Accepted Manuscript

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PII: S0040-4020(18)31006-8

DOI: 10.1016/j.tet.2018.08.040

Reference: TET 29760

To appear in: *Tetrahedron*

Received Date: 27 July 2018

Revised Date: 21 August 2018

Accepted Date: 23 August 2018

Please cite this article as: Huang Q, Qin L, Zard SZ, Xanthate-mediated intermolecular alkylation of pyrazines, *Tetrahedron* (2018), doi: 10.1016/j.tet.2018.08.040.

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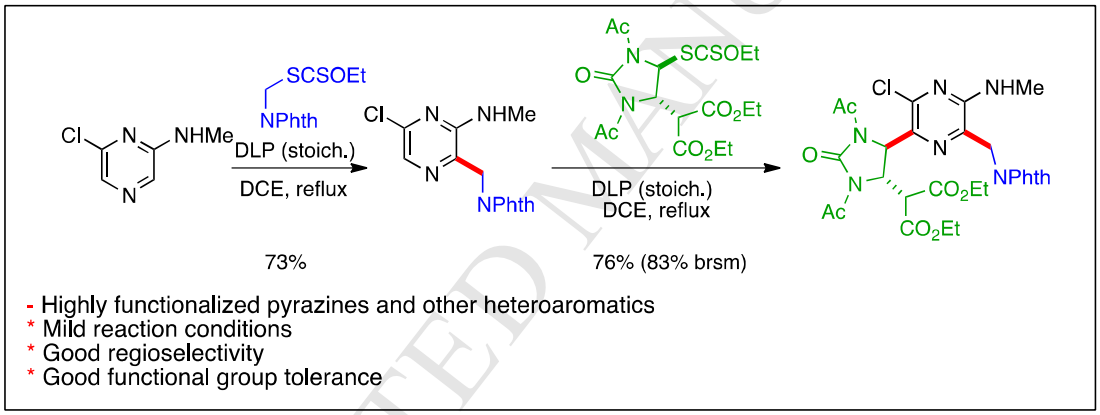
Graphical abstract



Xanthate-mediated intermolecular alkylation of pyrazines

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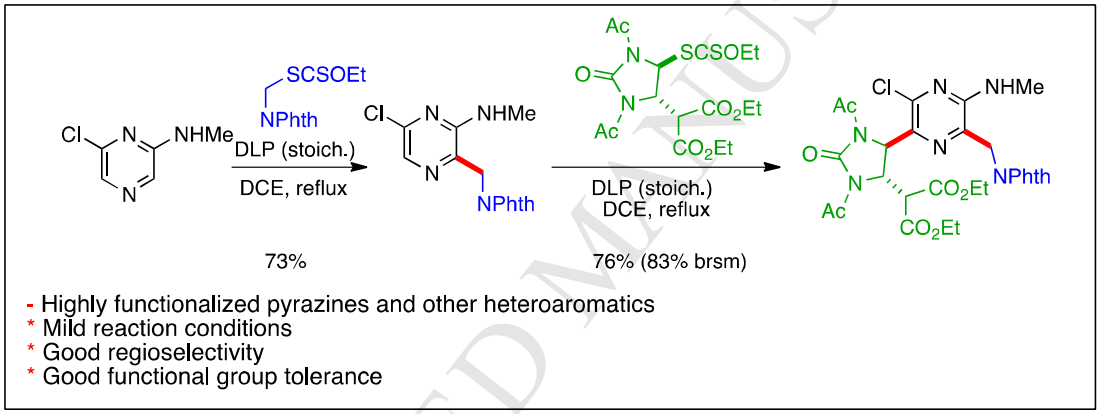
† This paper is dedicated with respect and admiration to Professor Léon Ghosez.

Graphical abstract



Abstract: An expedient approach for the intermolecular C-H functionalization of pyrazines and other heteroarenes by the radical chemistry of xanthates is reported. Incorporation of a multitude of functional alkyl groups onto these heteroarenes proceeds in good yield and good to excellent regioselectivity, leading to highly functionalized heteroaromatics.

Keywords: Minisci reaction; xanthates; pyrazines; C-H functionalization of heteroaromatics

1. Introduction

Pyrazines constitute an important member of the class of diazines due to their wide ranging applications as flavoring agents,[1] in material sciences,[2] and in medicines. For example, disubstituted 2-*sec*-butyl-3-methoxypyrazine is present in

Cabernet-Sauvignon wine. 2,5-Dimethyl-3-(pentan-3-yl)-pyrazine serves as an ant alarm pheromone. As for drugs, amiloride, a potassium-sparing diuretic, is used in the management of hypertension and congestive heart failure. After more than two decades' efforts, a potent small molecule named SHP099 containing a pyrazine core was finally found as inhibitor of SHP2 phosphatase, a stimulator of cancer growth (Figure 1).[3]

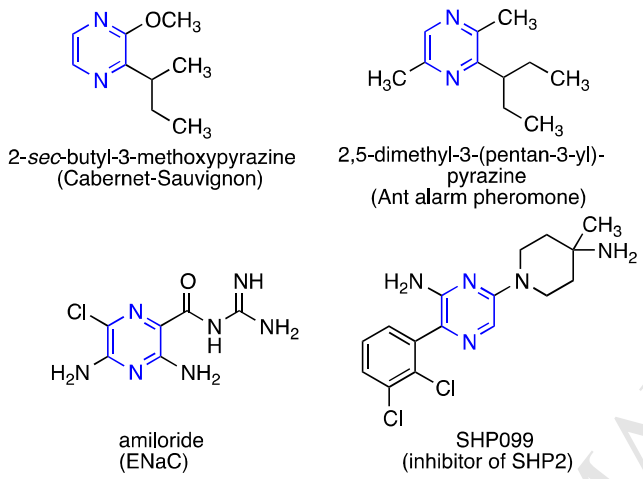


Figure 1. Selected examples of biologically active pyrazines

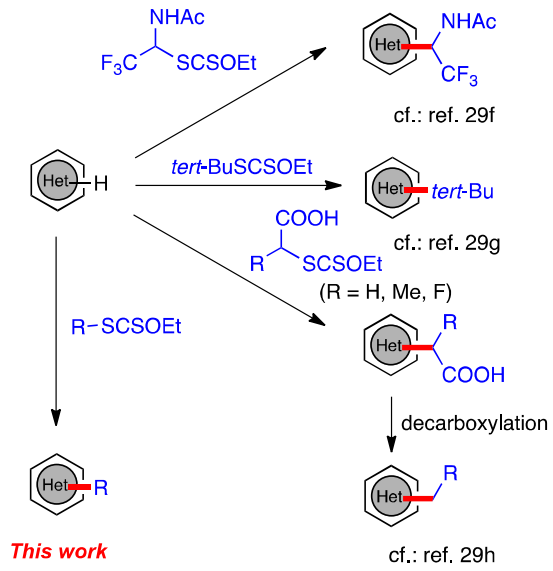
Conventional methods for the preparation of pyrazines include cyclocondensation,[4] modification of pyrazinones,[5] transition metal catalyzed cross-coupling with halogenopyrazines[6] and metalation.[7] These pathways, however, suffer from various limitations, such as inaccessible substitution patterns, harsh reaction conditions, prefunctionalized substrates, etc. These disadvantages limit the exploitation of the potential of pyrazines.

Recently, radical chemistry has arisen to prominence due to its high promise in the early- and late-stage C-H functionalization of pharmaceutical leads.[8] This demand from industry has resulted in the revival of Minisci-type reactions as powerful tools for the modification of heteroaromatics. Since the seminal work by Minisci *et al.*, in which the radicals were generated from carboxylic acids by silver-catalyzed oxidative decarboxylation[9] or from alkyl iodides with H_2O_2 and $Fe(II)SO_4 \cdot 7H_2O$ in DMSO,[10] the toolkits for the generation of radicals useful in this context have considerably expanded. For example, alkyl radicals generated by decarboxylation can now be accessed via Barton's esters,[11] amino acids[12] or from acid chlorides and anhydrides

under photoredox conditions.[13] Starting from alkyl halides, alkyl radicals can be produced through palladium catalysis[14] or by photoredox.[15] A multitude of other radical precursors suitable for Minisci reactions have been developed, including: alkanes,[16] alkyltrifluoroborates,[17] organoboronic acids[18], peracetates,[19] aldehydes,[20] alcohols,[21] sulfonyl halides,[22] sulfones,[23] sulfinates,[24] 1,4-dihydropyridines[25] and olefins,[26] among others. *The alkyl groups introduced, however, are mostly scarcely functionalized.*

For over two decades, the unique degenerate addition-fragmentation of xanthates has evolved into a powerful method in the creation of carbon-carbon bonds.[27] Its adoption in the intermolecular functionalization of heteroaromatics, however, dates back to 1992, when Minisci *et al.* reported in a sole paper the cyclohexylation of heteroarenes via a Barton-McCombie-type dithiocarbonate.[28] Employment of alternative cleavage of the carbon-sulfur bond in xanthates for the intermolecular C-H alkylation of heteroarenes is more recent.[29] For our part, we have developed for example the trifluoroethylamination[29f] and *tert*-butylation[29g] of a wide array of electron-rich and electron-poor heteroaromatics, demonstrating also a high tolerance towards polar functional groups. Moreover, methyl and related alkyl groups were incorporated into heteroarenes by the intermolecular addition of carboxylic acid xanthates, followed by spontaneous or thermal-induced decarboxylation.[29h] These methods provide an expedient inexpensive alternative for the functionalization of heteroaromatics.

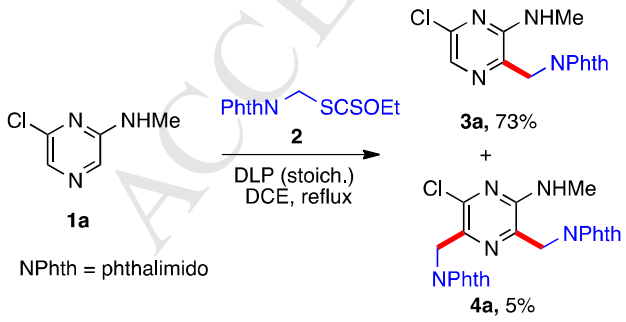
Herein, we would like to report further progress in the introduction of highly functionalized alkyl groups into pyrazines and other heteroaromatics mediated by xanthates under mild reaction conditions (Scheme 1).



Scheme 1. Previous work on the xanthate-mediated Minisci-type alkylations

2. Results and Discussion

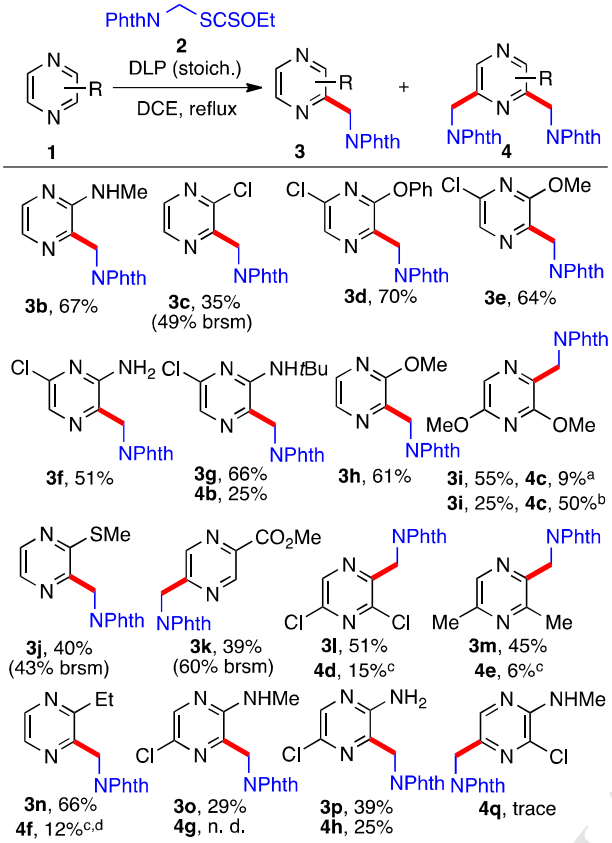
Our investigation commenced with 2-chloro-6-methylaminopyrazine **1a**, which was previously examined in the *tert*-butylation process.[29g] We were pleased to find that exposure of pyrazine **1a** and 2.0 equivalents of mildly nucleophilic phthalimidomethyl xanthate **2** to portionwise addition of stoichiometric dilauroyl peroxide (DLP) in refluxing 1,2-dichloroethane (DCE) afforded readily aminomethylated product **3a** in 73% yield, together with 5% of double alkylation product **4a**, displaying therefore good regioselectivity.



Scheme 2. First example of pyrazine alkylation

This inspiring result encouraged us to explore the scope of pyrazine substrates. Our observations are summarized in Scheme 3 (brsm = based on recovered starting

material). Compound **3b** containing a methylamino group was obtained in 67% yield, while chlorine-bearing product **3c** was obtained in 35% yield, with part of the starting pyrazine recovered. Electron-donating methylamino group is therefore a better activating group than chlorine. Variation from the electron-donating methylamino group to other groups was then investigated, including phenoxy, methoxy, amino, *tert*-butylamino. The corresponding desired products **3d-g** were indeed isolated in good yield. It is worth noting that the *tert*-butylamino group can serve as a protected amino group in the place of Boc, since the protection of the amino group with Boc failed under standard conditions. By changing the relative equivalents of 2,6-dimethoxypyrazine and xanthate **2**, mono-substituted product **3i** and double substituted product **4c** could be obtained in variable ratio and in good combined yields. 2-Methylthiopyrazine was also successfully involved in the alkylation to afford pyrazine **3j** in moderate yield (40%). Alkylation of methyl pyrazine-2-carboxylate containing an electron-withdrawing group gave exclusively the *para*-substituted product **3k** in a moderate yield of 39%. As for the reaction involving 2,6-dichloropyrazine and alkylpyrazines, activation of the ring with trifluoroacetic acid (TFA) proved necessary and the corresponding monoalkylated products **3l-n** and double alkylated products **4d-f** were obtained in good combined yields. The other two regioisomers of pyrazine **1a**, namely 2-chloro-5-methylaminopyrazine and 2-chloro-3-methylaminopyrazine, were exposed to the same reaction conditions to further confirm the *ortho*-activation of electron-donating group. Starting from the former and its non-methylated analog, mono-addition products **3o-p** were isolated in 29% and 39% yield, respectively. While the yield of **4g** was not determined due to difficulties in purification, double-addition compound **4h** was isolated in 25% yield, a comparatively higher yield than that of product **4a**. This is probably due to the *meta*-deactivating *ortho*-activating chlorine atom. As for the alkylation of the 2,3-disubstituted pyrazine, only traces of the desired product **4q** were observed.

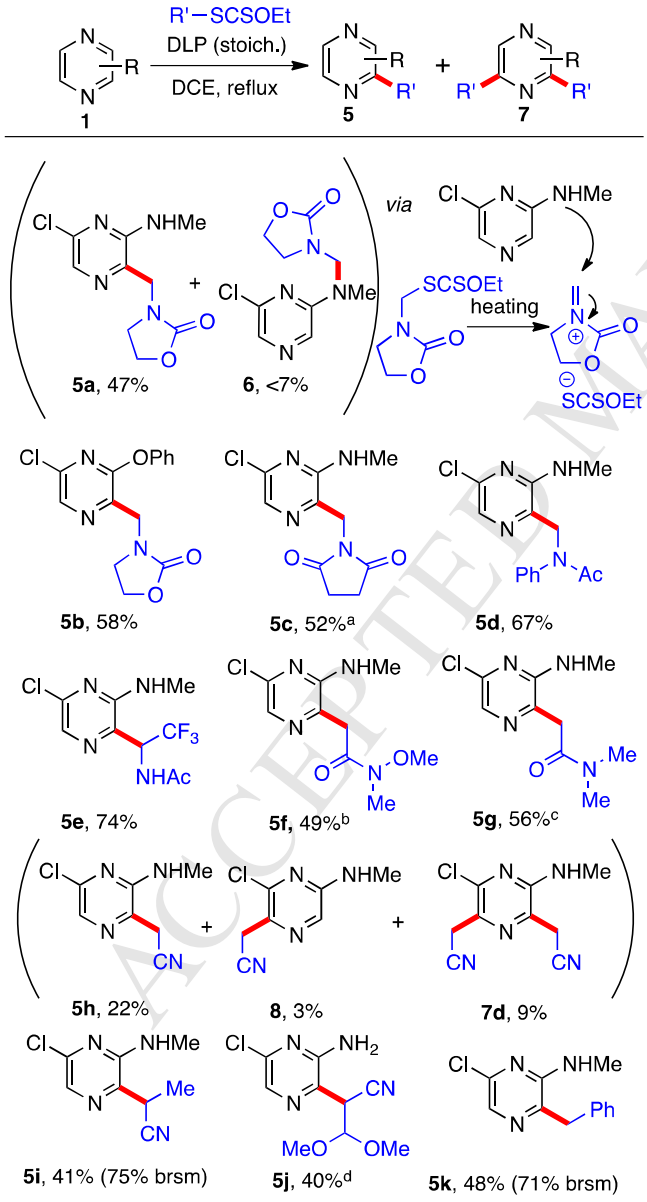


[a] Ratio of pyrazine **1**:xanthate **2** = 2:1. [b] Ratio of pyrazine **1**: xanthate **2** = 1:3. [c] 1.2 equiv of TFA was added. [d] **4f** was isolated as a 1:1 regioisomers.

Scheme 3. Scope of pyrazine substrates

Apart from xanthate **2**, which introduces a useful and conveniently protected aminomethyl group, this protocol proved applicable to alkylation with various other xanthates (Scheme 4). For instance, in the addition involving oxazolidinonemethyl xanthate, the desired product **5a** was isolated in 47% yield, while a minor by-product **7** resulting from the ionic attack of the methylamino group on the thermally produced iminium intermediate was observed in less than 7% yield. When a nucleophilic amino group was absent, as in pyrazine **5b** containing a phenoxy group, the expected adduct was obtained in 58% yield, without complication from side products arising from unwanted ionic pathways. Pyrazines arising from alkylation with other alkyl groups, including succinimidomethyl (**5c**), phenylacetamidomethyl (**5d**), trifluoroethylacetamido (**5e**), Weinreb amide (**5f**) and amide (**5g**) were delivered smoothly in moderate to good yields. However, the reaction involving highly

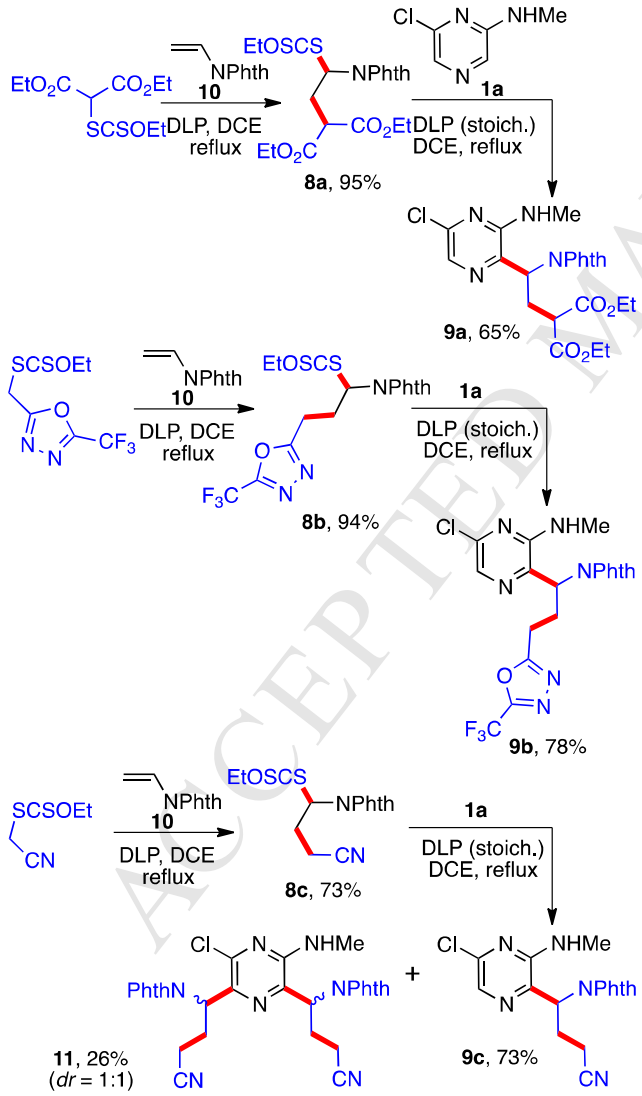
electrophilic cyanomethyl radical furnished the two regioisomers **5h** and **8** in 22% and 3% yield, respectively, together with the double alkylated product **7d** in 9% yield. To our surprise, however, addition of 2-propionitrile xanthate to pyrazine **1a** gave adduct **5i** cleanly in 41% yield, even though some starting pyrazine was recovered. The reason for this divergence in behavior is presently not clear. The sensitive acetal group also proved compatible, as in compound **5j**. Equally noteworthy is the benzylated product **5k**, which was secured in 48% yield. Benzyl radicals tend to be somewhat unreactive.



[a] Dialkylated product **7a** was isolated in 28% yield.
[b] Dialkylated product **7b** was isolated in 11% yield.
[c] Dialkylated product **7c** was isolated in 14% yield.
[d] Reaction was carried out in EtOAc at 60 °C.

Scheme 4. Scope of the xanthate partner

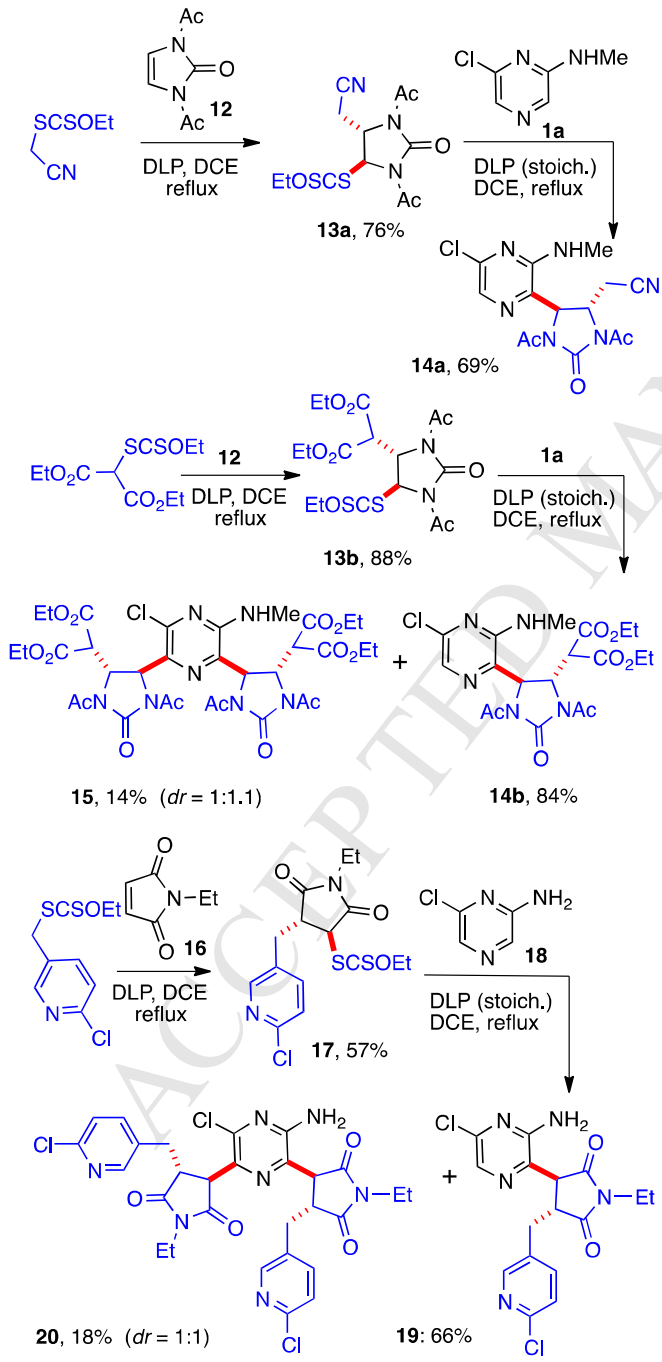
Even more heavily functionalized pyrazines can be readily accessed by performing an intermolecular addition of a xanthate to an alkene prior to the intermolecular alkylation of the pyrazines. For example, addition of malonyl xanthate to *N*-vinylphthalimide **10** led to a new xanthate **8a**,[30] which in turn added with high efficiency to pyrazine **1a** to deliver product **9a** in 65% yield (Scheme 5). Similarly, by simply varying the starting xanthate, pyrazines containing trifluoromethyloxadiazo (**9b**) and cyano (**9c**) were readily obtained. The minor double addition products were not isolated, except for compound **11**, which was formed in 26% yield.



Scheme 5. Incorporation of substituted aminoalkyl groups into pyrazines

In the same manner, reaction with xanthates **13a** and **13b**, generated by intermolecular

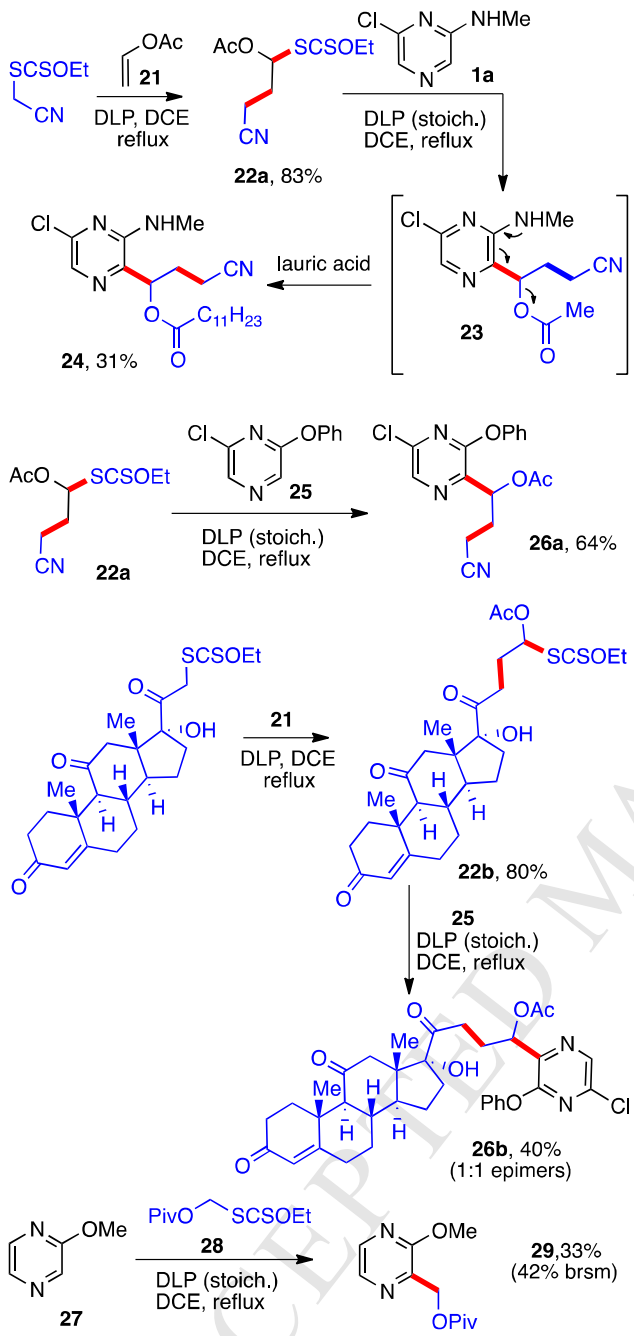
addition to *N*,*N*-diacetyl imidazolone **12**, afforded the corresponding functionalized pyrazines **14a** and **14b** containing the protected 1,2-diamine motif in good yield (Scheme 6). An unusual example is the synthesis of molecule **19** containing both a pyridine and a pyrazine ring, arising from the addition of the pyridine-bearing xanthate **17**[31] to 2-amino-6-chloropyrazine **18**. Double addition products **15** and **20** were isolated as minor components in this series.



Scheme 6. Incorporation of highly functional motifs into pyrazines

In the case of pyrazine **23** derived from α-acetoxy substituted xanthate **22a**, however,

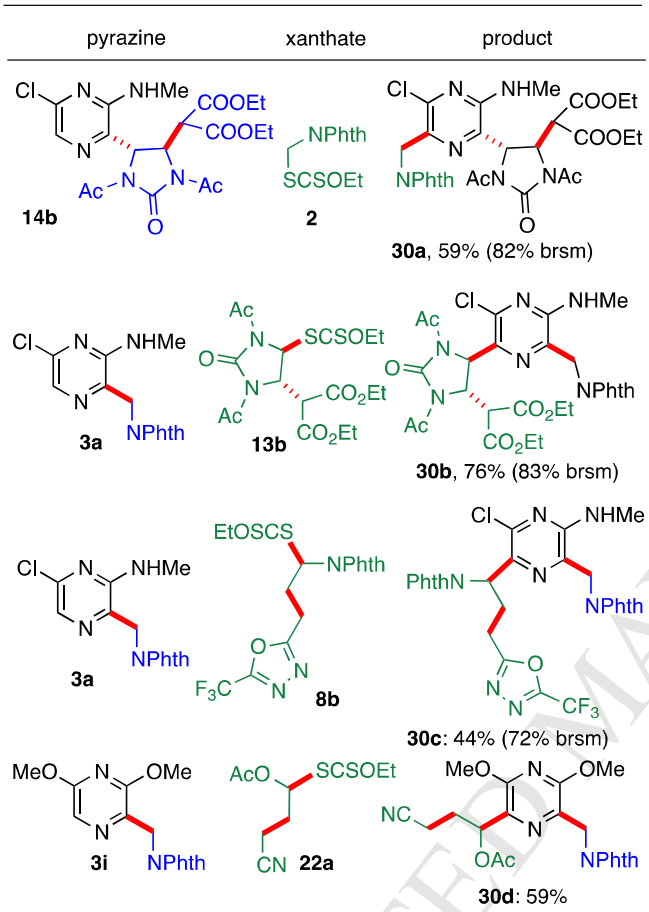
we noted its tendency to undergo elimination of the acetate group followed by nucleophilic attack by the lauric acid present in the reaction medium to give compound **24**, isolated in 31% yield (Scheme 7). In contrast, the reaction of phenoxypyrazine **25** and xanthate **22a** did not suffer from such complication and afforded smoothly the corresponding adduct **26a** in 64% yield. The preparation of the highly complex cortisone derived pyrazine **26b**, arising from initial radical adduct **22b** is of particular significance. Finally, the reaction of methoxypyrazine **27** with pivaloyloxymethyl xanthate **28** furnished readily the corresponding adduct **29**, albeit in moderate yield, probably due to the low stability (and higher and less controllable reactivity) of the incoming pivaloyloxymethyl radical generated from **28**.[32]



Scheme 7. Incorporation of *α*-acyloxy substituted fragments into pyrazines

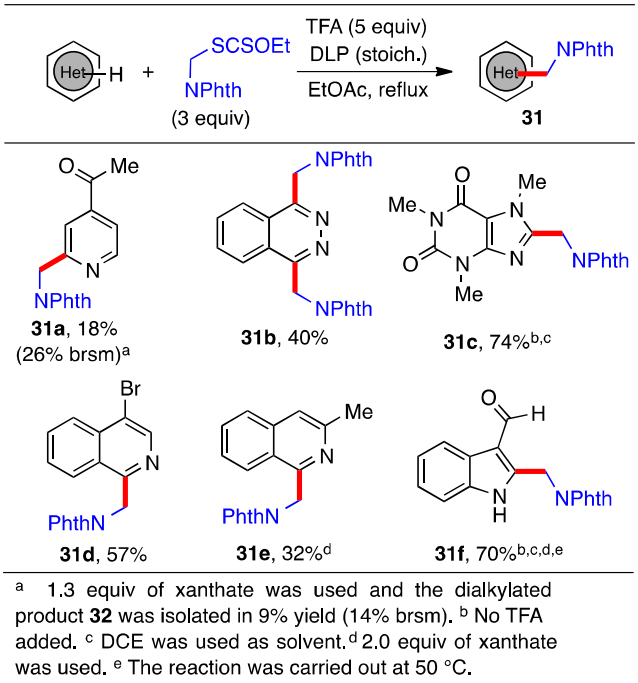
Considering that double alkylated products were sometimes isolated in significant yield, functionalization of the last position available on the pyrazine ring should be therefore feasible by treating the mono-alkylated products produced above with a different xanthate. Indeed, addition of phthalimidomethyl xanthate **2** to pyrazine **14b** gave a new pyrazine **30a** in 59% yield (Scheme 8). The sequence of the introduction of the two alkyl groups can be easily inverted, as demonstrated by the synthesis of **30b** from addition of xanthate **13b** to pyrazine **3a**. Tetrasubstituted pyrazines **30c** and

30d are two further examples. In the latter case, with an electron-donating group *ortho* to the last available position, the alkylation turned out to be quite efficient, furnishing pyrazine **30d** in good yield (59%) from pyrazine **3i**.



Scheme 8. Access to tetrasubstituted pyrazines

This chemistry is obviously not limited to pyrazines. Even though beyond the scope of the present study, the few examples, obtained under non-optimized reaction conditions and assembled in Scheme 9, are included to draw attention to the vast possibilities offered by this approach. These include pyridine (**31a**), phthalazine (**31b**), caffeine (**31c**), isoquinoline (**31d-e**) and indole (**31f**). In the case of electron-rich caffeine and indole, no acid was required for the reaction to proceed. Interestingly, phthalazine was readily doubly aminomethylated (**31b**) and product **31f** was obtained in 70% by simple evaporation of the solvent and trituration with diethyl ether of the crude residue followed by recrystallization from ethyl acetate.



[a] 1.3 equiv of xanthate was used and the dialkylated product **32** was isolated in 9% yield (14% brsm). [b] No TFA added. [c] DCE was used as solvent. [d] 2.0 equiv of xanthate was used. [e] The reaction was carried out at 50 °C.

Scheme 9. Alkylation of other heteroaromatics

To conclude, we have been able to expand the use of the unique radical chemistry of xanthates to the functionalization of pyrazines and briefly to other heteroaromatic systems. This approach involves very inexpensive reagents, mild metal-free reaction conditions, and remarkably good functional group tolerance. Indeed, most of the structures described would be very tedious, if not impossible, to obtain by other more conventional methods. The ability to place together so many different functional groups in close proximity opens manifold post-modification routes, such as ring closures by ionic condensation of the latent amino group with other functionalities present in the structure. Studies along these lines are currently underway.

3. Experimental section

3.1 General experimental methods

All reactions were carried out under dry, oxygen free nitrogen. Thin Layer Chromatography (TLC) was performed on alumina plates precoated with silica gel (Merck silica gel, 60 F_{254}), which were visualized by the quenching of UV fluorescence when applicable (max = 254 nm and/or 366 nm) and/or by staining with

anisadehyde in acidic ethanol solution and/or $KMnO_4$ in basic water followed by heating. Flash chromatography was carried out on Kieselgel 60 (40-63 µm). Petroleum ether refers to the fraction of petroleum boiling between 40 °C and 60 °C. Infrared spectra were recorded on a Perkin-Elmer Spectrum Two. Absorption maxima (υ_{max}) are reported in wavenumbers (cm^{-1}). Nuclear magnetic resonance spectra were recorded at ambient temperature on a Bruker Avance DPX 400 instrument. Proton magnetic resonance spectra (^{1}H NMR) were recorded at 400 MHz and coupling constants (*J*) are reported to ± 0.5 Hz. The following abbreviations were utilized to describe peak patterns when appropriate: br = broad, s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet. Carbon magnetic resonance spectra (^{13}C NMR) were recorded at 100 MHz. Chemical shifts (H, C) are quoted in parts per million (ppm) and are referenced to the residual solvent peak ($CDCl_3$: δ_H= 7.27 and δ_C= 77.1). High-resolution mass spectra were recorded by electron impact ionization (EI) on a JMS-GCmateII mass spectrometer. The quoted masses are accurate to ± 5 ppm.

3.2 General procedures for the xanthate-mediated alkylation

A magnetically stirred solution of xanthate (2.0 equiv) and pyrazine (1.0 equiv) in 1, 2-dichloroethane (1.0 mmol/mL according to the xanthate) was refluxed for 15 min under a flow of nitrogen. Then dilauroyl peroxide (DLP) was added portionwise (20 mol % according to the xanthate) every hour until total consumption of one substrate. The reaction mixture was then cooled to room temperature and the solvent was evaporated under reduced pressure. Unless otherwise specified, the crude product was purified by flash chromatography on silica gel.

3.2.1 *2-((5-Chloro-3-(methylamino)pyrazin-2-yl)methyl)isoindoline-1,3-dione (**3a**)*. According to the general procedure, the reaction was carried out with xanthate **2**[33] (155 mg, 0.55 mmol) and pyrazine **1a** (40 mg, 0.28 mmol) in 0.6 mL DCE and needed 5 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/Et_2O = 1/2 to 0/1) afforded the desired product **3a** as a white solid (62 mg, 0.20 mmol, 73% yield). **^{1}H NMR** (δ, ppm) (400 MHz, $CDCl_3$) 7.92 – 7.84 (m,

2H), 7.77 – 7.73 (m, 2H), 7.71 (s, 1H), 6.04 (br, 1H, *N*H), 4.84 (s, 2H), 3.01 (d, *J* = 4.7 Hz, 3H). **^{13}C NMR** (*δ*, ppm) (101 MHz, $CDCl_3$) 168.7 (C=O), 153.2, 147.1, 134.6, 133.8, 132.0, 129.2, 123.9, 39.9, 28.6. **IR** (*ν*, cm^{-1}, $CDCl_3$) 3384, 2942, 1771, 1714, 1582, 1511, 1429, 1392, 1382, 1329, 1235, 1106, 1084. **HRMS** (EI+) calculated for $C_{14}H_{11}ClN_4O_2$: 302.0571; Found: 302.0575. **mp**: 175-176 °C.

3.2.2 *2,2'-((3-Chloro-5-(methylamino)pyrazine-2,6-diyl)bis(methylene))bis (isoindoline-1,3-dione) (**4a**).* The dialkylated product **4a** was isolated as a white solid (7 mg, 0.01 mmol, 5% yield). **^{1}H NMR** (*δ*, ppm) (400 MHz, $CDCl_3$) 7.90 – 7.85 (m, 3H), 7.85 – 7.78 (m, 2H), 7.75 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.70 (s, 1H), 5.91 (br, *J* = 4.4 Hz, 1H, *N*H), 4.97 (s, 2H), 4.81 (s, 2H), 2.99 (d, *J* = 4.7 Hz, 3H). **^{13}C NMR** (*δ*, ppm) (101 MHz, $CDCl_3$) 168.3, 168.2, 167.9, 153.1, 143.7, 134.6, 134.5, 133.66, 132.0, 131.5, 129.2, 124.3, 123.8, 123.7, 41.3, 39.9, 28.5. **IR** (*ν*, cm^{-1}, $CDCl_3$) 3386, 1775, 1719, 1582, 1512, 1394, 1392, 1235, 1105, 1086. **HRMS** (EI+) calculated for $C_{23}H_{16}ClN_5O_4$: 461.0891; Found: 461.0902.

3.2.3 *2-((3-(Methylamino)pyrazin-2-yl)methyl)isoindoline-1,3-dione (**3b**).* Following the general procedure, the reaction was carried out with xanthate **2** (566 mg, 2.01 mmol) and 2-methylaminopyrazine (110 mg, 1.01 mmol) in 2.0 mL DCE and needed 6 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/Et_2O = 1:1 to 0:1) afforded the desired product **3b** as a light yellow solid (181 mg, 0.67 mmol, 67% yield). **^{1}H NMR** (*δ*, ppm) (400 MHz, $CDCl_3$) 7.98 (d, *J* = 2.7 Hz, 1H), 7.87 (dd, *J* = 5.4, 3.0 Hz, 2H), 7.74 (ddd, *J* = 7.3, 4.7, 2.8 Hz, 3H), 5.68 (br, 1H, *N*H), 4.85 (s, 2H), 3.00 (d, *J* = 4.7 Hz, 3H). **^{13}C NMR** (*δ*, ppm) (101 MHz, $CDCl_3$) 168.7, 153.6, 142.0, 136.2, 134.4, 132.2, 131.5, 123.8, 40.4, 28.4. **IR** (*ν*, cm^{-1}, $CDCl_3$) 3398, 2930, 1772, 1714, 1587, 1523, 1422, 1392, 1334, 1205, 1084. **HRMS** (EI+) calculated for $C_{14}H_{12}N_4O_2$: 268.0960; Found: 268.0959. **mp**: 168-169 °C.

3.2.4 *2-((3-Chloropyrazin-2-yl)methyl)isoindoline-1,3-dione (**3c**).* Following the

general procedure, the reaction was carried out with xanthate **2** (258 mg, 0.92 mmol) and 2-chloropyrazine (52 mg, 0.46 mmol) in 0.9 mL DCE and needed 7 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/EtOAC = 10:1 to 4:1) afforded the desired product **3c** as a white solid (44 mg, 0.16 mmol, 35% yield), and 15 mg 2-chloropyrazine (0.13 mmol) was recovered. **^{1}H NMR** (δ, ppm) (400 MHz, $CDCl_3$) 8.31 (d, J = 2.5 Hz, 1H), 8.26 (d, J = 2.5 Hz, 1H), 7.91 (dd, J = 5.4, 3.1 Hz, 2H), 7.77 (dd, J = 5.4, 3.1 Hz, 2H), 5.14 (s, 2H). **^{13}C NMR** (δ, ppm) (101 MHz, $CDCl_3$) 168.1, 149.0, 147.7, 142.8, 142.2, 134.3, 132.5, 123.8, 40.1. **IR** (ν, cm^{-1}, $CDCl_3$) 2930, 1775, 1720, 1602, 1421, 1395, 1331, 1192, 1153, 1115, 1083, 1063. **HRMS** (EI+) calculated for $C_{13}H_8ClN_3O_2$: 273.0305; Found: 273.0309. **mp**: 137-140 °C.

3.2.5 *2-((5-Chloro-3-phenoxypyrazin-2-yl)methyl)isoindoline-1,3-dione* (***3d***). Following the general procedure, the reaction was carried out with xanthate **2** (287 mg, 1.02 mmol) and pyrazine (105 mg, 0.51 mmol) in 1.0 mL DCE and needed 7 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/Et_2O = 3:1 to 1:1) afforded the desired product **3d** as a white solid (130 mg, 0.36 mmol, 70% yield). **^{1}H NMR** (δ, ppm) (400 MHz, $CDCl_3$) 8.06 (s, 1H), 7.92 (dd, J = 5.4, 3.1 Hz, 2H), 7.79 – 7.75 (m, 2H), 7.47 – 7.41 (m, 2H), 7.28 (d, J = 7.4 Hz, 1H), 7.24 – 7.19 (m, 2H), 5.17 (s, 2H). **^{13}C NMR** (δ, ppm) (101 MHz, $CDCl_3$) 168.2, 155.9, 152.4, 144.4, 138.5, 136.7, 134.2, 132.4, 129.9, 125.9, 123.7, 121.4, 38.0. **IR** (ν, cm^{-1}, $CDCl_3$) 2929, 1775, 1719, 1601, 1542, 1490, 1419, 1396, 1384, 1219, 1175, 1114. **HRMS** (EI+) calculated for $C_{19}H_{12}ClN_3O_3$: 365.0567; Found: 365.0576. **mp**: 170-173 °C.

3.2.6 *2-((5-Chloro-3-methoxypyrazin-2-yl)methyl)isoindoline-1,3-dione* (***3e***). Following the general procedure, the reaction was carried out with xanthate **2** (342 mg, 1.22 mmol) and pyrazine (88 mg, 0.61 mmol) in 1.2 mL DCE and needed 3 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of toluene/dichloromethane = 4:1 to 2:1) afforded the desired product **3e** as a white solid

(119 mg, 0.39 mmol, 64% yield). **^{1}H NMR** (δ, ppm) (400 MHz, $CDCl_3$) 7.93 (s, 1H), 7.89 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.75 (dd, *J* = 5.4, 3.1 Hz, 2H), 4.97 (s, 2H), 4.06 (s, 3H). **^{13}C NMR** (δ, ppm) (101 MHz, $CDCl_3$) 168.2, 156.8, 144.3, 138.2, 134.4, 134.2, 132.4, 123.7, 54.8, 37.9. **IR** (*v*, cm^{-1}, $CDCl_3$) 3422, 3360, 2944, 1686, 1580, 1541, 1508, 1447, 1376, 1328, 1278, 1259, 1214, 1177, 1124. **HRMS** (EI+) calculated for $C_{14}H_{10}ClN_3O_3$: 303.0411; Found: 303.0405. **mp**: 185-186 °C.

3.2.7 *2-((3-Amino-5-chloropyrazin-2-yl)methyl)isoindoline-1,3-dione (**3f**)*. Following the general procedure, the reaction was carried out with xanthate **2** (434 mg, 1.54 mmol) and pyrazine (100 mg, 0.78 mmol) in 1.5 mL DCE and needed 5 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/Et_2O = 2:3 to 0:1) afforded the desired compound **3f** as a white solid (114 mg, 0.39 mmol, 51% yield). **^{1}H NMR** (δ, ppm) (400 MHz, $CDCl_3$) 7.89 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.87 (s, 1H), 7.75 (dd, *J* = 5.5, 3.0 Hz, 2H), 5.45 (s, 2H, *N*H_2), 4.89 (s, 2H). **^{13}C NMR** (δ, ppm) (101 MHz, $CDCl_3$) 168.6, 152.8, 146.7, 134.6, 133.4, 132.1, 132.0, 123.9, 39.9. **IR** (*v*, cm^{-1}, $CDCl_3$) 3481, 3363, 1771, 1714, 1624, 1536, 1439, 1423, 1392, 1327, 1234, 1208, 1083. **HRMS** (EI+) calculated for $C_{13}H_9ClN_4O_2$: 288.0414; Found: 288.0412. **mp**: 220-221 °C.

3.2.8 *2-((3-(tert-Butylamino)-5-chloropyrazin-2-yl)methyl)isoindoline-1,3-dione (**3g**)*. Following the general procedure, the reaction was carried out with xanthate **2** (579 mg, 2.06 mmol) and pyrazine (191 mg, 1.03 mmol) in 2.1 mL DCE and needed 4 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/Et_2O = 2:1 to 1:2) afforded the single addition product **3g** as a white solid (234 mg, 0.68 mmol, 66% yield). **^{1}H NMR** (δ, ppm) (400 MHz, $CDCl_3$) 7.89 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.75 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.68 (s, 1H), 5.74 (br, 1H, *N*H), 4.80 (s, 2H), 1.48 (s, 9H). **^{13}C NMR** (δ, ppm) (101 MHz, $CDCl_3$) 168.6, 152.0, 146.1, 134.5, 133.7, 132.0, 128.7, 123.8, 52.6, 40.0, 28.7. **IR** (*v*, cm^{-1}, $CDCl_3$) 3374, 2968, 1772, 1714, 1575, 1545, 1457, 1429, 1392, 1366, 1328, 1256, 1233, 1213, 1117, 1079, 987. **HRMS** (EI+) calculated for $C_{17}H_{17}ClN_4O_2$: 344.1040; Found: 344.1042.

mp: 158-159 °C.

3.2.9 *2,2'-((3-(tert-Butylamino)-5-chloropyrazine-2,6-diyl)bis(methylene))bis-(isoindoline-1,3-dione)* (***4b***). The dialkylated product **4b** was isolated as a white solid (128 mg, 0.25 mmol, 25% yield). **^{1}H NMR** (δ, ppm) (400 MHz, $CDCl_3$) 7.74 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.69 (q, *J* = 3.1, 2.4 Hz, 2H), 7.66 (m, 4H), 5.25 (s, 1H, *N*H), 4.89 (s, 2H), 4.57 (s, 2H), 1.46 (s, 9H). **^{13}C NMR** (δ, ppm) (101 MHz, $CDCl_3$) 168.2, 167.9, 150.9, 143.2, 134.1, 133.8, 133.2, 132.40, 131.9, 131.5, 123.5, 123.3, 52.6, 39.2, 39.1, 28.8. **IR** (*v*, cm^{-1}, $CDCl_3$) 3373, 2968, 1775, 1718, 1576, 1503, 1469, 1456, 1428, 1396, 1365, 1322, 1213, 1187, 1112, 1087, 1036. **HRMS** (EI+) calculated for $C_{26}H_{22}ClN_5O_4$: 503.1360; Found: 503.1355. **mp**: 242-244 °C.

3.2.10 *2-((3-Methoxypyrazin-2-yl)methyl)isoindoline-1,3-dione (**3h**).* Following the general procedure, the reaction was carried out with xanthate **2** (331 mg, 1.18 mmol) and pyrazine (65 mg, 0.59 mmol) in 1.2 mL DCE and needed 3 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/Et_2O = 3:1 to 2:1) afforded the desired product **3h** as a white solid (96 mg, 0.36 mmol, 61% yield). **^{1}H NMR** (δ, ppm) (400 MHz, $CDCl_3$) 7.96 (d, *J* = 2.7 Hz, 1H), 7.92 (d, *J* = 2.8 Hz, 1H), 7.90 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.74 (dd, *J* = 5.4, 3.1 Hz, 2H), 5.01 (s, 2H), 4.03 (s, 3H). **^{13}C NMR** (δ, ppm) (101 MHz, $CDCl_3$) 168.4, 157.9, 140.4, 139.5, 135.8, 134.1, 132.5, 123.6, 53.8, 38.4. **IR** (*v*, cm^{-1}, $CDCl_3$) 2952, 1774, 1718, 1602, 1548, 1462, 1424, 1395, 1360, 1172, 1144, 1011. **HRMS** (EI+) calculated for $C_{14}H_{11}N_3O_3$: 269.0800; Found: 269.0796. **mp**: 158-160 °C.

3.2.11 *2-((3,5-Dimethoxypyrazin-2-yl)methyl)isoindoline-1,3-dione (**3i**). **Entry 1***: A magnetically stirred solution of xanthate **2** (281 mg, 1.00 mmol, 1.0 equiv) and 2,6-dimethoxypyrazine (283 mg, 2.00 mmol, 2.0 equiv) in 1 mL DCE was refluxed for 15 min under a flow of nitrogen. 20 mol % of DLP was then added every hour until the total consumption of one substrate. After 6 h, the reaction mixture was cooled to room temperature and the solvent was then evaporated. The crude product

was purified by flash chromatography on silica gel (toluene/EtOAc = 5:1) to give the mono addition product **3i** as a white solid (166 mg, 0.55 mmol, 55% yield). ***Entry 2***: A magnetically stirred solution of xanthate **2** (452 mg, 1.61 mmol, 3.0 equiv) and 2,6-dimethoxypyrazine (75 mg, 0.54 mmol, 1.0 equiv) in 1 mL DCE was refluxed for 15 min under a flow of nitrogen. 20 mol % of DLP was then added every hour until the total consumption of one substrate. After 6 h, the reaction mixture was cooled to room temperature and the solvent was then evaporated. The crude product was purified by flash chromatography on silica gel (toluene/EtOAc = 5:1) to give the mono addition product **3i** as a white solid (41 mg, 0.17 mmol, 25% yield). **^{1}H NMR** (δ, ppm) (400 MHz, $CDCl_3$) 7.87 (dd, J = 5.4, 3.0 Hz, 2H), 7.74 – 7.69 (m, 2H), 7.60 (s, 1H), 4.94 (s, 2H), 4.00 (s, 3H), 3.91 (s, 3H). **^{13}C NMR** (δ, ppm) (101 MHz, $CDCl_3$) 168.4, 158.7, 155.9, 134.0, 132.6, 129.5, 123.5, 123.2, 53.9, 53.7, 37.8. **IR** (ν, cm^{-1}, $CDCl_3$) 2849, 1774, 1717, 1584, 1547, 1485, 1456, 1423, 1398, 1380, 1365, 1313, 1176, 1112, 1047, 1013. **HRMS** (EI+) calculated for $C_{15}H_{13}N_3O_4$: 299.0906; Found: 299.0906. **mp**: 197-198 °C.

3.2.12 *2,2'-((3,5-Dimethoxypyrazine-2,6-diyl)bis(methylene))bis(isoindoline-1,3-dione) (**4c**)*. ***Entry 1***: Dialkylated product **4c** was isolated as a white solid (42 mg, 0.09 mmol, 9% yield). ***Entry 2***: Dialkylated product **4c** was isolated as a white solid (123 mg, 0.27 mmol, 50% yield). **^{1}H NMR** (δ, ppm) (400 MHz, $CDCl_3$) 7.58 (dt, J = 7.1, 3.5 Hz, 4H), 7.55 – 7.48 (m, 4H), 4.78 (s, 4H), 3.99 (s, 6H). **^{13}C NMR** (δ, ppm) (101 MHz, $CDCl_3$) 167.8, 155.2, 133.6, 132.1, 128.0, 123.1, 53.9, 37.2. **IR** (ν, cm^{-1}, $CDCl_3$) 2988, 2946, 1775, 1721, 1479, 1455, 1430, 1419, 1396, 1353, 1199, 1184, 1112, 1014. **HRMS** (EI+) calculated for $C_{24}H_{18}N_4O_6$: 458.1226; Found: 458.1235. **mp**: 318-319°C.

3.2.13 *2-((3-(Methylthio)pyrazin-2-yl)methyl)isoindoline-1,3-dione* (***3j***). Following the general procedure, the reaction was carried out with xanthate **2** (332 mg, 1.18 mmol) and pyrazine (74 mg, 0.59 mmol) in 1.2 mL DCE and needed 7 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of

petroleum ether/Et_2O = 4:1 to 2:1) afforded the desired product **3j** as a white solid (67 mg, 0.23 mmol, 40% yield) and 4 mg (0.05 mmol) pyrazine was recovered. **^{1}H NMR** (δ, ppm) (400 MHz, $CDCl_3$) 8.25 (d, *J* = 2.7 Hz, 1H), 8.01 (d, *J* = 2.6 Hz, 1H), 7.89 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.74 (dd, *J* = 5.5, 3.1 Hz, 2H), 4.94 (s, 2H), 2.62 (s, 3H). **^{13}C NMR** (δ, ppm) (101 MHz, $CDCl_3$) 168.2, 154.8, 147.3, 142.4, 138.1, 134.1, 132.5, 123.6, 39.4, 12.7. **IR** (ν, cm^{-1}, $CDCl_3$) 3055, 2932, 1775, 1718, 1520, 1470, 1422, 1396, 1324, 1192, 1154, 1114, 1088, 1066. **HRMS** (EI+) calculated for $C_{14}H_{11}N_3O_2S$: 285.0572; Found: 285.0579. **mp**: 172-173 °C.

3.2.14 *Methyl 5-((1,3-dioxoisoindolin-2-yl)methyl)pyrazine-2-carboxylate (**3k**).* Following the general procedure, the reaction was carried out with xanthate **2** (416 mg, 1.48 mmol) and methyl 2-pyrazinecarboxylate (102 mg, 0.74 mmol) in 1.5 mL DCE and needed 7 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/EtOAc = 3/1 to 1/2) afforded the desired product **3k** as a white solid (84 mg, 0.28 mmol, 38% yield), and 36 mg pyrazine (0.26 mmol) was recovered. **^{1}H NMR** (δ, ppm) (400 MHz, $CDCl_3$) 9.17 (d, *J* = 1.4 Hz, 1H), 8.75 (d, *J* = 1.4 Hz, 1H), 7.90 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.76 (dd, *J* = 5.5, 3.1 Hz, 2H), 5.12 (s, 2H), 4.01 (s, 3H). **^{13}C NMR** (δ, ppm) (101 MHz, $CDCl_3$) 167.9, 164.4, 154.4, 145.7, 143.1, 142.3, 134.4, 132.2, 123.8, 53.2, 40.8. **IR** (ν, cm^{-1}, $CDCl_3$) 2929, 1776, 1721, 1602, 1423, 1395, 1316, 1273, 1135, 1032. **HRMS** (EI+) calculated for $C_{15}H_{11}N_3O_4$: 297.0750; Found: 297.0759. **mp**: 167-170 °C.

3.2.15 *2-((3,5-Dichloropyrazin-2-yl)methyl)isoindoline-1,3-dione* (***3l***). Following the general procedure, the reaction was carried out with xanthate **2** (281 mg, 1.00 mmol, 2.0 equiv), 2,6-dichloropyrazine (74 mg, 0.50 mmol, 1.0 equiv) and TFA (68 mg, 48 μL, 0.6 mmol, 1.2 equiv) in 1.0 mL DCE and needed 6 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/dichloromethane = 1:1 to 2:3, then ethyl acetate/petroleum ether = 1:1) afforded the desired product **3l** as a white solid (78 mg, 0.25 mmol, 51% yield). **^{1}H NMR** (δ, ppm) (400 MHz, $CDCl_3$) 8.31 (s, 1H), 7.91 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.77 (dd, *J* = 5.5,

3.1 Hz, 2H), 5.10 (s, 2H). **^{13}C NMR** (δ, ppm) (101 MHz, $CDCl_3$) 167.9, 146.9, 146.5, 145.6, 141.9, 134.4, 132.2, 123.8, 39.5. **IR** (ν, cm^{-1}, $CDCl_3$) 1776, 1722, 1520, 1470, 1424, 1415, 1395, 1322, 1290, 1258, 1195, 1174, 1156, 1116, 1072. **HRMS** (EI+) calculated for $C_{13}H_7Cl_2N_3O_2$: 306.9915; Found: 306.9906. **mp**: 175-176 °C.

3.2.16 *2,2'-((3,5-Dichloropyrazine-2,6-diyl)bis(methylene))bis(isoindoline-1,3-dione) (**4d**)*. Product **4d** was isolated as a white solid (36 mg, 0.08 mmol, 15% yield). **^{1}H NMR** (δ, ppm) (400 MHz, $CDCl_3$) 7.62 – 7.57 (m, 4H), 7.53 – 7.48 (m, 4H), 4.96 (s, 4H).**^{13}C NMR** (δ, ppm) (101 MHz, $CDCl_3$) 167.2, 146.5, 144.1, 134.0, 131.7, 123.4, 39.1. **IR** (ν, cm^{-1}, $CDCl_3$) 1777, 1726, 1602, 1470, 1422, 1404, 1381, 1310, 1194, 1163, 1104. **HRMS** (EI+) calculated for $C_{22}H_{12}Cl_2N_4O_4$: 466.0236; Found: 466.0241. **mp**: 303-304 °C.

3.2.17 *2-((3,5-Dimethylpyrazin-2-yl)methyl)isoindoline-1,3-dione (**3m**)*. Following the general procedure, the reaction was carried out with xanthate **2** (563 mg, 2.00 mmol, 2.0 equiv), 2,6-dimethylpyrazine (108 mg, 1.00 mmol, 1.0 equiv) and TFA (137 mg, 92 μL, 1.20 mmol, 1.2 equiv) in 1.0 mL DCE and needed 6 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/diethyl ether = 1:1 to 2:3, then ethyl acetate/petroleum ether = 1:1 to 2:1) afforded product **3m** (120 mg, 0.45 mmol, 45% yield) as a white solid. **^{1}H NMR** (δ, ppm) (400 MHz, $CDCl_3$) 8.08 (s, 1H, H_1), 7.91 – 7.84 (m, 2H), 7.76 – 7.70 (m, 2H), 4.97 (s, 2H), 2.63 (s, 3H), 2.45 (s, 3H). **^{13}C NMR** (δ, ppm) (101 MHz, $CDCl_3$) 168.4, 151.6, 150.1, 145.1, 141.2, 134.1, 132.4, 123.6, 39.8, 21.2. **IR** (ν, cm^{-1}, $CDCl_3$) 3052, 2928, 1774, 1716, 1469, 1420, 1396, 1345, 1324, 1276, 1194, 1175, 1133, 1111, 1089. **HRMS** (EI+) calculated for $C_{15}H_{13}N_3O_2$: 267.1008; Found: 267.1000. **mp**: 137-138 °C.

3.2.18 *2,2'-((3,5-Dimethylpyrazine-2,6-diyl)bis(methylene))bis(isoindoline-1,3-dione) (**4e**)*. Product **4e** was isolated as a white solid (26 mg, 0.08 mmol, 6% yield). **^{1}H NMR** (δ, ppm) (400 MHz, $CDCl_3$) 7.64 – 7.58 (m, 4H), 7.56 – 7.49 (m, 4H), 4.81 (s, 4H), 2.59 (s, 6H). **^{13}C NMR** (δ, ppm) (101 MHz, $CDCl_3$) 167.7, 148.7, 144.7, 133.7,

132.0, 123.2, 39.4, 20.6. **IR** (*v*, cm^{-1}, $CDCl_3$) 1775, 1721, 1469, 1428, 1397, 1343, 1323, 1198, 1178, 1112. **HRMS** (EI+) calculated for $C_{24}H_{18}N_4O_4$: 426.1328; Found: 426.1324. **mp**: 282-283 °C.

3.2.19 *2-((3-Ethylpyrazin-2-yl)methyl)isoindoline-1,3-dione (**3n**).* Following the general procedure, the reaction was carried out with xanthate **2** (563 mg, 2.00 mmol, 2.0 equiv), 2-ethylpyrazine (108 mg, 1.00 mmol, 1.0 equiv) and TFA (137 mg, 92 μL, 1.20 mmol, 1.2 equiv) in 1.0 mL DCE and needed 5 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/diethyl ether = 3:2 to 1:2) afforded product **3n** (43 mg, 0.16 mmol, 16% yield) as a white solid. **^{1}H NMR** (*δ*, ppm) (400 MHz, $CDCl_3$) 8.37 (d, *J* = 2.6 Hz, 1H), 8.21 (d, *J* = 2.5 Hz, 1H), 7.93 – 7.87 (m, 2H), 7.79 – 7.72 (m, 2H), 5.04 (s, 2H), 2.97 (q, *J* = 7.5 Hz, 2H), 1.40 (t, *J* = 7.5 Hz, 3H). **^{13}C NMR** (*δ*, ppm) (101 MHz, $CDCl_3$) 168.4, 155.8, 148.0, 142.8, 141.5, 134.2, 132.5, 123.6, 39.7, 27.3, 12.1. **IR** (*v*, cm^{-1}, $CDCl_3$) 3056, 2978, 2939, 2879, 1774, 1718, 1602, 1469, 1426, 1410, 1395, 1351, 1325, 1193, 1161, 1112, 1089. **HRMS** (EI+) calculated for $C_{15}H_{13}N_3O_2$: 267.1008; Found: 267.1019. **mp**: 142-143 °C.

3.2.20 *2,2'-((3-Ethylpyrazine-2,6-diyl)bis(methylene))bis(isoindoline-1,3-dione) and 2,2'-((3-ethylpyrazine-2,5-diyl)bis(methylene))bis(isoindoline-1,3-dione) (**4f**).* Products **4f** was isolated in 1:1 mixture as a white solid (48 mg, 0.11 mmol, 11% yield). **^{1}H NMR** (*δ*, ppm) (400 MHz, $CDCl_3$) 8.20 (s, 1H), 8.15 (s, 1H), 7.88 (dddd, *J* = 12.7, 4.5, 3.7, 2.3 Hz, 8H), 7.74 (qd, *J* = 5.4, 3.0 Hz, 8H), 5.20 (s, 2H), 5.14 (s, 2H), 4.98 (d, *J* = 1.9 Hz, 4H), 2.87 (q, *J* = 7.5 Hz, 2H), 2.60 (q, *J* = 7.5 Hz, 2H), 1.23 (t, *J* = 7.5 Hz, 3H), 1.01 (t, *J* = 7.5 Hz, 3H). **^{13}C NMR** (*δ*, ppm) (101 MHz, $CDCl_3$) 168.34, 168.31, 168.2, 168.0, 156.8, 154.9, 148.6, 146.7, 146.4, 144.7, 142.0, 139.4, 134.23, 134.16, 134.13, 134.11, 132.5, 132.44, 132.40, 132.2, 123.7, 123.60, 123.58, 40.6, 39.7, 39.4, 39.3, 28.0, 26.9, 12.6, 11.7. **HRMS** (EI+) calculated for $C_{24}H_{18}N_4O_4$: 426.1328; Found: 426.1338.

3.2.21 *2-((6-Chloro-3-(methylamino)pyrazin-2-yl)methyl)isoindoline-1,3-dione (**3o**).* Following the general procedure, the reaction was carried out with xanthate **2** (231 mg, 0.82 mmol) and pyrazine (59 mg, 0.41 mmol) in 0.8 mL DCE and needed 5 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/Et_2O = 3:2 to 1:3) afforded the desired product **3o** as a light yellow solid (36 mg, 0.12 mmol, 29% yield). **^{1}H NMR** (δ, ppm) (400 MHz, $CDCl_3$) 8.00 (s, 1H), 7.88 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.75 (dd, *J* = 5.4, 3.1 Hz, 2H), 5.74 (br, 1H, *N*H), 4.83 (s, 2H), 2.99 (d, *J* = 4.7 Hz, 3H). **^{13}C NMR** (δ, ppm) (101 MHz, $CDCl_3$) 168.5, 152.3, 141.2, 134.9, 134.5, 134.4, 132.0, 123.9, 40.0, 28.8. **IR** (ν, cm^{-1}, $CDCl_3$) 3392, 2944, 1773, 1714, 1582, 1511, 1427, 1389, 1370, 1327, 1210, 1083. **HRMS** (EI+) calculated for $C_{14}H_{11}ClN_4O_2$: 302.0571; Found: 302.0559. **mp**: 185-186 °C.

3.2.22 *2-((3-Amino-6-chloropyrazin-2-yl)methyl)isoindoline-1,3-dione (**3p**).* Following the general procedure, the reaction was carried out with xanthate **2** (563 mg, 2.00 mmol) and pyrazine (130 mg, 1.00 mmol) in 2.0 mL DCE and needed 6 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of EtOAc/petroleum ether = 1:4 to 1:0) afforded product **3p** as a white solid (112 mg, 0.39 mmol, 39% yield). **^{1}H NMR** (δ, ppm) (400 MHz, $CDCl_3$) 7.96 (s, 1H, H_4), 7.88 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.75 (dd, *J* = 5.5, 3.0 Hz, 2H), 5.25 (s, 2H, *N*H_2), 4.86 (s, 2H). **^{13}C NMR** (δ, ppm) (101 MHz, $CDCl_3$) 168.5, 151.9, 141.7, 136.6, 134.6, 131.9, 123.9, 40.1. **IR** (ν, cm^{-1}, $CDCl_3$) 3485, 3372, 1774, 1715, 1623, 1448, 1428, 1399, 1387, 1352, 1325, 1201, 1171, 1079. **HRMS** (EI+) calculated for $C_{13}H_9ClN_4O_2$: 288.0414; Found: 288.0426. **mp**: 199-200 °C.

3.2.23 *2,2'-((3-Amino-6-chloropyrazine-2,5-diyl)bis(methylene))bis(isoindoline-1,3-dione) (**4h**).* Product **4h** was isolated as a white solid (112 mg, 0.25 mmol, 25% yield). **^{1}H NMR** (δ, ppm) (400 MHz, $CDCl_3$) 7.89-7.85 (m, 4H), 7.77-7.73 (m, 4H), 5.12 (s, 2H, *N*H_2), 4.94 (s, 2H), 4.82 (s, 2H). **^{13}C NMR** (δ, ppm) (101 MHz, $CDCl_3$) 168.4, 168.1, 151.7, 145.7, 134.5, 134.2, 133.7, 133.3, 132.4, 131.9, 123.8, 123.6, 39.7, 39.6. **IR** (ν, cm^{-1}, $CDCl_3$) 3484, 3368, 1775, 1718, 1622, 1470, 1418, 1392, 1321,

1213, 1193, 1115, 1087. **HRMS** (EI+) calculated for $C_{22}H_{14}ClN_5O_4$: 447.0734; Found: 447.0736. **mp**: 256-258 °C.

3.2.24 *3-((5-Chloro-3-(methylamino)pyrazin-2-yl)methyl)oxazolidin-2-one (**5a**).* Following the general procedure, the reaction was carried out with xanthate[33] (308 mg, 1.39 mmol) and pyrazine **1a** (100 mg, 0.70 mmol) in 1.4 mL DCE and needed 6 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/Et_2O = 1:1 to EtOAc/petroleum ether = 2:1) afforded the desired product **5a** as a white solid (79 mg, 0.33 mmol, 47% yield). **^{1}H NMR** (δ, ppm) (400 MHz, $CDCl_3$) 7.62 (s, 1H), 6.40 (br, 1H, *N*H), 4.41 (s, 2H), 4.40 – 4.36 (m, 2H), 3.61 – 3.57 (m, 2H), 2.97 (d, J = 4.7 Hz, 3H). **^{13}C NMR** (δ, ppm) (101 MHz, $CDCl_3$) 159.8, 153.8, 147.6, 134.0, 128.1, 62.6, 47.1, 44.7, 28.4. **IR** (ν, cm^{-1}, $CDCl_3$) 3361, 2941, 1732, 1585, 1512, 1444, 1383, 1272, 1237, 1103, 1088, 1037. **HRMS** (EI+) calculated for $C_9H_{11}ClN_4O_2$: 242.0571; Found: 242.0580. **mp**: 167-169 °C.

3.2.25 *3-((5-Chloro-3-phenoxypyrazin-2-yl)methyl)oxazolidin-2-one (**5b**).* Following the general procedure, the reaction was carried out with xanthate[33] (314 mg, 1.42 mmol) and pyrazine **1a** (147 mg, 0.71 mmol) in 1.4 mL DCE and needed 6 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/Et_2O = 1:2 to 1:0) afforded the desired product **5b** as a white solid (125 mg, 0.41 mmol, 58% yield). **^{1}H NMR** (δ, ppm) (400 MHz, $CDCl_3$) 8.21 (s, 1H, H_3), 7.48 – 7.39 (m, 2H), 7.29 – 7.26 (m, 1H, H_8), 7.17 (dd, J = 5.4, 3.4 Hz, 2H), 4.75 (s, 2H), 4.43 (dd, J = 8.7, 7.3 Hz, 2H), 3.76 (dd, J = 8.7, 7.3 Hz, 2H). **^{13}C NMR** (δ, ppm) (101 MHz, $CDCl_3$) 159.0, 156.3, 152.4, 144.6, 139.3, 136.8, 129.9, 125.9, 121.3, 62.3, 45.4, 44.4. **IR** (ν, cm^{-1}, $CDCl_3$) 2923, 1755, 1600, 1541, 1490, 1426, 1376, 1277, 1219, 1195, 1184, 1172, 1162, 1114, 1042. **HRMS** (EI+) calculated for $C_{14}H_{12}ClN_3O_3$: 305.0567; Found: 305.0555. **mp** : 129-131 °C.

3.2.26 *1-((5-Chloro-3-(methylamino)pyrazin-2-yl)methyl)pyrrolidine-2,5-dione (**5c**).* Following the general procedure, the reaction was carried out with xanthate[32] (284 mg,

1.22 mmol) and pyrazine **1a** (87 mg, 0.61 mmol) in 1.2 mL DCE and needed 6 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/EtOAc = 3:2 to 0:1) afforded the desired product **5c** as a white solid (81 mg, 0.32 mmol, 52% yield). **^{1}H NMR** (δ, ppm) (400 MHz, $CDCl_3$) 7.69 (s, 1H), 6.00 (s, 1H, *N*H), 4.65 (s, 2H), 2.97 (d, *J* = 4.7 Hz, 3H), 2.79 (s, 4H). **^{13}C NMR** (δ, ppm) (101 MHz, $CDCl_3$) 177.6, 153.2, 147.0, 133.1, 129.1, 40.6, 28.4, 28.3. **IR** (ν, cm^{-1}, $CDCl_3$) 3376, 2944, 1779, 1704, 1583, 1543, 1511, 1430, 1397, 1383, 1337, 1266, 1236, 1217, 1175, 1154, 1102. **HRMS** (EI+) calculated for $C_{10}H_{11}ClN_4O_2$: 254.0571; Found: 254.0578. **mp**: 139-140 °C.

3.2.27 *1,1'-((3-Chloro-5-(methylamino)pyrazine-2,6-diyl)bis(methylene))bis-(pyrrolidine-2,5-dione) (**7a**).* Product **7a** was isolated as a white solid (64 mg, 0.17 mmol, 28% yield). **^{1}H NMR** (δ, ppm) (400 MHz, $CDCl_3$) 5.95 (br, 1H, *N*H), 4.75 (s, 2H), 4.52 (s, 2H), 2.96 (d, *J* = 4.7 Hz, 3H), 2.87 (s, 4H), 2.74 (s, 4H). **^{13}C NMR** (δ, ppm) (101 MHz, $CDCl_3$) 177.8, 177.5, 152.8, 144.6, 132.9, 131.4, 40.0, 39.4, 28.7, 28.6, 28.4. **IR** (ν, cm^{-1}, $CDCl_3$) 3376, 2944, 1778, 1705, 1586, 1514, 1428, 1401, 1359, 1329, 1294, 1233, 1173, 1153, 1018. **HRMS** (EI+) calculated for $C_{15}H_{16}ClN_5O_4$: 365.0891; Found: 365.0887. **mp**: 111-114 °C.

3.2.28 *N-((5-Chloro-3-(methylamino)pyrazin-2-yl)methyl)-N-phenylacetamide (**5d**).* Following the general procedure, the reaction was carried out with xanthate[34] (345 mg, 1.28 mmol) and pyrazine **1a** (92 mg, 0.64 mmol) in 1.3 mL DCE and needed 5 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/Et_2O = 1:1 to 1:2) afforded the desired product **5d** as a white solid (125 mg, 0.43 mmol, 67% yield). **^{1}H NMR** (δ, ppm) (400 MHz, $CDCl_3$) 7.43 (s, 1H, H_3), 7.40 – 7.33 (m, 3H), 7.13 (br, 1H, *N*H), 6.95 – 6.93 (m, 2H), 4.91 (s, 2H), 3.01 (d, *J* = 4.7 Hz, 3H), 1.88 (s, 3H). **^{13}C NMR** (δ, ppm) (101 MHz, $CDCl_3$) 172.5, 153.8, 147.1, 141.5, 135.0, 130.1, 128.8, 128.1, 127.7, 51.6, 28.4, 22.7. **IR** (ν, cm^{-1}, $CDCl_3$) 3320, 3126, 2944, 1637, 1596, 1516, 1495, 1440, 1385, 1299, 1239, 1198, 1104, 1013. **HRMS** (EI+) calculated for $C_{14}H_{15}ClN_4O$: 290.0934; Found: 290.0930. **mp**:

133-135 °C.

3.2.29 *N-(1-(5-chloro-3-(methylamino)pyrazin-2-yl)-2,2,2-trifluoroethyl)acetamide (**5e**).* Following the general procedure, the reaction was carried out with xanthate[35] (522 mg, 2.00 mmol) and pyrazine **1a** (143 mg, 1.00 mmol) in 2.0 mL DCE and needed 5 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/EtOAc = 3:1 to 1:1) afforded the desired product **5e** as a white solid (208 mg, 0.74 mmol, 74% yield). **^{1}H NMR** (δ, ppm) (400 MHz, $CDCl_3$) 7.74 (s, 1H), 6.97 (br, 1H, *N*H), 6.08 (br, 1H, *N*H), 6.01 – 5.92 (m, 1H), 2.99 (d, *J* = 4.7 Hz, 3H), 2.14 (s, 3H). **^{13}C NMR** (δ, ppm) (101 MHz, $CDCl_3$) 170.5, 153.1, 148.1, 130.1, 128.5, 124.2 (q, *J* = 282.1 Hz, CF_3), 49.1 (q, *J* = 31.8 Hz), 28.5, 23.3. **IR** (*v*, cm^{-1}, $CDCl_3$) 3422, 3360, 2944, 1686, 1580, 1541, 1508, 1447, 1376, 1328, 1278, 1259, 1214, 1177, 1124. **HRMS** (EI+) calculated for $C_9H_{10}ClF_3N_4O$: 282.0495; Found: 282.0490. **mp**: 201-202 °C.

3.2.30 *2-(5-Chloro-3-(methylamino)pyrazin-2-yl)-N-methoxy-N-methylacetamide (**5f**).* Following the general procedure, the reaction was carried out with xanthate[36] (632 mg, 2.83 mmol) and pyrazine **1a** (203 mg, 1.41 mmol) in 2.8 mL DCE and needed 7 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of diethyl ether/petroleum ether = 1:1 to 4:1, then diethyl ether/MeOH = 15:1 to 5:1) afforded the mono addition product **5f** as a white solid (169 mg, 0.69 mmol, 49% yield). **^{1}H NMR** (δ, ppm) (400 MHz, $CDCl_3$) 7.68 (s, 1H), 6.64 (br, 1H, ***N***H), 3.89 (s, 2H), 3.74 (s, 3H), 3.21 (s, 3H), 2.98 (d, *J* = 4.7 Hz, 3H). **^{13}C NMR** (δ, ppm) (101 MHz, $CDCl_3$) 170.3, 154.9, 146.0, 134.9, 128.9, 62.2, 39.0, 32.3, 28.4. **IR** (*v*, cm^{-1}, $CDCl_3$) 3345, 2941, 1637, 1588, 1516, 1443, 1391, 1383, 1286, 1231, 1188, 1108, 1004. **HRMS** (EI+) calculated for $C_9H_{13}ClN_4O_2$: 244.0727; Found: 244.0731. **mp**: 142-143 °C.

3.2.31 *2,2'-(3-Chloro-5-(methylamino)pyrazine-2,6-diyl)bis(N-methoxy-N-methyl-acetamide) (**7b**).* Product **7b** was isolated as a white solid (52 mg, 0.15 mmol, 11%

yield). **^{1}H NMR** (δ, ppm) (400 MHz, $CDCl_3$) 6.51 (br, 1H, *N*H), 3.94 (s, 2H), 3.89 (s, 2H), 3.74 (s, 3H), 3.70 (s, 3H), 3.20 (s, 3H), 3.18 (s, 3H), 2.97 (d, J = 4.8 Hz, 3H). **^{13}C NMR** (δ, ppm) (101 MHz, $CDCl_3$) 171.2, 170.4, 153.9, 145.4, 134.5, 133.3, 62.4, 61.5, 39.0, 37.9, 32.5, 32.3, 28.6. **IR** (ν, cm^{-1}, $CDCl_3$) 3345, 2969, 2940, 2903, 1639, 1588, 1517, 1443, 1421, 1387, 1372, 1337, 1283, 1172, 1027, 1003. **HRMS** (EI+) calculated for $C_{13}H_{20}ClN_5O_4$: 345.1204; Found: 345.1218. **mp**: 141-142 °C.

3.2.32 *2-(5-Chloro-3-(methylamino)pyrazin-2-yl)-N,N-dimethylacetamide (**5g**).* Following the general procedure, the reaction was carried out with xanthate **S5** (586 mg, 2.83 mmol) and pyrazine **1a** (203 mg, 1.41 mmol) in 2.8 mL DCE and needed 7 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of diethyl ether/petroleum ether = 3:2 to 4:1, then diethyl ether/MeOH = 15:1 to 5/1) afforded the mono addition product **7c** as a white solid (179 mg, 0.78 mmol, 56% yield). **^{1}H NMR** (δ, ppm) (400 MHz, $CDCl_3$) 7.63 (s, 1H), 6.87 (s, 1H, *N*H), 3.78 (s, 2H), 3.18 (s, 3H), 2.97 (d, J = 4.8 Hz, 3H), 2.94 (s, 3H). **^{13}C NMR** (δ, ppm) (101 MHz, $CDCl_3$) 169.0, 154.8, 146.0, 134.7, 128.2, 41.6, 38.4, 35.9, 28.3. **IR** (ν, cm^{-1}, $CDCl_3$) 3341, 2941, 1631, 1591, 1518, 1441, 1404, 1384, 1287, 1230, 1199, 1189, 1116, 1100, 1059, 974. **HRMS** (EI+) calculated for $C_9H_{13}ClN_4O$: 228.0778; Found: 228.0768. **mp**: 149-150 °C.

3.2.33 *2,2'-(3-Chloro-5-(methylamino)pyrazine-2,6-diyl)bis(N,N-dimethylacetamide) (**7c**).* Product **7c** was isolated as a white solid (63 mg, 0.20 mmol, 14% yield). **^{1}H NMR** (δ, ppm) (400 MHz, $CDCl_3$) 6.65 (q, J = 5.0 Hz, 1H, *N*H), 3.83 (s, 2H), 3.76 (s, 2H), 3.16 (s, 3H), 3.06 (s, 3H), 2.97 (s, 3H), 2.96 (d, J = 4.8 Hz, 3H), 2.91 (s, 3H). **^{13}C NMR** (δ, ppm) (101 MHz, $CDCl_3$) 169.7, 168.9, 153.8, 145.1, 134.2, 133.2, 41.6, 39.0, 38.3, 37.6, 35.9, 35.7, 28.5. **IR** (ν, cm^{-1}, $CDCl_3$) 3348, 2939, 1633, 1592, 1518, 1402, 1374, 1338, 1288, 1264, 1189, 11134, 1068, 1029. **HRMS** (EI+) calculated for $C_{13}H_{20}ClN_5O_2$: 313.1306; Found: 313.1294. **mp**: 171-173 °C.

3.2.34 *2-(5-Chloro-3-(methylamino)pyrazin-2-yl)acetonitrile (**5h**).* Following the

general procedure, the reaction was carried out with cyanomethyl xanthate[37] (478 mg, 2.98 mmol) and pyrazine **1a** (214 mg, 1.49 mmol) in 3.0 mL DCE and needed 6 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/Et_2O = 2:1 to 0:1) gave two portions. The first portion was further purified by flash chromatography on silica gel (gradient of petroleum ether/EtOAc = 3:1 to 1:1) afforded **5h** (60 mg, 0.33 mmol, 22% yield) as a white solid. **^{1}H NMR** (δ, ppm) (400 MHz, $CDCl_3$) 7.79 (s, 1H), 4.56 (br, 1H, *N*H), 3.75 (s, 2H), 3.07 (d, *J* = 4.8 Hz, 3H). **^{13}C NMR** (δ, ppm) (101 MHz, $CDCl_3$) 152.3, 147.5, 130.2, 129.0, 114.9, 28.8, 22.9. **IR** (ν, cm^{-1}, $CDCl_3$) 3470, 2947, 1577, 1541, 1507, 142, 1408, 1375, 1282, 1228, 1209, 1181, 1099. **HRMS** (EI+) calculated for $C_7H_7ClN_4$: 182.0359; Found: 182.0364. **mp**: 190-191 °C.

3.2.35 *2-(3-Chloro-5-(methylamino)pyrazin-2-yl)acetonitrile (**8**).* Product **8** was isolated as a light yellow solid (8 mg, 0.04 mmol, 3% yield). **^{1}H NMR** (δ, ppm) (400 MHz, $CDCl_3$) 7.78 (s, 1H), 4.86 (br, 1H, *N*H), 3.90 (s, 2H), 3.00 (d, *J* = 5.1 Hz, 3H). **^{13}C NMR** (δ, ppm) (101 MHz, $CDCl_3$) 154.7, 145.7, 129.8, 129.1, 116.4, 28.7, 23.4. **IR** (ν, cm^{-1}, $CDCl_3$) 3459, 2948, 1591, 1519, 1415, 1376, 1329, 1144, 1063. **HRMS** (EI+) calculated for $C_7H_7ClN_4$: 182.0359; Found: 182.0350.

3.2.36 *2,2'-(3-Chloro-5-(methylamino)pyrazine-2,6-diyl)diacetonitrile (**7d**).* Product **7d** was isolated as a light yellow solid (31 mg, 0.14 mmol, 9% yield). **^{1}H NMR** (δ, ppm) (400 MHz, CD_3CN) 5.66 (br, 1H, *N*H), 3.93 (s, 2H), 3.78 (s, 2H), 2.89 (d, *J* = 4.7 Hz, 3H). **^{13}C NMR** (δ, ppm) (101 MHz, CD_3CN) 153.1, 145.4, 132.4, 128.9, 117.6, 116.4, 28.4, 23.5, 23.2. **IR** (ν, cm^{-1}, $CDCl_3$) 3468, 1580, 1513, 1411, 1367, 1178, 1025. **HRMS** (EI+) calculated for $C_9H_8ClN_5$: 221.0468; Found: 221.0461. **mp**: 185-186 °C.

3.2.37 *2-(5-Chloro-3-(methylamino)pyrazin-2-yl)propanenitrile (**5i**).* Following the general procedure, the reaction was carried out with xanthate (522 mg, 2.98 mmol) and pyrazine **1a** (214 mg, 1.49 mmol) in 3.0 mL DCE and needed 6 h for the reaction

to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/EtOAc = 8:1 to 4:1) afforded the desired product **5i** as a white solid (121 mg, 0.62 mmol, 41% yield), and 95 mg (0.66 mmol) pyrazine **1a** was recovered. **^{1}H NMR** (δ, ppm) (400 MHz, $CDCl_3$) 7.80 (s, 1H), 4.74 (br, 1H, *N*H), 3.89 (q, *J* = 7.2 Hz, 1H), 3.06 (d, *J* = 4.8 Hz, 3H), 1.70 (d, *J* = 7.2 Hz, 3H). **^{13}C NMR** (δ, ppm) (101 MHz, $CDCl_3$) 151.7, 147.1, 133.3, 129.9, 119.3, 28.8, 28.7, 16.1. **IR** (ν, cm^{-1}, $CDCl_3$) 3470, 2996, 2946, 1574, 1539, 1505, 1442, 1371, 1310, 1245, 1209, 1191, 1105, 986. **HRMS** (EI+) calculated for $C_8H_9ClN_4$: 196.0516; Found: 196.0521. **mp**: 142-144 °C.

3.2.38 *2-(3-Amino-5-chloropyrazin-2-yl)-3,3-dimethoxypropanenitrile (**5j**)*. A solution of xanthate (732 mg, 2.64 mmol, 2.0 equiv) and pyrazine **12** (171 mg, 1.32 mmol, 1.0 equiv) in 2.6 mL ethyl acetate was heated at 60 °C and DLP was added portionwise (100 mol %/12 h). It took 24 h for the reaction to go to completion. The reaction mixture was then cooled to room temperature and the solvent was then evaporated under reduced pressure. Flash chromatography on silica gel (gradient of ethyl acetate = 1:4 to 1:1) gave the desired product **5j** as a white powder (129 mg, 0.53 mmol, 40% yield). **^{1}H NMR** (δ, ppm) (400 MHz, $CDCl_3$) 7.97 (s, 1H, H_3), 5.16 (s, 2H, *N*H), 4.75 (d, *J* = 6.1 Hz, 1H, H_6), 4.26 (d, *J* = 6.1 Hz, 1H, H_5), 3.59 (s, 3H, H_7), 3.46 (s, 3H, H_7). **^{13}C NMR** (δ, ppm) (101 MHz, $CDCl_3$) 153.0 (C_1), 146.9 (C_4), 132.8 (C_3), 130.7 (C_2), 115.6 (C_8), 105.4 (C_6), 57.1 (C_7), 56.4 (C_7), 42.1 (C_5). **IR** (ν, cm^{-1}, $CDCl_3$) 3481, 3383, 2941, 2841, 1615, 1556, 1535, 1434, 1236, 1194, 1112, 1083, 1048. **HRMS** (EI+) calculated for $C_9H_{11}ClN_4O_2$: 242.0571; M-OMe: $C_8H_8ClN_4O$: 211.0381, Found: 211.0378. **mp**: 109-110 °C.

3.2.39 *3-Benzyl-6-chloro-N-methylpyrazin-2-amine (**5k**).* Following the general procedure, the reaction was carried out with benzyl xanthate[38] (226 mg, 1.06 mmol) and pyrazine **1a** (76 mg, 0.53 mmol) in 1.1 mL DCE and needed 5 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/Et_2O = 8:1 to 1:1) afforded the desired product **5k** as a light brown solid (59 mg, 0.25 mmol, 48% yield), and 25 mg **1a** (0.17 mmol) was recovered. **^{1}H NMR** (δ, ppm)

(400 MHz, CD_2Cl_2) 7.73 (s, 1H), 7.31 (t, *J* = 7.2 Hz, 2H), 7.25 (t, *J* = 7.2 Hz, 1H), 7.17 (d, *J* = 7.2 Hz, 2H), 4.52 (br, 1H, *N*H), 4.00 (s, 2H), 2.87 (d, *J* = 4.8 Hz, 3H). **^{13}C NMR** (δ, ppm) (101 MHz, CD_2Cl_2) 153.6, 145.8, 140.3, 137.0, 129.5, 129.4, 129.1, 127.6, 40.2, 28.7. **IR** (*v*, cm^{-1}, $CDCl_3$) 3456, 3067, 3030, 2944, 1573, 1539, 1509, 1441, 1373, 1299, 1267, 1234, 1188, 1148, 1100. **HRMS** (EI+) calculated for $C_{12}H_{12}ClN_3$: 233.0720; Found: 233.0710. **mp**: 135-137 °C.

3.2.40 *Diethyl 2-(2-(5-chloro-3-(methylamino)pyrazin-2-yl)-2-(1,3-dioxoisoindolin-2-yl)ethyl) malonate (**9a**).* Following the general procedure, the reaction was carried out with xanthate **8a**[30] (660 mg, 1.46 mmol) and pyrazine **1a** (105 mg, 0.73 mmol) in 1.5 mL DCE and needed 6 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/Et_2O = 3:1 to 2:3) afforded the desired product **9a** as a colorless oil (226 mg, 0.48 mmol, 65% yield). **^{1}H NMR** (δ, ppm) (400 MHz, $CDCl_3$) 7.85 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.74 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.69 (s, 1H), 5.87 (br, 1H, *N*H), 5.36 (dd, *J* = 10.0, 4.7 Hz, 1H), 4.27 – 4.11 (m, 4H), 3.42 (dd, *J* = 9.4, 5.3 Hz, 1H), 3.26 (ddd, *J* = 15.1, 10.0, 5.3 Hz, 1H), 2.99 (d, *J* = 4.7 Hz, 3H), 2.91 (ddd, *J* = 14.4, 9.4, 4.7 Hz, 1H), 1.26 (t, *J* = 7.2 Hz, 3H), 1.23 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (δ, ppm) (101 MHz, $CDCl_3$) 169.4, 168.7, 168.6, 152.2, 146.7, 134.8, 134.5, 131.7, 128.5, 123.8, 62.2, 62.0, 49.4, 49.2, 28.6, 27.1, 14.1. **IR** (*v*, cm^{-1}, $CDCl_3$) 3396, 2985, 2941, 1773, 1717, 1579, 1511, 1470, 1446, 1379, 1331, 1279, 1217, 1192, 1116, 1099, 1030. **HRMS** (EI+) calculated for $C_{22}H_{23}ClN_4O_6$: 474.1306; Found: 474.1305.

3.2.41 *2-(1-(5-Chloro-3-(methylamino)pyrazin-2-yl)-3-(5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl)propyl)isoindoline-1,3-dione (**9b**).* Following the general procedure, the reaction was carried out with xanthate **8b** (359 mg, 0.81 mmol) and pyrazine **1a** (58 mg, 0.40 mmol) in 0.8 mL DCE and needed 5 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/Et_2O = 4:1 to 1:1) afforded the desired product **9b** as a white solid (145 mg, 0.31 mmol, 78% yield). **^{1}H NMR** (δ, ppm) (400 MHz, $CDCl_3$) 7.85 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.76 (dd,

J = 5.6, 2.9 Hz, 2H), 7.76 (s, 1H, H_3), 5.73 (br, 1H, *N*H), 5.43 (t, *J* = 7.2 Hz, 1H), 3.17 – 3.10 (m, 2H), 3.10 – 3.04 (m, 2H), 2.97 (d, *J* = 4.7 Hz, 3H). **^{13}C NMR** (*δ*, ppm) (101 MHz, $CDCl_3$) 168.6, 168.4, 155.7 (q, *J* = 44.2 Hz), 152.5, 147.1, 134.8, 134.0, 131.5, 128.8, 123.9, 116.3 (q, *J* = 269.9 Hz, CF_3), 49.8, 28.6, 24.8, 22.8. **IR** (*v*, cm^{-1}, $CDCl_3$) 3417, 2943, 1775, 1714, 1581, 1510, 1407, 1380, 1215, 1177, 1132. **HRMS** (EI+) calculated for $C_{19}H_{14}ClF_3N_6O_3$: 466.0768; Found: 466.0771. **mp**: 54-55 °C.

3.2.42 *4-(5-Chloro-3-(methylamino)pyrazin-2-yl)-4-(1,3-dioxoisoindolin-2-yl)-butanenitrile (**9c**).* Following the general procedure, the reaction was carried out with xanthate **8c**[30] (362 mg, 1.08 mmol) and pyrazine **1a** (78 mg, 0.54 mmol) in 1.1 mL DCE and needed 4 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/Et_2O = 1:1 to 0:1) afforded the single addition product **9c** (141 mg, 0.40 mmol, 73% yield) as a white solid. **^{1}H NMR** (*δ*, ppm) (400 MHz, $CDCl_3$) 7.88 – 7.82 (m, 2H), 7.80 (s, 1H), 7.77 (td, *J* = 5.2, 2.0 Hz, 2H), 5.49 (br, 1H, *N*H), 5.34 (t, *J* = 7.5 Hz, 1H), 3.04 (tt, *J* = 10.8, 5.4 Hz, 1H), 2.94 (d, *J* = 4.7 Hz, 3H), 2.82 (td, *J* = 14.4, 7.7 Hz, 1H), 2.57 – 2.41 (m, 2H). **^{13}C NMR** (*δ*, ppm) (101 MHz, $CDCl_3$) 168.5, 152.7, 147.3, 134.8, 133.3, 131.4, 128.9, 124.0, 118.6, 49.2, 28.7, 25.1, 15.0. **IR** (*v*, cm^{-1}, $CDCl_3$) 3418, 2944, 1779, 1765, 1713, 1576, 1508, 1448, 1383, 1380, 1351, 1331, 1270, 1191, 1100. **HRMS** (EI+) calculated for $C_{17}H_{14}ClN_5O_2$: 355.0836; Found: 355.0839. **mp**: 146-147 °C.

3.2.43 *4,4'-(3-Chloro-5-(methylamino)pyrazine-2,6-diyl)bis(4-(1,3-dioxoisoindolin-2-yl)butanenitrile) (**11**).* Product **11** (81 mg, 0.14 mmol, 26% yield) was isolated as a mixture of diastereoisomers (*dr* = 1:1) as colorless oil. ***1st diastereoisomer:* ^{1}H NMR** (*δ*, ppm) (400 MHz, $CDCl_3$) 7.86 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.82 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.78 (td, *J* = 5.3, 2.0 Hz, 2H), 7.75 – 7.71 (m, 2H), 5.67 – 5.57 (m, 2H), 5.39 (dd, *J* = 9.1, 6.0 Hz, 1H), 3.48 – 3.37 (m, 1H), 3.07 (dtd, *J* = 14.1, 8.5, 5.5 Hz, 1H), 2.92 (d, *J* = 4.7 Hz, 3H), 2.83 (ddd, *J* = 16.8, 8.4, 5.5 Hz, 1H), 2.73 (ddd, *J* = 7.7, 6.3, 3.3 Hz, 2H), 2.67 – 2.42 (m, 3H). **^{13}C NMR** (*δ*, ppm) (101 MHz, $CDCl_3$) 168.4, 167.6, 152.4, 146.5, 134.9, 134.4, 131.8, 131.7, 131.4, 131.4, 124.0, 123.6, 119.3, 119.0, 50.3, 48.6,

28.8, 26.8, 25.3, 14.7, 14.6. ***2nd diastereoisomer:*** **^{1}H NMR** (δ, ppm) (400 MHz, $CDCl_3$) 7.87 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.78 (dd, *J* = 5.6, 3.0 Hz, 2H), 7.76 – 7.68 (m, 4H), 5.67 (dd, *J* = 9.3, 4.9 Hz, 1H), 5.54 (q, *J* = 4.6 Hz, 1H), 5.31 (t, *J* = 7.5 Hz, 1H), 2.92 (d, *J* = 4.7 Hz, 3H), 2.84 (dt, *J* = 14.0, 7.0 Hz, 1H), 2.75 – 2.64 (m, 3H), 2.57 (dd, *J* = 16.8, 10.4 Hz, 1H), 2.51 – 2.42 (m, 2H), 2.39 (t, *J* = 7.1 Hz, 1H). **^{13}C NMR** (δ, ppm) (101 MHz, $CDCl_3$) 168.5, 168.2, 152.2, 145.2, 134.7, 134.3, 133.4, 132.5, 132.0, 131.4, 124.0, 123.6, 119.0, 118.6, 51.5, 49.1, 31.0, 28.8, 26.5, 24.9, 15.0. **IR** (ν, cm^{-1}, $CDCl_3$) 3414, 2943, 1779, 1766, 1715, 1579, 1511, 1470, 1384, 1364, 1331, 1217, 1176, 1111, 1087. **HRMS** (EI+) calculated for $C_{29}H_{22}ClN_7O_4$: 567.1422; Found: 567.1438.

3.2.44 *2-(1,3-Diacetyl-5-(5-chloro-3-(methylamino)pyrazin-2-yl)-2-oxoimidazolidin-4-yl)acetonitrile (**14a**).* Following the general procedure, the reaction was carried out with xanthate **13a**[29m] (272 mg, 0.83 mmol) and pyrazine **1a** (59 mg, 0.41 mmol) in 0.8 mL DCE and needed 5 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/Et_2O = 1:1 to1:3) afforded the desired product **14a** as a light brown oil (99 mg, 0.28 mmol, 69% yield). **^{1}H NMR** (δ, ppm) (400 MHz, $CDCl_3$) 7.68 (s, 1H), 6.15 (br, 1H, *N*H), 5.12 (d, *J* = 1.3 Hz, 1H), 4.69 (ddd, *J* = 6.3, 3.3, 1.3 Hz, 1H), 3.01 (dd, *J* = 17.1, 3.4 Hz, 1H), 2.98 (d, *J* = 4.8 Hz, 3H), 2.84 (dd, *J* = 17.1, 3.4 Hz, 1H), 2.60 (s, 3H), 2.55 (s, 3H). **^{13}C NMR** (δ, ppm) (101 MHz, $CDCl_3$) 171.9, 170.6, 152.9, 150.7, 147.7, 134.9, 130.0, 116.0, 54.1, 53.0, 28.6, 24.4, 24.0, 22.2. **IR** (ν, cm^{-1}, $CDCl_3$) 3362, 2938, 1769, 1705, 1577, 1537, 1507, 1370, 1265, 1245, 1212, 1160, 1120, 1093, 984. **HRMS** (EI+) calculated for $C_{14}H_{15}ClN_6O_3$: 350.0894; Found: 350.0901.

3.2.45 *Diethyl 2-(1,3-diacetyl-5-(5-chloro-3-(methylamino)pyrazin-2-yl)-2-oxoimidazolidin-4-yl)malonate (**14b**).* Following the general procedure, the reaction was carried out with xanthate **13b**[29m] (457 mg, 1.02 mmol) and pyrazine **1a** (73 mg, 0.51 mmol) in 1.0 mL DCE and needed 4 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/Et_2O = 4:1 to 1:2) afforded

the desired product **14b** as a white solid (202 mg, 0.43 mmol, 84% yield). **^{1}H NMR** (δ, ppm) (400 MHz, $CDCl_3$) 7.60 (s, 1H), 6.73 (br, 1H, *N*H), 5.46 (s, 1H), 4.65 (dd, *J* = 4.2, 0.6 Hz, 1H), 4.30 – 4.13 (m, 4H), 4.11 (d, *J* = 4.2 Hz, 1H), 3.03 (d, *J* = 4.7 Hz, 3H), 2.55 (s, 3H), 2.50 (s, 3H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.27 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (δ, ppm) (101 MHz, $CDCl_3$) 170.8, 170.4, 168.1, 166.7, 152.4, 151.7, 147.1, 134.9, 128.8, 62.9, 62.8, 54.5, 52.7, 51.3, 28.4, 24.3, 24.0, 13.98, 13.97. **IR** (ν, cm^{-1}, $CDCl_3$) 3384, 2987, 2942, 1769, 1741, 1724, 1703, 1586, 1514, 1372, 1331, 1262, 1211, 1161, 1117, 1034. **HRMS** (EI+) calculated for $C_{19}H_{24}ClN_5O_7$: 469.1364; Found: 469.1358. **mp**: 152-153 °C.

3.2.46 ***(15)***. Product **15** was isolated as a colorless oil (56 mg, 0.07 mmol, 14% yield, *dr* = 1.0:1.1). **^{1}H NMR** (δ, ppm) (400 MHz, $CDCl_3$) 7.18 (br, 1H, 2nd dia), 6.87 (br, 1H, 1st dia), 5.77 (d, *J* = 2.2 Hz, 1H, 2nd dia), 5.70 (d, *J* = 2.2 Hz, 1H, 1st dia), 5.41 (s, 1H, 1st dia), 5.37 (s, 1H, 2nd dia), 4.57 (dd, *J* = 4.0, 2.3 Hz, 1H, 1st dia), 4.51 (d, *J* = 4.1 Hz, 1H, 2nd dia), 4.50 (dd, *J* = 4.0, 2.3 Hz, 1H, 2nd dia), 4.04 (d, *J* = 4.1 Hz, 2H), 4.39 (d, *J* = 4.2 Hz, 1H, 1st dia), 4.34 – 4.06 (m, 32H, 1st and 2nd dia), 4.04 (d, *J* = 4.1 Hz, 2H, 2nd dia), 4.01 (d, *J* = 4.1 Hz, 1H, 1st dia), 3.03 (d, *J* = 4.4Hz, 3H, 1st dia), 3.00 (d, *J* = 4.4Hz, 3H, 2nd dia), 2.65 (s, 6H, 1st and 2nd dia), 2.55 (s, 3H, 1st dia), 2.45 (s, 6H, 2nd dia), 2.36 (s, 3H, 2nd dia), 2.35 (s, 3H, 1st dia), 2.33 (s, 3H, 1st dia), 1.30 – 1.20 (m, 24H, 1st and 2nd dia). **^{13}C NMR** (δ, ppm) (101 MHz, $CDCl_3$) 171.3, 171.1, 170.7, 169.6, 169.5, 169.4, 169.4, 168.7, 168.4, 166.6, 166.6, 166.4, 166.2, 152.0, 151.9, 151.6, 151.5, 151.4, 146.0, 145.8, 135.3, 134.9, 134.7, 134.0, 63.1, 63.0, 62.9, 62.8, 62.4, 62.4, 62.2, 62.2, 55.8, 55.5, 54.2, 53.5, 53.2, 53.0, 52.0, 50.7, 50.6, 28.5, 28.4, 24.8, 24.8, 24.2, 24.2, 24.0, 24.0, 23.6, 23.4, 14.1, 14.0, 14.0, 13.98, 13.93, 13.89. **IR** (ν, cm^{-1}, $CDCl_3$) 3378, 2986, 2924, 1770, 1744, 1725, 1702, 1589, 1524, 1368, 1332, 1265, 1204, 1164, 1117, 1036. **HRMS** (EI+) calculated for $C_{33}H_{42}ClN_7O_{14}$: 795.2478; Found: 795.2434.

3.2.47 *(3,4-trans)-3-(3-Amino-5-chloropyrazin-2-yl)-4-((6-chloropyridin-3-yl)-methyl)-1-ethylpyrrolidine-2,5-dione* ***(19)***. Following the general procedure, the

reaction was carried out with xanthate **17**[31] (373 mg, 1.00 mmol) and pyrazine **18** (65 mg, 0.50 mmol) in 1.0 mL DCE and needed 5 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of EtOAc/petroleum ether = 1:3 to 2:1, then DCM/diethyl ether = 4:1 to 7:3) afforded the single addition product **19** as a white solid (127 mg, 0.33 mmol, 66% yield). **^{1}H NMR** (δ, ppm) (400 MHz, $CDCl_3$) 8.18 (d, J = 2.6 Hz, 1H), 7.80 (s, 1H), 7.46 (dd, J = 8.2, 2.6 Hz, 1H), 7.21 (d, J = 8.2 Hz, 1H), 5.50 (s, 2H, NH_2), 4.43 (dt, J = 7.2, 5.6 Hz, 1H), 3.75 (d, J = 5.5 Hz, 1H), 3.59 – 3.47 (m, 2H), 3.18 – 3.03 (m, 2H), 1.12 (t, J = 7.2 Hz, 3H). **^{13}C NMR** (δ, ppm) (101 MHz, $CDCl_3$) 177.3, 176.0, 154.4, 150.6, 150.2, 146.4, 139.6, 132.6, 131.8, 131.5, 124.4, 48.3, 43.0, 34.5, 31.8, 13.1. **IR** (ν, cm^{-1}, $CDCl_3$) 3461, 3356, 2985, 2941, 1775, 1701, 1617, 1589, 1563, 1533, 1462, 1432, 1405, 1381, 1352, 1227, 1140, 1110, 1049, 1026, 957. **HRMS** (EI+) calculated for $C_{16}H_{15}Cl_2N_5O_2$: 379.0603; Found: 379.0598. **mp**: 185-186 °C.

3.2.48 *4,4'-(3-Amino-5-chloropyrazine-2,6-diyl)bis(3-((6-chloropyridin-3-yl)methyl)-1-ethylpyrrolidine-2,5-dione) (**20**).* Product **20** was isolated as a light brown solid (56 mg, 0.09 mmol, 18% yield). **^{1}H NMR** (δ, ppm) (400 MHz, $CDCl_3$) 8.22 (dd, J = 5.5, 2.5 Hz, 2H), 8.15 (dd, J = 9.3, 2.5 Hz, 2H), 7.50 – 7.36 (m, 4H), 7.28 – 7.19 (m, 4H), 5.63 (4H), 4.16 – 4.01 (m, 4H), 3.71 (dd, J = 21.0, 5.4 Hz, 2H), 3.64 – 3.47 (m, 8H), 3.30 – 2.93 (m, 10H), 1.12 (m, 12H). **^{13}C NMR** (δ, ppm) (101 MHz, $CDCl_3$) 176.9, 176.9, 176.8, 175.4, 175.3, 174.7, 174.4, 153.9, 153.8, 150.8, 150.7, 150.42, 150.38 , 150.2, 150.1, 145.61, 145.57, 139.7, 139.6, 136.6, 136.1, 133.2, 132.9, 131.3, 131.1, 131.0, 124.6, 124.6, 124.4, 124.4, 48.7, 48.6, 48.2, 48.1, 47.9, 47.8, 43.1, 43.0, 34.7, 34.6, 34.51, 34.48, 32.0, 31.9, 31.6, 31.3, 13.2, 13.1, 13.0. **IR** (ν, cm^{-1}, $CDCl_3$) 3461, 3352, 2984, 2940, 1778, 1705, 1617, 1588, 1563, 1462, 1445, 1403, 1387, 1352, 1227, 1133, 1111, 1042, 1027. **HRMS** (EI+) calculated for $C_{28}H_{26}Cl_3N_7O_4$: 629.1112; Found: not found.

3.2.49 *1-(5-Chloro-3-(methylamino)pyrazin-2-yl)-3-cyanopropyl dodecanoate (**24**).* Following the general procedure, the reaction was carried out with xanthate **22a**[33]

(356 mg, 1.44 mmol) and pyrazine **1a** (103 mg, 0.72 mmol) in 1.4 mL DCE and needed 6 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/EtOAc = 4:1) afforded compound **16** as a light brown oil (92 mg, 0.22 mmol, 31% yield). **^{1}H NMR** (δ, ppm) (400 MHz, $CDCl_3$) 7.73 (s, 1H), 5.86 (m, 2H), 2.98 (d, J = 4.7 Hz, 3H), 2.48 (m, 3H), 2.38 (m, 3H), 1.65 – 1.56 (m, 2H), 1.24 (s, 16H), 0.87 (t, J = 6.8 Hz, 3H). **^{13}C NMR** (δ, ppm) (101 MHz, $CDCl_3$) 174.7, 153.3, 147.6, 134.6, 129.2, 118.8, 69.7, 34.2, 32.0, 29.7, 29.7, 29.5, 29.4, 29.3, 29.1, 28.5, 27.8, 24.9, 22.8, 14.2, 14.0. **IR** (v, cm^{-1}, $CDCl_3$) 3391, 2928, 2856, 1721, 1578, 1540, 1508, 1446, 1379, 1261, 1222, 1187, 1155, 1103, 1029. **HRMS** (EI+) calculated for $C_{21}H_{33}ClN_4O_2$: 408.2292; Found: 408.2284.

3.2.50 *1-(5-Chloro-3-phenoxypyrazin-2-yl)-3-cyanopropyl acetate (**26a**).* Following the general procedure, the reaction was carried out with xanthate **22a** (327 mg, 1.32 mmol) and pyrazine **25** (137 mg, 0.66 mmol) in 1.3 mL DCE and needed 6 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/Et_2O = 5:1 to 3:1) afforded the desired compound **26a** as a colorless oil (141 mg, 0.42 mmol, 64% yield). **^{1}H NMR** (δ, ppm) (400 MHz, $CDCl_3$) 8.24 (s, 1H), 7.42 (dt, J = 10.6, 2.2 Hz, 2H), 7.28 – 7.25 (m, 1H), 7.17 (dd, J = 5.4, 3.4 Hz, 2H), 6.18 (dd, J = 7.0, 5.6 Hz, 1H), 2.62 – 2.56 (m, 2H), 2.46 – 2.38 (m, 2H), 2.15 (s, 3H). **^{13}C NMR** (δ, ppm) (101 MHz, $CDCl_3$) 170.1, 156.0, 152.6, 145.6, 140.6, 137.1, 129.9, 126.0, 121.3, 118.8, 69.1, 28.5, 20.8, 13.7. **IR** (v, cm^{-1}, $CDCl_3$) 3071, 2940, 1743, 1595, 1538, 1490, 1427, 1372, 1235, 1218, 1172, 1161, 1052, 1024. **HRMS** (EI+) calculated for $C_{16}H_{14}ClN_3O_3$: 331.0724; Found: 331.0718.

3.2.51 *1-(5-Chloro-3-phenoxypyrazin-2-yl)-4-((8S,9S,10R,13S,14S,17R)-17-hydroxy-10,13-dimethyl-3,11-dioxo-2,3,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-17-yl)-4-oxobutyl acetate (**26b**).* Following the general procedure, the reaction was carried out with xanthate **22b**[39] (433 mg, 0.79 mmol) and pyrazine **20** (81 mg, 0.39 mmol) in 0.8 mL DCE and needed 4 h for the reaction to go to completion. Flash chromatography on silica gel 60 (SDS, Merck, 15-40 μm)

(gradient of toluene/EtOAc = 2:1 to 1:1) afforded the desired product **26b** as a white solid (98 mg, 0.15 mmol, 40% yield, 1:1 epimers). **^{1}H NMR** (δ, ppm) (400 MHz, $CDCl_3$) 8.19 (d, J = 10.4 Hz, 1H), 7.41 (t, J = 7.5 Hz, 2H), 7.26 – 7.22 (m, 1H), 7.20 – 7.14 (m, 2H), 6.10 (dd, J = 7.5, 4.5 Hz, 1H), 5.71 (s, 1H), 3.22 (br, 1H, *O*H), 3.10 – 2.96 (m, 1H), 2.84 (d, J = 12.3 Hz, 1H), 2.81 – 2.67 (m, 2H), 2.52 – 2.25 (m, 8H), 2.12 (s, 1.5 H, 1st epimer), 2.10 (s, 1.5 H, 2nd epimer), 2.10 – 2.03 (m, 1H), 2.00 – 1.85 (m, 4H), 1.73 – 1.56 (m, 2H), 1.49 – 1.33 (m, 1H), 1.39 (s, 3H, H_{19}), 1.31 – 1.24 (m, 1H), 0.62 (s, 1.5H, 1st epimer), 0.61 (s, 1.5H, 2nd epimer). **^{13}C NMR** (δ, ppm) (101 MHz, $CDCl_3$) 211.0, 210.9, 209.65, 209.59, 199.9, 170.7, 170.5, 168.8, 155.85, 155.84, 152.7, 152.6, 145.0, 144.9, 142.1, 141.8, 136.9, 136.7, 129.9, 125.8, 124.7, 121.32, 121.30, 89.15, 89.07, 70.0, 69.8, 62.62, 62.60, 51.22, 51.18, 50.3, 49.7, 38.3, 36.59, 36.58, 34.8, 34.64, 34.59, 34.2, 34.1, 33.8, 32.4, 32.3, 26.7, 26.6, 23.5, 21.1, 21.0, 17.3, 16.09, 16.06. **IR** (ν, cm^{-1}, $CDCl_3$) 3505, 2941, 1739, 1706, 1667, 1617, 1595, 1539, 1490, 1428, 1372, 1274, 1235, 1218, 1185, 1172, 1162, 1117, 1071, 1051, 1023. **mp**: 97-100 °C.

3.2.52 *(3-Methoxypyrazin-2-yl)methyl pivalate (**29**).* Following the general procedure, the reaction was carried out with xanthate **28** (544 mg, 2.30 mmol) and pyrazine **27** (127 mg, 1.15 mmol) in 2.3 mL DCE and needed 5 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/Et_2O = 3:1 to 3:2) afforded the desired product **29** as a yellow oil (85 mg, 0.38 mmol, 33% yield), and 26 mg pyrazine **27** (0.24 mmol) was recovered. **^{1}H NMR** (δ, ppm) (400 MHz, $CDCl_3$) 8.09 (d, J = 2.8 Hz, 1H), 8.05 (d, J = 2.8 Hz, 1H), 5.22 (s, 2H), 3.98 (s, 3H), 1.24 (s, 9H). **^{13}C NMR** (δ, ppm) (101 MHz, $CDCl_3$) 178.3, 158.5, 141.3, 140.4, 135.9, 62.4, 53.8, 39.0, 27.3. **IR** (ν, cm^{-1}, $CDCl_3$) 2974, 2956, 2931, 2856, 1728, 1549, 1480, 1463, 1452, 1396, 1367, 1284, 1139, 1012. **HRMS** (EI+) calculated for $C_{11}H_{16}N_2O_3$: 224.1161; Found: 224.1166.

3.2.53 *Diethyl 2-(1,3-diacetyl-5-(5-chloro-6-((1,3-dioxoisoindolin-2-yl)methyl)-3-(methylamino)pyrazin-2-yl)-2-oxoimidazolidin-4-yl)malonate (**30a**).* Following the

general procedure, the reaction was carried out with xanthate **2** (131 mg, 0.46 mmol) and pyrazine **14b** (109 mg, 0.23 mmol) in 0.5 mL DCE and needed 6 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/Et_2O = 3:1 to 1:3) afforded the desired product **30a** as a white solid (85 mg, 0.13 mmol, 59% yield) and 30 mg (0.06 mmol) pyrazine **14b** was recovered. **^{1}H NMR** (δ, ppm) (400 MHz, $CDCl_3$) 7.88 – 7.85 (m, 2H), 7.78 – 7.73 (m, 2H), 6.83 (br, 1H, *N*H), 5.37 (s, 1H), 4.94 (d, *J* = 16.6 Hz, 1H), 4.86 (d, *J* = 16.6 Hz, 1H), 4.43 (d, *J* = 4.2 Hz, 1H), 4.24 (dddd, *J* = 18.0, 10.8, 7.2, 3.6 Hz, 2H), 4.11 – 4.00 (m, 2H), 3.97 (d, *J* = 4.2 Hz, 1H), 3.02 (d, *J* = 4.6 Hz, 3H), 2.19 (s, 3H), 2.06 (s, 3H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.19 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (δ, ppm) (101 MHz, $CDCl_3$) 170.7, 169.6, 168.3, 167.8, 166.4, 151.6, 150.9, 144.7, 134.0, 133.5, 132.4, 131.3, 123.7, 62.9, 62.7, 53.9, 52.5, 50.8, 38.5, 28.5, 23.5, 23.2, 13.9, 13.9. **IR** (ν, cm^{-1}, $CDCl_3$) 3385, 2986, 2941, 1774, 1720, 1587, 1516, 1426, 1396, 1373, 1325, 1263, 1203, 1165, 1116, 1036. **HRMS** (EI+) calculated for $C_{28}H_{29}ClN_6O_9$: 628.1685; Found: 628.1680. **mp**: 166-167 °C.

3.2.54 *Diethyl 2-(1,3-diacetyl-5-(3-chloro-6-((1,3-dioxoisoindolin-2-yl)methyl)-5-(methylamino)pyrazin-2-yl)-2-oxoimidazolidin-4-yl)malonate (**30b**).* Following the general procedure, the reaction was carried out with xanthate **13b** (414 mg, 0.92 mmol, 1.7 equiv) and pyrazine **3a** (164 mg, 0.54 mmol, 1.0 equiv) in 1.8 mL DCE (0.5 mmol/mL of xanthate) and needed 6 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/EtOAc = 5:1 to 1:1) afforded the desired product **30b** as a white solid (260 mg, 0.41 mmol, 76% yield) and 15 mg (0.05 mmol) pyrazine **3a** was recovered. **^{1}H NMR** (δ, ppm) (400 MHz, $CDCl_3$) 7.85 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.74 (td, *J* = 5.2, 2.1 Hz, 2H), 5.93 (br, 1H, *N*H), 5.68 (d, *J* = 1.7 Hz, 1H), 4.69 (s, 2H), 4.63 (dd, *J* = 4.3, 1.7 Hz, 1H), 4.27 – 4.14 (m, 4H), 4.12 (d, *J* = 4.3 Hz), 3.00 (d, *J* = 4.7 Hz, 3H), 2.48 (s, 3H), 2.40 (s, 3H), 1.23 (q, *J* = 7.2 Hz, 6H). **^{13}C NMR** (δ, ppm) (101 MHz, $CDCl_3$) 171.0, 170.0, 168.1, 166.6, 166.3, 152.5, 152.1, 144.7, 135.4, 134.5, 134.2, 131.9, 123.8, 62.3, 62.1, 56.0, 53.5, 52.6, 39.2, 28.7, 24.3, 24.2, 14.1, 14.0. **IR** (ν, cm^{-1}, $CDCl_3$) 3379, 2985, 1761, 1714, 1584,

1520, 1426, 1389, 1368, 1336, 1264, 1116, 1038. **HRMS** (EI+) calculated for $C_{28}H_{29}ClN_6O_9$: 628.1685; Found: 628.1670. **mp**: 157-158 °C.

3.2.55 *2-(1-(3-Chloro-6-((1,3-dioxoisoindolin-2-yl)methyl)-5-(methylamino)pyrazin-2-yl)-3-(5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl)propyl)isoindoline-1,3-dione (**30c**).* Following the general procedure, the reaction was carried out with xanthate **8b** (200 mg, 0.45 mmol) and pyrazine **3a** (89 mg, 0.30 mmol) in 0.9 mL DCE (0.5 mmol/mL of xanthate) and needed 8 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/EtOAc = 2:1 to 2:3) afforded the desired product **30c** as a white solid (81 mg, 0.13 mmol, 44% yield) and 36 mg (0.12 mmol) pyrazine **3a** was recovered. **^{1}H NMR** (δ, ppm) (400 MHz, $CDCl_3$) 7.83 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.77 – 7.74 (m, 2H), 7.73 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.69 (dd, *J* = 5.6, 3.0 Hz, 2H), 5.79 (br, 1H, *N*H), 5.57 (t, *J* = 7.2 Hz, 1H), 4.90 (d, *J* = 15.2 Hz, 1H), 4.83 (d, *J* = 15.2 Hz), 3.23 – 3.11 (m, 1H), 3.08 (dd, *J* = 9.5, 5.5 Hz, 1H), 3.04 – 2.95 (m, 1H), 2.99 (d, *J* = 4.8 Hz, 3H), 2.71 – 2.59 (m, 1H). **^{13}C NMR** (δ, ppm) (101 MHz, $CDCl_3$) 168.7, 168.4, 167.8, 155.4 (q, *J* = 43.8 Hz), 152.3, 145.4, 134.4, 134.2, 133.1, 132.7, 132.1, 131.7, 123.7, 123.5, 116.5 (q, *J* = 269.9 Hz, CF_3), 50.8, 39.6, 28.6, 27.0, 22.8. **IR** (ν, cm^{-1}, $CDCl_3$) 3385, 1773, 1716, 1582, 1389, 1371, 1214, 1174, 1134. **HRMS** (EI+) calculated for $C_{28}H_{19}ClF_3N_7O_5$: 625.1088; Found: 625.1117. **mp**: 99-101 °C.

3.2.56 *3-Cyano-1-(6-((1,3-dioxoisoindolin-2-yl)methyl)-3,5-dimethoxypyrazin-2-yl)propyl acetate (**30d**).* Following the general procedure, the reaction was carried out with xanthate **22a** (230 mg, 0.93 mmol) and pyrazine **3i** (139 mg, 0.46 mmol) in 1.4 mL DCE (0.66 mmol/mL of xanthate) and needed 6 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/EtOAc = 5:1 to 1:1) afforded the desired product **30d** as a white solid (116 mg, 0.27 mmol, 59% yield). **^{1}H NMR** (δ, ppm) (400 MHz, $CDCl_3$) 7.90 (dt, *J* = 7.0, 3.5 Hz, 2H), 7.77 (td, *J* = 5.3, 2.1 Hz, 2H), 5.90 (t, *J* = 5.9 Hz, 1H), 4.96 (d, *J* = 16.8 Hz, 1H), 4.89 (d, *J* = 16.8 Hz, 1H), 4.01 (s, 3H), 3.94 (s, 3H), 2.26 – 2.14 (m, 2H), 2.14 – 2.03 (m, 1H),

2.03 – 1.92 (m, 1H), 1.85 (s, 3H). **^{13}C NMR** (δ, ppm) (101 MHz, $CDCl_3$) 170.1, 168.5, 155.9, 155.9, 134.3, 132.4, 129.1, 128.1, 123.5, 119.3, 68.1, 54.1, 54.0, 37.8, 27.8, 20.7, 12.9. **IR** (ν, cm^{-1}, $CDCl_3$) 2990, 2948, 1774, 1718, 1560, 1481, 1455, 1429, 1396, 1342, 1241, 1185, 1110, 1012. **HRMS** (EI+) calculated for $C_{21}H_{20}N_4O_6$: 424.1383; Found: 424.1383. **mp**: 129-130 °C.

3.2.57 *2-((4-Acetylpyridin-2-yl)methyl)isoindoline-1,3-dione (**31a**).* Following the general procedure, the reaction was carried out with xanthate **2** (389 mg, 1.28 mmol, 1.3 equiv), 4-acetylpyridine (131 mg, 1.08 mmol, 1.0 equiv) and TFA (616 mg, 413 μL, 5.40 mmol, 5.0 equiv) in 1.3 mL ethyl acetate and was stopped after 6 h. Flash chromatography on silica gel (gradient of petroleum ether/ethyl acetate = 1:1 to 2:3) afforded mono-addition product **31a** (54 mg, 0.19 mmol, 18% yield) as a white solid. **^{1}H NMR** (δ, ppm) (400 MHz, $CDCl_3$) 8.70 (dd, J = 5.1, 0.9 Hz, 1H), 7.89 (dd, J = 5.4, 3.1 Hz, 2H), 7.75 (dd, J = 5.5, 3.1 Hz, 2H), 7.72 (t, J = 1.2 Hz, 1H), 7.60 (dd, J = 5.0, 1.6 Hz, 1H), 5.09 (s, 2H), 2.61 (s, 3H). **^{13}C NMR** (δ, ppm) (101 MHz, $CDCl_3$) 197.2, 168.2, 157.0, 151.0, 143.7, 134.3, 132.3, 123.7, 120.4, 119.3, 43.0, 26.9. **IR** (ν, cm^{-1}, $CDCl_3$) 1774, 1718, 1701, 1602, 1560, 1470, 1426, 1392, 1362, 1278, 1199, 1188, 1114, 1088. **HRMS** (EI+) calculated for $C_{16}H_{12}N_2O_3$: 280.0848; Found: 280.0852. **mp**: 135-136 °C.

3.2.58 *2,2'-((4-Acetylpyridine-2,6-diyl)bis(methylene))bis(isoindoline-1,3-dione) (**32**).* Product **32** was isolated as a white solid (42 mg, 0.10 mmol, 9% yield), and 43 mg (0.35 mmol) of the starting 4-acetylpyridine was recovered. **^{1}H NMR** (δ, ppm) (400 MHz, $CDCl_3$) 7.75 – 7.67 (m, 8H), 7.57 (s, 2H), 4.97 (s, 4H), 2.59 (s, 3H). **^{13}C NMR** (δ, ppm) (101 MHz, $CDCl_3$) 197.0, 167.9, 156.7, 144.5, 134.1, 132.1, 123.5, 118.0, 42.6, 27.0. **IR** (ν, cm^{-1}, $CDCl_3$) 1775.1721, 1603, 1567, 1470, 1426, 1392, 1365, 1319, 1301, 1202, 1190, 1111, 1088. **HRMS** (EI+) calculated for $C_{25}H_{17}N_3O_5$: 439.1168; Found: 439.1152.

3.2.59 *2,2'-(Phthalazine-1,4-diylbis(methylene))bis(isoindoline-1,3-dione) (**31b**).*

Following the general procedure, the reaction was carried out with xanthate **2** (422 mg, 1.50 mmol, 3.0 equiv), phthalazine (65 mg, 0.50 mmol, 1.0 equiv) and TFA (285 mg, 191 μL, 2.50 mmol, 5.0 equiv) in 1.5 mL ethyl acetate and needed 3 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of petroleum ether/ethyl acetate = 1:1 to dichloromethane/ethyl acetate = 4:1) afforded the desired product **31b** (91 mg, 0.20 mmol, 40% yield) as a white solid. **^{1}H NMR** (δ, ppm) (400 MHz, $CDCl_3$) 8.21 (dd, J = 6.3, 3.2 Hz, 2H), 7.98 (dd, J = 6.3, 3.3 Hz, 2H), 7.82 (dd, J = 5.4, 3.0 Hz, 4H), 7.67 (dd, J = 5.5, 3.1 Hz, 4H), 5.53 (s, 4H). **^{13}C NMR** (δ, ppm) (101 MHz, $CDCl_3$) 168.1, 152.6, 134.1, 132.8, 132.5, 124.6, 123.6, 123.6, 39.0. **IR** (v, cm^{-1}, $CDCl_3$) 3074, 2931, 1774, 1718, 1618, 1602, 1571, 1470, 1425, 1399, 1357, 1257, 1114, 1089. **HRMS** (EI+) calculated for $C_{26}H_{16}N_4O_4$: 448.1172; Found: 448.1171. **mp**: 300-302 °C.

3.2.60 *8-((1,3-Dioxoisoindolin-2-yl)methyl)-1,3,7-trimethyl-3,7-dihydro-1H-purine-2,6-dione (**31c**).* Following the general procedure, the reaction was carried out with xanthate **2** (422 mg, 1.50 mmol, 3.0 equiv), caffeine (97 mg, 0.50 mmol, 1.0 equiv) in 1.5 mL DCE and needed 5 h for the reaction to go to completion. Flash chromatography on silica gel (gradient of dichloromethane/ethyl acetate = 3:2 to 1:1) afforded the desired product **31c** (131 mg, 0.37 mmol, 74% yield) as a white solid. **^{1}H NMR** (δ, ppm) (400 MHz, $CDCl_3$) 7.90 (dd, J = 5.4, 3.1 Hz, 2H), 7.77 (dd, J = 5.5, 3.0 Hz, 2H), 4.94 (s, 2H), 4.11 (s, 3H), 3.45 (s, 3H), 3.37 (s, 3H). **^{13}C NMR** (δ, ppm) (101 MHz, $CDCl_3$) 167.5, 155.5, 151.7, 147.9, 147.3, 134.6, 132.0, 123.9, 108.2, 33.5, 32.3, 30.0, 28.0. **IR** (v, cm^{-1}, $CDCl_3$) 2954, 1776, 1722, 1703, 1657, 1606, 1550, 1470, 1448, 1424, 1390, 1346, 1221, 1087, 1041, 982. **HRMS** (EI+) calculated for $C_{17}H_{15}N_5O_4$: 353.1124; Found: 353.1126. **mp**: 239-241 °C.

3.2.61 *2-((4-Bromoisoquinolin-1-yl)methyl)isoindoline-1,3-dione (**31d**).* Following the general procedure, the reaction was carried out with xanthate **2** (422 mg, 1.50 mmol, 3.0 equiv), 4-bromoisoquinoline (104 mg, 0.50 mmol, 1.0 equiv) and TFA (285 mg, 191 μL, 2.50 mmol, 5.0 equiv) in 1.5 mL ethyl acetate and needed 2 h for the reaction

to go to completion. Trituration from diethyl ether gave the desired product **31d** (111 mg, 0.30 mmol, 57% yield) as a white solid. **^{1}H NMR** (δ, ppm) (400 MHz, $CDCl_3$) 8.51 (s, 1H), 8.21 (dt, *J* = 8.5, 1.3 Hz, 2H), 7.92 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.83 (ddd, *J* = 8.5, 6.9, 1.2 Hz, 1H), 7.79 – 7.70 (m, 3H), 5.49 (s, 2H). **^{13}C NMR** (δ, ppm) (101 MHz, $CDCl_3$) 168.6, 152.7, 143.7, 134.9, 134.1, 132.6, 131.5, 128.6, 127.13, 127.08, 124.2, 123.7, 119.4, 40.6. **IR** (ν, cm^{-1}, $CDCl_3$) 3074, 2931, 1774, 1718, 1618, 1602, 1571, 1470, 1425, 1399, 1357, 1257, 1114, 1089. **HRMS** (EI+) calculated for $C_{18}H_{11}BrN_2O_2$: 366.0004; Found: 366.0008. **mp**: 251-252 °C.

3.2.62 *2-((3-Methylisoquinolin-1-yl)methyl)isoindoline-1,3-dione (**31e**).* According to the general procedure, the reaction was carried out with xanthate **2** (563 mg, 2.00 mmol), 3-methylisoquinoline (143 mg, 1.00 mmol) and TFA (570 mg, 382 μL, 5.00 mmol) in 2.0 mL EtOAc and needed 3 h for the reaction to go to completion. Purification by flash chromatography on silica gel (EtOAc/petroleum ether = 2:3) afforded the desired product **31e** as a white solid (97 mg, 0.32 mmol, 32% yield). **^{1}H NMR** (δ, ppm) (400 MHz, $CDCl_3$) 8.16 (dq, *J* = 8.4, 1.0 Hz, 1H), 7.94 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.80 – 7.73 (m, 3H), 7.65 (ddd, *J* = 8.2, 6.8, 1.2 Hz, 1H), 7.57 (ddd, *J* = 8.3, 6.8, 1.4 Hz, 1H), 7.36 (s, 1H), 5.52 (s, 2H), 2.46 (s, 3H). **^{13}C NMR** (δ, ppm) (101 MHz, $CDCl_3$) 168.8, 152.2, 150.7, 137.2, 134.0, 132.7, 130.0, 127.0, 126.5, 124.1, 123.8, 123.5, 118.3, 41.1, 24.4. **IR** (ν, cm^{-1}, $CDCl_3$) 1774, 1716, 1628, 1594, 1571, 1428, 1399, 1113. **HRMS** (EI+) calculated for $C_{19}H_{14}N_2O_2$: 302.1055; Found: 302.1044. **mp**: 193-194 °C.

3.2.63 *2-((1,3-Dioxoisoindolin-2-yl)methyl)-1H-indole-3-carbaldehyde (**31f**).* A solution of xanthate **2** (281 mg, 1.00 mmol, 2.0 equiv) and indole-3-carboxaldehyde (73 mg, 0.50 mmol, 1.0 equiv) in 1.0 mL DCE was heated at 50 °C and DLP was added portionwise (100 mol %/12 h). It took 24 h for the reaction to go to completion. After evaporation of the solvent, the residue was triturated from diethyl ether. The desired product **31f** (107 mg, 0.35 mmol, 70% yield) was obtained by recrystallization from ethyl acetate as a white powder. **^{1}H NMR** (δ, ppm) (400 MHz, $CDCl_3$) 10.49 (s,

1H, H_9), 9.33 (br, 1H, *N*H), 8.33 – 8.25 (m, 1H), 7.88 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.78 – 7.73 (m, 2H), 7.41 – 7.36 (m, 1H), 7.32 – 7.25 (m, 2H), 5.32 (s, 2H). **^{13}C NMR** (δ, ppm) (101 MHz, $CDCl_3$) 184.9, 168.2, 141.7, 135.4, 134.8, 131.8, 125.1, 124.7, 124.0, 123.3, 122.1, 115.6, 111.5, 32.1. **IR** (ν, cm^{-1}, $CDCl_3$) 3416, 1770, 1716, 1658, 1602, 1456, 1429, 1392, 1362, 1337, 1323, 1157, 1108, 1097, 1016, 990, 959. **HRMS** (EI+) calculated for $C_{18}H_{12}N_2O_3$: 304.0848; Found: 304.0834. **mp**: 241-242 °C.

Acknowledgements
We thank Ecole Polytechnique for a scholarship to Q. H. and L. Q.. We also thank Mr Vincent Jactel (Ecole Polytechnique) for HRMS measurements.

Supplementary data
Supplementary data related to this article can be found at

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