, 2H, $^3J_{(H,H)}$ = 2.3 Hz), 7.52–7.54 (m, 3H), 8.12–8.14 (m, 2H), 12.01 (s, 1H) ppm; (more polar isomer, representative signals) δ 3.65 (s, 3H), 3.68 (s, 3H), 3.77 (s, 6H), 3.84 (s, 6H), 5.25 (s, 1H), 5.56 (s, 1H), 12.07 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): (less polar isomer) δ 50.9, 51.2, 55.3 (2C), 55.5 (2C), 74.1, 91.3, 99.2, 102.8 (2C), 106.4, 107.7 (2C), 115.3, 127.0 (2C), 128.9 (2C), 131.2, 131.9, 132.3, 144.5, 148.1, 153.4, 156.2, 160.77 (2C), 160.79 (2C), 164.7, 165.1, 170.3 ppm; FTIR ($CHCl_3$): (less polar isomer) ν = 1727.5, 1672.3, 1633.5, 1598.2, 1562.3, 1460.9, 1431.6, 1283.0, 1249.8, 1158.4 cm^{-1}; LRMS (70 eV): *m*/*z* (%): (less polar isomer) 616 (M$^+$, 14), 451 (47), 436 (33), 403 (37), 377 (33), 376 (29), 375 (29), 182 (100), 165 (51), 122 (29). Elemental analysis calcd (%) for $C_{33}H_{32}N_2O_{10}$: (less polar isomer) C, 64.28; H, 5.23; N, 4.54. Found: C, 64.01; H, 5.26; N, 4.90. Yellow amorphous solid.

*(Z)-Methyl 2-(7-Benzoyl-6-oxo-2,4a-diphenylfuro[3,2-d]-pyrimidin-4(3H,4aH,6H)-ylidene)acetate (**8aa**).* (65 mg; 14% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.43 (s, 3H), 6.12 (s, 1H), 7.36–7.50 (m, 9H), 7.55 (tt, 1H, $^3J_{(H,H)}$ = 7.3 and 1.2 Hz), 7.61 (tt, 1H, $^3J_{(H,H)}$ = 7.3 and 1.2 Hz), 7.79–7.81 (m, 2H), 7.96–7.98 (m, 2H), 11.47 (s, 1H) ppm; 13C NMR (100 MHz, $CDCl_3$): δ 52.0, 77.8, 96.8, 112.7, 125.8 (2C), 128.1 (2C), 128.3 (2C), 129.1 (2C), 129.2 (2C), 129.8 (2C), 130.2, 130.3, 133.5, 133.7, 135.6, 137.0, 149.8, 153.8, 168.1, 168.9, 169.5, 187.7 ppm; FTIR ($CHCl_3$): ν = 1768.8, 1650.9, 1599.9, 1587.9, 1541.2, 1469.3, 1434.5, 1358.9, 1252.5 cm^{-1}; LRMS (70 eV): *m*/*z* (%): 464 (M+, 31), 432 (10), 405 (8.2), 387 (11), 365 (17), 359 (12), 105 (100), 77 (41). Elemental analysis calcd (%) for C28H20N2O5: C 72.41; H 4.34; N 6.03. Found: C 72.38; H 4.48; N 5.95. Yellow amorphous solid.

*(Z)-Methyl 2-(7-(4-chlorobenzoyl)-4a-(4-chlorophenyl)-6-oxo-2-phenylfuro[3,2-d]pyrimidin-4(3H,4aH,6H)-ylidene)acetate (**8ba**).* (64 mg; 12% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.83 (s, 3H), 6.11 (s, 1H), 7.33–7.39 (m, 4H), 7.44–7.48 (m, 4H), 7.59 (tt, 1H, $^3J_{(H,H)}$ = 7.3 and 1.2 Hz), 7.82 (dd, 2H, $^3J_{(H,H)}$ = 7.3 and 1.2 Hz), 7.88 (dd, 2H, $^3J_{(H,H)}$ = 7.3 and 1.2 Hz), 11.51 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 52.2, 77.1, 97.2, 112.1, 127.2 (2C), 128.1 (2C), 128.7 (2C), 129.3 (2C), 129.5 (2C), 130.0, 131.2 (2C), 134.0, 134.1, 135.5, 136.4, 140.0, 149.2, 154.2, 167.8, 168.7, 169.5, 186.2 ppm; FTIR ($CHCl_3$): ν = 1771.8, 1652.0, 1588.2, 1539.0, 1492.36, 1467.8, 1434.6, 1358.6, 1253.4 cm^{-1}; LRMS (70 eV): *m*/*z* (%): 534 (31), 533 (15), 532 (M+, 41), 435 (18), 433 (25), 141 (33), 139 (100), 11 (22); HRMS calculated for $C_{28}H_{18}Cl_2N_2O_5$: 532.0593, found 532.0604. Yellowish amorphous solid.

*(Z)-Methyl 2-(7-(3,5-dimethoxybenzoyl)-4a-(3,5-dimethoxyphenyl)-6-oxo-2-phenylfuro[3,2-d]pyrimidin-4(3H,4aH,6H)-ylidene)-acetate (**8ca**).* (40 mg; 11% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.73 (s, 6H), 3.78 (s, 6H), 3.82 (s, 3H), 6.08 (s, 1H), 6.42 (t, 1H, $^3J_{(H,H)}$ = 2.2 Hz), 6.60 (d, 2H, $^3J_{(H,H)}$ = 2.4 Hz), 6.70 (t, 1H, $^3J_{(H,H)}$ = 2.4 Hz), 7.17 (d, 2H, $^3J_{(H,H)}$ = 2.3 Hz), 7.43 (t, 2H, $^3J_{(H,H)}$ = 7.8 Hz), 7.54–7.58 (m, 1H), 7.84–7.86 (m, 2H), 11.41 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 52.0, 55.4, 55.5, 77.6, 96.9, 101.4, 104.3, 106.5, 107.5, 112.9, 127.6, 128.1, 129.16, 129.21, 130.4, 133.7, 137.8, 138.8, 149.6, 153.9, 160.7, 161.3, 168.0, 168.8, 168.9, 187.3 ppm; LRMS (70 eV): *m*/*z* (%): 584 (M$^+$, 13), 510 (14), 321 (35), 165 (100), 137 (28), 122 (27), 91 (42), 73 (53); HRMS calculated for $C_{32}H_{28}N_2O_9$: 584.1795, found 584.1772. Yellowish amorphous solid.

*Conversion of **6aa** into 2-Methoxy-1-(6-(2-methoxy-2-oxoethyl)-2,5-diphenyl-pyrimidin-4-yl)-2-oxoethyl Benzoate (**5aa**).* **6aa** (248 mg; 0.50 mmol) was absorbed on silica gel (2.0 g, with the aid of CH_2Cl_2 which was then removed under reduced pressure), and the mixture was heated at 105 °C for 3 days. The silica gel was thoroughly washed with ethyl acetate, and the filtrate was concentrated and flash chromatographed (silica gel, 20% *n*-hexane/EtOAc) to afford the pure **5aa** (218 mg; 88%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.65 (s, 3H), 3.74 (s, 2H), 3.80 (s, 3H), 6.25 (s, 1H), 7.21–7.22 (m, 1H), 7.27–7.31 (m, 1H), 7.36–7.48 (m, 8H), 7.54–7.58 (m, 1H), 8.01–8.03 (m, 2H), 8.49–8.52 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 41.9, 52.1, 52.6, 72.5, 128.4 (2C), 128.5 (4C), 128.8, 128.9, 129.0, 129.3, 129.4, 130.1 (2C), 131.0, 132.6, 133.39, 133.44, 136.7, 160.7, 162.8, 163.2, 165.0, 167.5, 169.8 ppm. One carbon signal was buried under the aromatic region; FTIR ($CHCl_3$) 1768.2, 1735.0, 1562.6, 1536.0, 1437.5, 1408.6, 1264.9 cm^{-1}; LRMS (70 eV) *m*/*z* (%): 496 (M$^+$, 25), 392 (16), 391 (66), 333 (20), 105 (100), 77 (18). Elemental analysis calcd (%) for $C_{29}H_{24}N_2O_6$: C, 70.15; H, 4.87; N, 5.64. Found: C, 70.41; H, 4.89; N, 5.42. Orange amorphous solid.

*2-Methoxy-1-(6-methyl-2,5-diphenylpyrimidin-4-yl)-2-oxoethyl Benzoate (**9aa**).* (22 mg; 0.05 mmol). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.42 (s, 3H), 3.80 (s, 3H), 6.25 (s, 1H), 7.20–7.22 (m, 1H), 7.29–7.51 (m, 9H), 7.54–7.58 (m, 1H), 8.02–8.04 (m, 2H), 8.51–8.54 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.5, 52.6, 72.6, 128.3 (4C), 128.45 (2C), 128.51, 128.8, 128.9, 129.0, 129.1, 129.2, 130.0 (2C), 130.7, 132.2, 133.4, 134.5, 137.2, 159.0, 162.9, 165.1, 167.0, 167.7 ppm; FTIR ($CHCl_3$): ν = 1767.1, 1730.7, 1562.6, 1536.3, 1406.6, 1270.5, 1108.3 cm^{-1}; LRMS (70 eV): *m*/*z* (%): 438 (M$^+$, 23), 333 (56), 245 (10), 115 (15), 105 (100), 77 (28). Elemental analysis calcd (%) for $C_{27}H_{22}N_2O_4$: C, 73.96; H, 5.06; N, 6.39. Found: C, 73.87; H, 5.28; N, 6.12. Yellowish amorphous solid.

*6-(6-(2-Methoxy-2-oxoethyl)-2,5-diphenylpyrimidin-4-yl)methyl Benzoate (**10aa**).* (2.2 mg; 0.005 mmol). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.65 (s, 3H), 3.72 (s, 2H), 5.26 (s, 2H), 7.30 (dd, 2H, $^3J_{(H,H)}$ = 8.1 and 1.8 Hz), 7.36–7.46 (m, 8H), 7.55–7.60 (m, 1H), 8.06 (dd, 2H, $^3J_{(H,H)}$ = 8.6 and 1.5 Hz), 8.40 (dd, 2H, $^3J_{(H,H)}$ = 7.8 and 1.3 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 41.6, 52.1, 64.6, 128.3

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(2C), 128.4 (4C), 128.7, 129.1 (4C), 129.8 (2C), 130.0, 130.7, 131.1, 133.0, 134.0, 137.2, 161.6, 161.7, 163.1, 166.1, 167.0 ppm; FTIR ($CHCl_3$): ν = 1729.9, 1561.4, 1538.3, 1408.1, 1266.9, 1114.5 cm^{-1}; LRMS (70 eV): m/z (%): 438 (M^+, 23), 334 (25), 333 (100), 115 (27), 105 (39), 77 (37); HRMS calculated for $C_{27}H_{22}N_2O_4$: 438.1580, found 438.1569. Yellowish amorphous solid.

*(6-Methyl-2,5-diphenylpyrimidin-4-yl)methyl Benzoate (**11aa**).* (4 mg; 0.01 mmol). ^1H NMR (400 MHz, $CDCl_3$): δ 2.38 (s, 3H), 5.23 (s, 2H), 7.27−7.29 (m, 2H), 7.37−7.47 (m, 8H), 7.57 (tt, 1H, $^3J_{(H,H)}$= 7.3 and 1.3 Hz), 8.04−8.06 (m, 2H), 8.39−8.41 (m, 2H), ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.1, 64.7, 128.22 (2C), 128.28 (2C), 128.31 (2C), 128.38, 128.9 (2C), 129.0, 129.8, 130.1, 130.4, 130.8, 135.1, 137.6, 160.6, 162.8, 165.8, 166.2 ppm; FTIR ($CHCl_3$): ν = 1721.2, 1603.4, 1560.4, 1540.0, 1404.2, 1275.5, 1115.6 cm^{-1}; LRMS (70 eV): m/z (%): 380 (M^+, 12), 276 (19), 275 (100), 115 (16), 105 (27), 77 (22). Elemental analysis calcd (%) for $C_{25}H_{20}N_2O_2$: C, 78.93; H, 5.30; N, 7.36. Found: C, 78.83; H, 5.44; N, 7.36. White amorphous solid.

General Procedure for the Synthesis of Pyrimidines 5. After skipped diyne **4a−f** (1.0 mmol) was dissolved in 1,2-dichloroethane (10 mL), amidine **1a−e** (1.20 mmol) was added and the reaction was heated to reflux for 1 h. After the mixture was cooled, the solvent was removed under reduced pressure. The resulting mixture was absorbed on silica gel (2.0 g, with the aid of CH_2Cl_2 which was then removed under reduced pressure), and it was heated for 3 days at 105 °C. Extraction of the products with ethyl acetate was followed by isolation of the desired products by flash column chromatography (silica gel, appropriate mixtures of *n*-hexane/EtOAc).

*1-(5-(4-Chlorophenyl)-6-(2-methoxy-2-oxoethyl)-2-phenylpyrimidin-4-yl)-2-methoxy-2-oxoethyl 4-Chlorobenzoate (**5ba**).* (179 mg; 42%). ^1H NMR (400 MHz, $CDCl_3$): δ 3.66 (s, 3H), 3.72 (s, 2H), 3.80 (s, 3H), 6.21 (s, 1H), 7.16 (dd, 1H, $^3J_{(H,H)}$= 8.3 and 2.3 Hz), 7.29−7.33 (m, 2H), 7.41 (d, 2H, $^3J_{(H,H)}$= 8.8 Hz), 6.45−7.50 (m, 4H), 7.95 (d, 2H, $^3J_{(H,H)}$= 8.6 Hz), 8.46−8.49 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 41.8, 52.2, 52.8, 72.5, 127.2, 128.5, 128.8, 129.1, 129.3, 130.8, 130.9, 131.2, 131.4, 131.9, 135.3, 136.5, 140.2, 160.0, 162.8, 163.5, 164.2, 167.2, 169.6 ppm. One carbon signal was buried under the aromatic region; FTIR ($CHCl_3$): ν = 1766.3, 1734.6, 1595.8, 1562.8, 1535.1, 1488.9, 1437.7, 1408.1, 1265.5, 1173.4, 1093.3 cm^{-1}; LRMS (70 eV): m/z (%): 566 (M^+, 11), 564 (M^+, 15), 427 (20), 425 (51), 141 (37), 139 (100). Elemental analysis calcd (%) for $C_{29}H_{22}Cl_2N_2O_6$: C, 61.60; H, 3.92; N, 4.95. Found: C, 61.78; H, 4.17; N, 5.06. Yellowish amorphous solid.

*1-(5-(3,5-Dimethoxyphenyl)-6-(2-methoxy-2-oxoethyl)-2-phenylpyrimidin-4-yl)-2-methoxy-2-oxoethyl 3,5-Dimethoxybenzoate (**5ca**).* (244 mg; 48%). ^1H NMR (400 MHz, $CDCl_3$): δ 3.53 (s, 3H), 3.68 (s, 3H), 3.77 (s, 2H), 3.79 (s, 3H), 3.79 (s, 6H), 3.81 (s, 3H), 6.30 (s, 1H), 6.32−6.33 (m, 1H), 6.44 (t, 1H, $^3J_{(H,H)}$= 2.3 Hz), 6.49−6.50 (m, 1H), 6.64 (t, 1H, $^3J_{(H,H)}$= 2.5 Hz), 7.17 (d, 2H, $^3J_{(H,H)}$= 2.5 Hz), 7.44−7.48 (m, 3H), 8.47−8.50 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 41.8, 52.2, 52.6, 55.2, 55.4, 55.6 (2C), 72.7, 101.0, 106.4, 107.1, 107.6 (2C), 107.7, 128.5 (4C), 130.8, 131.0, 132.5, 135.1, 136.8, 159.8, 160.7 (2C), 161.08, 161.12, 162.7, 163.2, 164.9, 167.5, 170.0 ppm; FTIR ($CHCl_3$): ν = 1766.3, 1736.9, 1601.4, 1461.2, 1407.4, 1352.1, 1330.4, 1158.2 cm^{-1}; LRMS (70 eV): m/z (%): 616 (M^+, 20), 452 (28), 451 (100), 165 (66), 137 (17), 122 (25). Elemental analysis calcd (%) for $C_{33}H_{32}N_2O_{10}$: C, 64.28; H, 5.23; N, 4.54. Found: C, 64.51; H, 5.50; N, 4.41. Yellowish solid.

*2-Methoxy-1-(6-(2-methoxy-2-oxoethyl)-2-phenyl-5-p-tolylpyrimidin-4-yl)-2-oxoethyl 4-Methylbenzoate (**5da**).* (241 mg; 52%).^1H NMR (400 MHz, $CDCl_3$): δ 2.35 (s, 3H), 2.40 (s, 3H), 3.66 (s, 3H), 3.74 (s, 2H), 3.79 (s, 3H), 6.23 (s, 1H), 7.09 (m, 2H), 7.21−7.28 (m, 4H), 7.45−7.48 (m, 3H), 7.92 (d, 2H, $^3J_{(H,H)}$= 8.3 Hz), 8.48−8.51 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.2, 21.7, 41.9, 52.1, 52.6, 72.4, 126.2, 128.5 (4C), 129.06 (2C), 129.15, 129.23, 129.5, 129.6, 130.1 (2C), 130.3, 130.9, 132.7, 136.8, 138.7, 144.2, 160.3, 162.96, 163.01, 165.1, 167.7, 169.9 ppm; FTIR ($CHCl_3$): ν = 1767.3, 1733.4, 1564.9, 1535.6, 1408.8, 1267.8, 1179.0, 1102.1 cm^{-1}; LRMS (70 eV): m/z (%): 524 (M^+, 14), 406 (12), 405 (44), 347 (3.3), 317 (4.0), 287 (3.7), 119 (100), 91 (24). Elemental analysis calcd (%) for $C_{31}H_{28}N_2O_6$: C, 70.98; H, 5.38; N, 5.34. Found: C, 70.97; H, 5.45; N, 5.39. Pale yellowish amorphous solid.

*1-(5-(4-Fluorophenyl)-6-(2-methoxy-2-oxoethyl)-2-phenylpyrimidin-4-yl)-2-methoxy-2-oxoethyl 4-Fluorobenzoate (**5ea**).* (215 mg; 42%). ^1H NMR (400 MHz, $CDCl_3$): δ 3.66 (s, 3H), 3.72 (s, 2H), 3.80 (s, 3H), 6.22 (s, 1H), 7.02 (td, 1H, $^3J_{(H,H)}$= 8.6 and 2.8 Hz), 7.10 (t, 2H, $^3J_{(H,H)}$= 8.6 Hz), 7.16−7.23 (m, 2H), 7.34−7.38 (m, 1H), 7.44−7.50 (m, 3H), 8.03−8.06 (m, 2H), 8.48−8.50 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 41.9, 52.2, 52.7, 72.4, 115.6 (2C) (d, $J_{(F,C)}$ = 22.6 Hz), 116.0 (d, $J_{(F,C)}$ = 21.9 Hz), 116.2 (d, $J_{(F,C)}$ = 21.9 Hz), 125.1 (d, $J_{(F,C)}$ = 2.8 Hz), 128.5 (4C), 129.3 (d, $J_{(F,C)}$ = 3.5 Hz), 131.1, 131.4 (2C) (d, $J_{(F,C)}$ = 8.5 Hz), 131.6, 132.7 (2C) (d, $J_{(F,C)}$ = 9.9 Hz), 136.6, 160.3, 162.97 (d, $J_{(F,C)}$ = 249 Hz), 163.03, 163.4, 164.0, 166.2 (d, $J_{(F,C)}$ = 256 Hz), 167.3, 169.7 ppm; FTIR ($CHCl_3$): ν = 1767.1, 1736.3, 1604.3, 1565.0, 1535.2, 1508.9, 1409.6, 1264.8, 1239.2, 1156.3 cm^{-1}; LRMS (70 eV): m/z (%): 532 (M^+, 16), 410 (8.6), 409 (33), 351 (3.9), 321 (4.6), 133 (9.3), 123 (100), 95 (15). Elemental analysis calcd (%) for $C_{29}H_{22}F_2N_2O_6$: C, 65.41; H, 4.16; N, 5.26. Found: C, 65.51; H, 4.30; N, 4.97. Pale yellowish amorphous solid.

*1-(5-(3-Chlorophenyl)-6-(2-methoxy-2-oxoethyl)-2-phenylpyrimidin-4-yl)-2-methoxy-2-oxoethyl 3-Chlorobenzoate (**5fa**).* (181 mg; 41%). 1:1 mixture of atropisomers. ^1H NMR (400 MHz, $CDCl_3$): δ 3.67 (s, 3H), 3.73 and 3.73 (s and s, 2H), 3.80 and 3.82 (s and s, 3H), 6.23 and 6.24 (s and s, 1H), 7.11−7.13 (m, 1/2H), 7.20−7.21 (m, 1/2H), 7.25−7.30 (m, 1H), 7.36−7.42 (m, 3H), 7.44−7.49 (m, 3H), 7.53−7.56 (m, 1H), 7.88−7.92 (m, 1H), 7.98−7.99 (m, 1H), 8.48−8.50 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 41.90 and 41.95, 52.3, 52.78 and 52.82, 72.8 and 72.9, 127.5, 127.6, 128.2, 128.5, 129.2, 129.3, 129.7, 129.8, 130.0, 130.1, 130.35, 130.38, 131.1 and 131.21, 131.25, 133.6, 134.7, 135.0, 135.1, 135.2, 135.3, 136.5, 159.8, 159.9, 162.75, 162.82, 163.6, 163.7, 163.9, 167.0, 167.1, 169.6 ppm; FTIR ($CHCl_3$): ν = 1768.2, 1736.9, 1564.3, 1536.1, 1417.3, 1400.8, 1252.6, 1224.8 cm^{-1}; LRMS (70 eV): m/z (%): 566 (11), 564 (M^+, 16), 427 (14), 425 (36), 141 (32), 139 (100), 111 (26). Elemental analysis calcd (%) for $C_{29}H_{22}Cl_2N_2O_6$: C, 61.60; H, 3.92; N, 4.95. Found: C, 61.60; H, 3.92; N, 4.73. Pale yellowish amorphous solid.

*2-Methoxy-1-(6-(2-methoxy-2-oxoethyl)-2-(3-nitrophenyl)-5-phenylpyrimidin-4-yl)-2-oxoethyl Benzoate (**5ab**).* (262 mg; 48%). ^1H NMR (400 MHz, $CDCl_3$): δ 3.67 (s, 3H), 3.77 (s, 2H), 3.82 (s, 3H), 6.29 (s, 1H), 7.24 (d, 1H, $^3J_{(H,H)}$ = 7.6 Hz), 7.30−7.35 (m, 3H), 7.43 (t, 2H, $^3J_{(H,H)}$ = 8.1 Hz), 7.49 (t, 1H, $^3J_{(H,H)}$ = 7.6 Hz), 7.57 (t, 1H, $^3J_{(H,H)}$ = 7.6 Hz), 7.65 (t, 1H, $^3J_{(H,H)}$ = 7.8 Hz), 8.01−8.03 (m, 2H), 8.31−8.34 (m, 1H), 8.80−8.83 (m, 1H), 9.31−9.32 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 41.8, 52.3, 52.8, 72.4, 123.4, 125.4, 128.4 (2C), 128.8, 128.9, 129.1, 129.17, 129.20, 129.23, 129.5, 130.0 (2C), 132.9, 133.6, 133.8, 134.0, 138.6, 148.8, 160.7, 161.0, 163.5, 165.0, 167.3, 169.6 ppm; FTIR ($CHCl_3$): ν = 3690.1, 3462.0, 3024.5, 1768.2, 1735.7, 1602.6, 1560.6, 1438.7, 1406.0, 1349.7, 1268.9, 1107.2 cm^{-1}; LRMS (70 eV): m/z (%): 541 (M^+, 3.0), 437 (4.6), 436 (18), 243 (3.4), 140 (5.7), 115 (5.8), 105 (100), 77 (19). Elemental analysis calcd (%) for $C_{29}H_{23}N_3O_8$: C, 64.32; H, 4.28; N, 7.76. Found: C, 64.50; H, 4.66; N, 7.71. Pale yellowish amorphous solid.

*1-(2-(4-Chlorophenyl)-6-(2-methoxy-2-oxoethyl)-5-phenylpyrimidin-4-yl)-2-methoxy-2-oxoethyl Benzoate (**5ac**).* (280 mg; 53%). ^1H NMR (400 MHz, $CDCl_3$): δ 3.65 (s, 3H), 3.73 (s, 2H), 3.79 (s, 3H), 6.25 (s, 1H), 7.21 (d, 1H, $^3J_{(H,H)}$ = 7.6 Hz), 7.30 (t, 1H, $^3J_{(H,H)}$ = 7.8 Hz), 7.35−7.50 (m, 7H), 7.57 (t, 1H, $^3J_{(H,H)}$ = 7.5 Hz), 8.01 (d, 2H, $^3J_{(H,H)}$ = 8.3 Hz), 8.44 (d, 2H, $^3J_{(H,H)}$ = 7.6 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 41.9, 52.2, 52.6, 72.4, 128.4 (2C), 128.7 (2C), 128.9, 129.0 (2C), 129.3, 129.4, 129.8 (2C), 130.0 (2C), 132.8, 133.2, 133.5, 135.3, 137.3, 160.2, 162.3, 163.0, 165.0, 167.4, 169.7 ppm. One carbon signal was buried under the aromatic region at 128.9 ppm; FTIR ($CHCl_3$): ν = 1766.3, 1735.3, 1562.2, 1534.7, 1408.4, 1266.5, 1176.0, 1092.6 cm^{-1}; LRMS (70 eV): m/z (%): 530 (M^+, 6.2), 427 (6.7), 425 (17), 141 (3.7), 140 (8.1), 115 (7.8), 105 (100), 77 (33). Elemental analysis calcd (%) for $C_{29}H_{23}ClN_2O_6$: C, 65.60; H, 4.37; N, 5.28. Found: C, 65.39; H, 4.52; N, 5.40. Pale yellowish amorphous solid.

*2-Methoxy-1-(6-(2-methoxy-2-oxoethyl)-5-phenyl-2-p-tolylpyrimidin-4-yl)-2-oxoethyl Benzoate (**5ad**).* (299 mg; 48%). ^1H NMR (400 MHz, $CDCl_3$): δ 2.42 (s, 3H), 3.65 (s, 3H), 3.73 (s, 2H), 3.79 (s,

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3H), 6.24 (s, 1H), 7.20−7.22 (m, 1H), 7.25−7.30 (m, 3H), 7.35−7.49 (m, 5H), 7.56 (t, 1H, $^3J_{(H,H)}$ = 7.5 Hz), 8.02 (d, 2H, $^3J_{(H,H)}$ = 7.3 Hz), 8.39 (d, 2H, $^3J_{(H,H)}$ = 8.1 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.5, 41.9, 52.1, 52.6, 72.6, 128.3 (2C), 128.5 (2C), 128.77, 128.84, 128.9, 129.2 (2C), 129.3, 129.5, 130.1 (2C), 132.2, 133.4, 133.5, 134.1, 141.3, 160.0, 162.7, 163.3, 165.0, 167.6, 169.8 ppm. One carbon signal was buried under the aromatic region; FTIR ($CHCl_3$): ν = 1766.3, 1734.4, 1561.3, 1533.7, 1438.0, 1408.9, 1347.7, 1266.7, 1176.9, 1107.6 cm^{-1}; LRMS (70 eV): m/z (%): 510 (M^+, 30), 405 (42), 347 (6.9), 317 (10), 140 (11), 116 (20), 105 (100), 77 (30). Elemental analysis calcd (%) for $C_{30}H_{26}N_2O_6$: C, 70.58; H, 5.13; N, 5.49. Found: C, 70.42; H, 5.26; N, 5.86. Pale yellowish amorphous solid.

*2-Methoxy-1-(6-(2-methoxy-2-oxoethyl)-2-methyl-5-phenylpyrimidin-4-yl)-2-oxoethyl Benzoate (**5ae**).* (161 mg; 37%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.77 (s, 3H), 3.60 (s, 3H), 3.62 (s, 2H), 3.75 (s, 3H), 6.16 (s, 1H), 7.15−7.17 (m, 1H), 7.27−7.32 (m, 1H), 7.35−7.47 (m, 5H), 7.53−7.57 (m, 1H), 7.98−8.01 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ 25.8, 41.6, 52.1, 52.6, 72.3, 128.3 (2C), 128.76, 128.80, 128.85, 128.88, 129.3, 129.5, 130.0 (2C), 131.9, 133.35, 133.43, 159.9, 162.3, 165.0, 167.3, 167.5, 169.7 ppm; FTIR ($CHCl_3$): ν = 1766.0, 1736.0, 1603.2, 1566.0, 1543.1, 1421.8, 1267.2, 1108.3 cm^{-1}; LRMS (70 eV): m/z (%): 434 (M^+, 10), 329 (22), 271 (22), 231 (39), 172 (19), 105 (100), 103 (41) 77 (40); HRMS calculated for $C_{24}H_{22}N_2O_6$: 434.1478, found 434.1490. Yellowish oil.

*(2′Z)-Dimethyl 2,2′-(5-(Isobutyryloxy)-5-isopropyl-2-phenylpyrimidine-4,6(1H,5H)-diylidene)diacetate (**6ga**).* Two isomers. Separated by flash chromatography (20% EtOc/Hexanes); major isomer (more polar) (263 mg; 60%), minor isomer (15 mg; 4%). (Major isomer): ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.96 (d, 3H, $^3J_{(H,H)}$ = 6.8 Hz), 0.99 (d, 3H, $^3J_{(H,H)}$ = 6.8 Hz), 1.19 (d, 6H, $^3J_{(H,H)}$ = 7.1 Hz), 2.22−2.29 (m, 1H), 2.55−2.62 (m, 1H), 3.72 (s, 3H), 3.74 (s, 3H), 5.09 (s, 1H), 5.35 (s, 1H), 7.44−7.53 (m, 3H), 8.07−8.09 (m, 2H), 11.87 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ 16.1, 16.2, 18.4, 18.5, 34.2, 41.8, 51.1, 51.3, 90.4, 108.3, 127.4 (2C), 128.9 (2C), 132.1, 132.4, 148.2, 153.4, 154.8, 165.7, 169.9, 173.9 ppm. One carbon signal was buried under the $CDCl_3$ signals; FTIR ($CHCl_3$): ν = 1744.2, 1720.8, 1675.1, 1632.1, 1591.7, 1567.6, 1435.3, 1283.8, 1251.3, 1159.4 cm^{-1}; LRMS (70 eV): m/z (%): 428 (M^+, 12), 358 (33), 357 (100), 284 (25), 283 (25), 270 (33), 251 (21), 210 (34). Elemental analysis calcd (%) for $C_{23}H_{28}N_2O_6$: C, 64.47; H, 6.59; N, 6.54. Found: C, 64.37; H, 6.58; N, 6.30. Orange amorphous solid.

*(5-Isopropyl-6-methyl-2-phenylpyrimidin-4-yl)methyl Isobutyrate (**12**).* (76 mg; 40%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.24 (d, 6H, $^3J_{(H,H)}$= 7.1 Hz), 1.38 (d, 6H, $^3J_{(H,H)}$ = 7.3 Hz), 2.62−2.73 (m, 1H), 2.67 (s, 3H), 3.27−3.34 (m, 1H), 5.29 (s, 2H), 7.42−7.45 (m, 3H), 8.38−8.41 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ 19.0 (2C), 20.9 (2C), 24.1, 27.5, 34.0, 65.1, 128.0 (2C), 128.3 (2C), 130.1, 134.2, 137.7, 160.9, 161.1, 165.8, 176.7 ppm; FTIR ($CHCl_3$): ν = 2977.5, 1732.6, 1545.5, 1469.0, 1436.2, 1401.8, 1189.5, 1155.9 cm^{-1}; LRMS (70 eV): m/z (%): 312 (M^+, 19), 242 (25), 241 (100), 224 (67), 200 (13), 104 (33), 57 (20). Elemental analysis calcd (%) for $C_{19}H_{24}N_2O_2$: C, 73.05; H, 7.74; N, 8.97. Found: C, 73.12; H, 7.81; N, 9.33. Yellowish oil.

*4,6-Dimethyl-2-phenylpyrimidin-5-yl Pivalate (**13**).* (63 mg; 35%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.42 (s, 9H), 2.42 (s, 6H), 7.43−7.47 (m, 3H), 8.39−8.41 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ 19.1 (2C), 27.1 (3C), 39.3, 128.2 (2C), 128.4 (2C), 130.1, 137.5, 141.9, 159.1 (2C), 160.9, 175.4 ppm; FTIR ($CHCl_3$): ν = 2978.9, 1748.9, 1601.7, 1573.4, 1535.4, 1435.7, 1403.6, 1348.5, 1273.0, 1226.4, 1107.1 cm^{-1}; LRMS (70 eV): m/z (%): 284 (M^+, 11), 251 (9.3), 200 (62), 130 (17), 104 (29), 85 (18), 57 (100). Elemental analysis calcd (%) for $C_{17}H_{20}N_2O_2$: C, 71.81; H, 7.09; N, 9.85. Found: C, 71.77; H, 7.30; N, 10.09. White amorphous solid.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Optimization of the reaction conditions for the conversion of **6aa** into **5aa**. Copies of ^{1}H NMR and ^{13}C NMR spectra for compounds **5**, **6**, **8**, **9**, **11**, and **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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