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Modular Synthesis of 3,6-Disubstituted-1,2,4-triazines via the Cyclodehydration of β-Keto-N-acylsulfonamides with Hydrazine Salts

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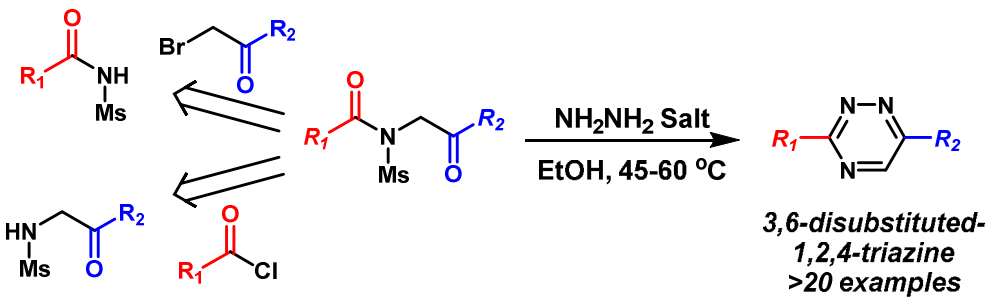


Abstract: A straightforward method for preparing 3,6-disubstituted-1,2,4-triazines through a redox-efficient cyclodehydration of β-keto-N-acylsulfonamides with hydrazine salts is described. Two approaches for synthesizing the requisite β-keto-N-acylsulfonamides are presented, which allow for the late stage incorporation of either the C3 or C6 substituent in a flexible manner from acid chlorides or α-bromoketones, respectively. The scope of this methodology includes primary and secondary sp^3-linked substituents at both the C3 and C6 positions, and the mild reaction conditions tolerate a variety of sensitive functionality.

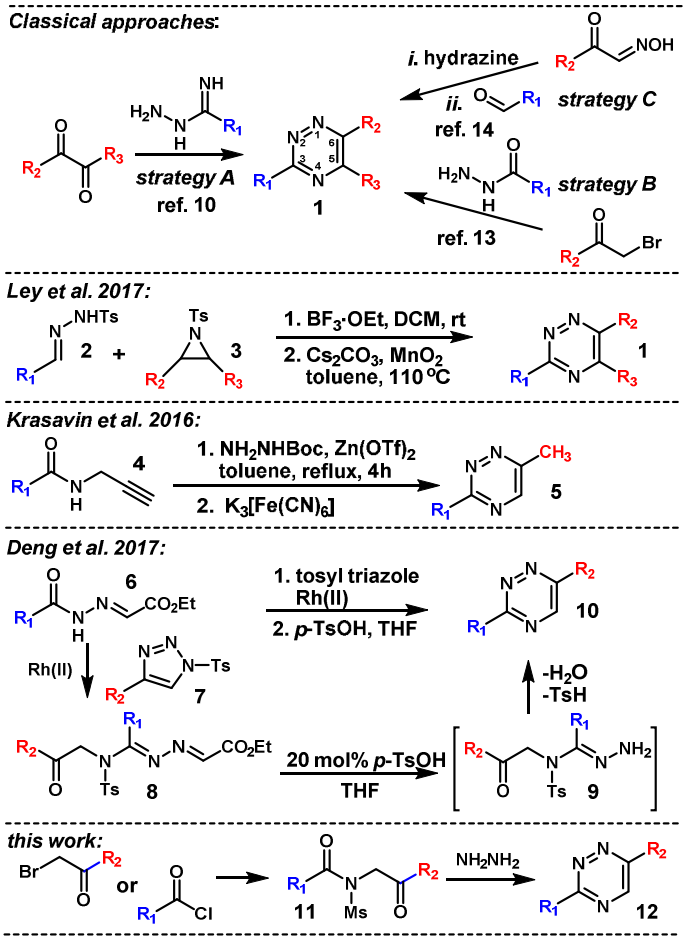
The incorporation of nitrogen atoms into aromatic rings is a powerful medicinal chemistry design tactic for improving physicochemical properties and modulating potency.[1] In this context the 1,2,4-triazine motif is notable as one of the most prevalent triazine heterocycles within medicinal chemistry, and has been demonstrated to improve physicochemical properties relative to a pyridine comparator[2] and inhibition of MAO-B relative to a diazine comparator.[3] Indeed, this heterocycle is present in numerous bioactive compounds including those targeting adenosine A_{2A},[4] mGluR5,[2] mPGES-1[5] as well as the marketed drug lamictal.[6] 1,2,4-Triazines have also found applications as ligands for metals,[7] in agrochemical research, and as clickable bio-orthogonal probes.[8] Additionally, this heterocycle has been extensively employed as a starting material for preparing highly substituted pyridines using inverse electron demand hetero-Diels–Alder chemistry.[9]

Due to the widespread utility of 1,2,4-triazines, numerous strategies have been reported for their synthesis. One of the most widely used strategies involves the condensation between amidrazones and either 1,2-diketones or -ketoaldehydes (Figure 1, strategy A).[10] This chemistry is most often used for preparing 1,2,4-triazines for which the 5- and 6- substituents are identical; unsymmetrical 1,2-diketones often produce regioisomeric mixtures,[11] while 1,2-ketoaldehydes favor formation of the 3,5-disubstituted 1,2,4-triazine.[12] Reported approaches for accessing 3,6-disubstituted 1,2,4-triazines include the coupling between two equivalents of an acyl hydrazine and an α-bromoketone,[13] (strategy B, Figure 1) and between an α-keto-oxime, hydrazine and an aldehyde with subsequent dehydration.[14] (strategy C, Figure 1). Almost all examples that employ strategy B involve aryl substitution at C6, while examples of strategy C are limited to 2- and 4- pyridyl substituents at C6.

Several new approaches for preparing 1,2,4-triazines have been reported in the last two years (Figure 1). For example, Krasavin recently described a method for accessing this heterocycle via hydrohydrazination of propargylamides **4** with boc-hydrazine followed by in situ oxidation.[15] While reasonable scope was demonstrated at C3, the C6 position is limited to a methyl substituent. Ley et al. recently reported chemistry for the regioselective construction of 3,6- and 3,5,6-substituted 1,2,4-triazines through the

coupling of tosyl hydrazones **2** and tosyl aziridines **3** followed by cyclization and in situ oxidation.[16] In this case, the scope at C6 is limited to aryl and a single example with alkyl substitution at C3 resulted in an 8% yield. Finally, Deng et al. recently described an approach to 3,6-disubstituted triazines via the coupling of tosyl triazole-derived rhodium carbenoids **7** with hydrazones of type **6**.[17] Subsequent treatment with catalytic *p*-TsOH led to hydrolysis of the terminal hydrazone and cyclization to the triazine **10** via intermediate **9**. However, the scope of this methodology was also limited to aryl substituents at both C3 and C6 positions.

Figure 1. Relevant precedent for the preparation of substituted 1,2,4-triazines.



In an effort to support medicinal chemistry and fragment-based screening campaigns, we sought to develop a new method for preparing 1,2,4-triazines. Particular importance was placed on the ability to incorporate sp^3-linked substituents onto the heterocycle, which is known to generally provide access to more developable physicochemical space[18] and is a limitation of many of the existing methods for preparing 1,2,4-triazines (vide supra). Other goals were to identify mild reaction conditions that enable the incorporation of sensitive functionality, to employ readily available starting materials in a modular manner, achieve complete regioselectivity, and to avoid a terminal oxidation step. Along these lines we took note of the chemistry developed by Deng[17] (Figure 1). This chemistry is postulated to proceed through the intermediacy of tosyl amidrazone **9**, which undergoes cyclodehydration with concomitant sulfinate elimination to afford the 3,6-disubstituted-1,2,4-triazine product. We postulated that a more direct approach to access an intermediate related to **9** could be achieved through condensation of hydrazine with an acylsulfonamide of type **11** (Figure 1). Acylsulfonamide **11** was expected to undergo initial condensation of hydrazine with the ketone functionality, followed by an analogous reaction pathways consisting of cyclization and elimination of sulfinate.[19] Proceeding through a sulfonamide intermediate provides two advantages: firstly, the need for a subsequent oxidation step is eliminated; and, secondly, the sulfonamide enables the preparation of β-keto-N-acylsulfonamide **11** from readily available starting materials via either alkylation using an α-bromoketone or acylation using an acid chloride. Therefore, the incorporation of either the C3 or C6 substituent should be possible in two steps from available starting materials in a modular manner. At the outset, our primary concern associated with this approach was competitive initial reaction of hydrazine with the acylsulfonamide, which is a known process that may lead to nonproductive cleavage of the acylsulfonamide.[20]

Scheme 1. Preparation of β-keto-N-acylsulfonamide **16**.

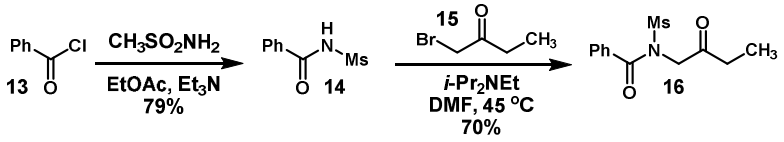
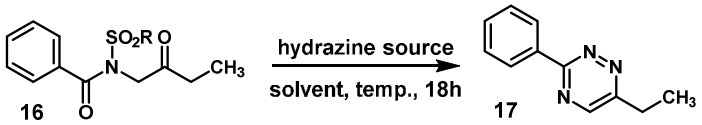


Table 1. Optimization of the synthesis of 1,2,4-triazine **17** from **16**.



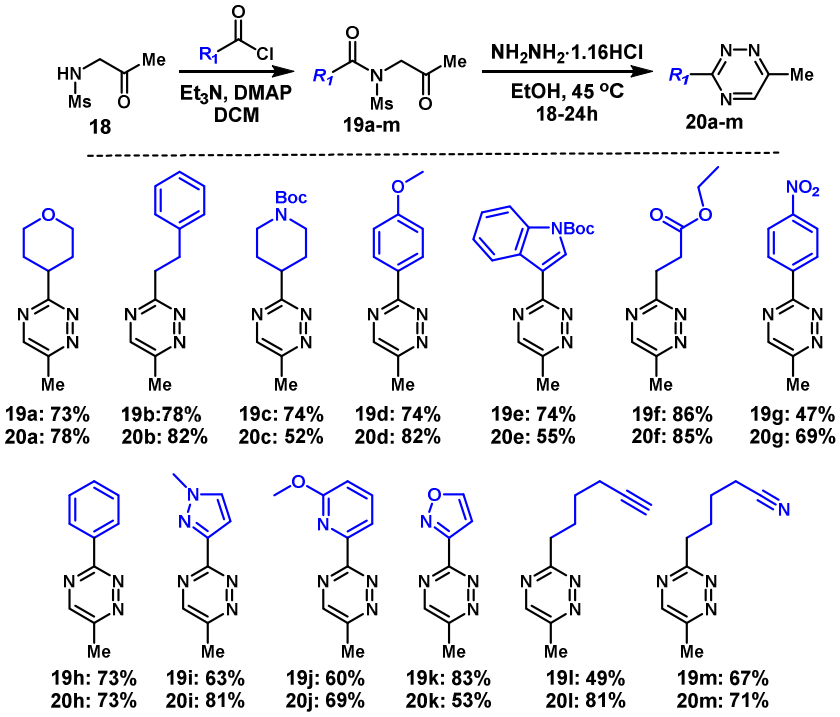
Entry	R	Hydrazine Source (1.5 equiv.)	Solvent	Temp. (°C)	%yield[a]
1	CH_3	$NH_2NH_2 \cdot H_2O$	EtOH	45	0
2	CH_3	$NH_2NH_2 \cdot HCl$	EtOH	45	67
3	4-CH_3Ph	$NH_2NH_2 \cdot HCl$	EtOH	45	60[52]
4	**CH_3**	**$NH_2NH_2 \cdot 1.16\ HCl$**	EtOH	**45**	**74[70]**
5	CH_3	$NH_2NH_2 \cdot 1.16\ HCl$	EtOH	55	65
6	CH_3	$NH_2NH_2 \cdot 1.16\ TsOH$	EtOH	45	60
7	4-CH_3Ph	$NH_2NH_2 \cdot 1.16\ HCl$	EtOH	45	65
8	CH_3	$NH_2NH_2 \cdot 1.33\ HCl$	EtOH	45	62
9	CH_3	$NH_2NH_2 \cdot 1.5\ HCl$	EtOH	45	57
10	CH_3	$NH_2NH_2 \cdot 2.0\ HCl$	EtOH	45	29
11	CH_3	$NH_2NH_2 \cdot 1.16\ HCl$	EtOH/(5% H_2O)	45	73
12	CH_3	$NH_2NH_2 \cdot 1.16\ HCl$	DMSO	45	0
13	CH_3	$NH_2NH_2 \cdot 1.16\ HCl$	1,4-dioxane	45	0

[a]Determined by analysis of crude ^{1}H NMR spectra using 2,6-dimethoxytoluene as an internal standard. Yield in parentheses refers to isolated yield after column chromatography.

In order to evaluate the feasibility of this approach, N-acylsulfonamide **16** was prepared in two steps from benzoyl chloride and methanesulfonamide (Scheme 1). Initial attempts to alkylate N-acylsulfonamide **14** by first deprotonating with strong bases (e.g. sodium hydride, potassium *t*-butoxide) followed by treatment with various α-bromoketones were not successful. However, this transformation was successfully accomplished in 70% yield in the presence of N,N-diisopropylethylamine in DMF at 45 °C. Treatment of **16** with 1.5 equivalents of hydrazine monohydrate in ethanol at 45 °C afforded a complex mixture of products (Table1, entry 1). Full consumption of the starting material **16** was observed under these conditions, however none of the desired 1,2,4-triazine product was detected; LCMS analysis of the crude reaction mixture showed major byproducts consistent with acyl group cleavage. In contrast, treatment of **16** with 1.5 equivalents of hydrazine monohydrochloride under otherwise identical conditions afforded the desired 1,2,4-triazine as the major product in 67% yield by ^{1}H NMR (entry 2); none of the deacylated material was detected by LCMS analysis of the crude reaction mixture. The yield

of **17** was improved to 74% by using a 1.16 fold excess of HCl relative to hydrazine (entry 4). Notably, attempts to improve the yield by increasing the reaction temperature (entry 5), using the analogous tosyl starting material (entry 7) or using the tosyl hydrazine salt in place of hydrazine hydrochloride (entry 6) were unsuccessful. Further increasing the amount of HCl relative to hydrazine afforded substantially reduced yields (entries 8-10). The use of wet (5% water) ethanol had little impact on the yield of the reaction (entry 11), however using DMSO or 1,4-dioxane[21] as solvent afforded no desired product (entry 12,13).

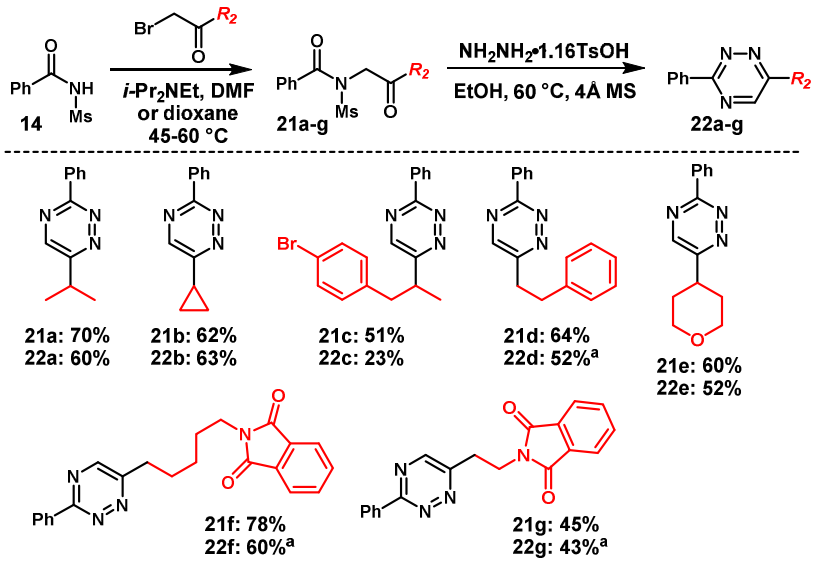
Scheme 2. Scope of 1,2,4-triazine synthesis at the C3 position.



With the optimized conditions identified, the scope of this transformation at the C3 position of the 1,2,4-triazine product was evaluated (Scheme 2). The β-keto-N-acylsulfonamide starting materials (**19a-m**) were prepared through acylation of sulfonamide **18**. A variety of functional groups are tolerated at the C3 position in this two-step sequence. For example, electron neutral (**20h**), rich (**20d**) and deficient (**20g**) aromatic systems all worked well in this transformation. Several hetero-aromatic systems that would be

difficult to prepare using standard transition-metal mediated cross-coupling methodologies were also found to be readily prepared using this approach (**20e**, **20i**, **20j**, **20k**). Additionally, both primary and secondary alkyl substituents were well tolerated, and the mild reactions conditions are compatible with sensitive functionality including esters (**20f**), boc-protected amines (**20c**, **20e**), and alkyl nitriles (**20m**). The scalability of this 1,2,4-triazine synthesis was demonstrated through the preparation of the pyrazole-substituted 1,2,4-triazine **20i** on 2.4 g scale from **19i** with no loss in isolated yield (81%).

Scheme 3. Scope of 1,2,4-triazine synthesis at the C6 position.



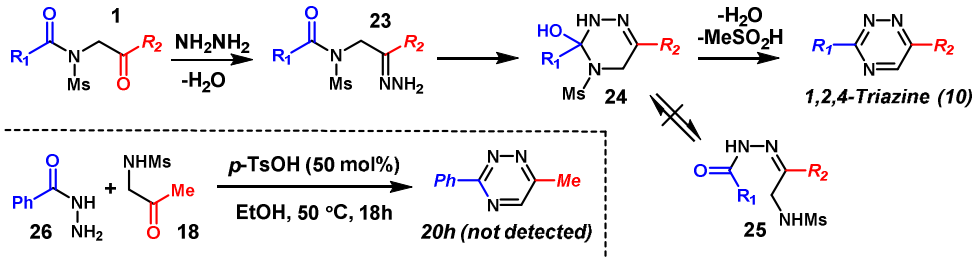
[a]Alternate reaction conditions were used. See experimental section for details.

The scope of this reaction with regards to the C6 position of the 1,2,4-triazine was also evaluated (Scheme 3). In this case the starting materials **21a-g** were prepared in one step through alkylation of N-acylsulfonamide **14** with available α-bromoketones using N,N-diisopropylethylamine in 1,4-dioxane or DMF (see experimental section for details). Unexpectedly, the effectiveness of the optimized conditions disclosed in Table 1 is dependent on the steric environment adjacent to the ketone. For example, applying the optimized conditions from Table 1, entry 4 to the isopropyl substrate **21a** produced only 3% of the corresponding 1,2,4-triazine **22a** by analysis of crude ^{1}H NMR (the remaining material balance constituted starting material). After optimization of the reaction parameters, the isolated yield of the

isopropyl-substituted 1,2,4-triazine **22a** was improved to 60% through the use of four equivalents of the hydrazine tosylate salt,[22] with heating at 60 °C in the presence of powdered 4Å molecular sieves (see supporting information for full optimization details). As shown in Scheme 3, a variety of primary and secondary alkyl substituents are tolerated at the C6 position of the heterocycle. The chemoselectivity of this transformation is demonstrated though the preparation of phthalimides **22f** and **22g**. The only C3 substituent that has been examined in this sequence is phenyl. Unfortunately, aryl substituents are not tolerated at the C6 position of the heterocycle using these conditions, presumably due to the decreased reactivity of the aryl ketone precursor. However, many of the existing methods for preparing C6-substituted 1,2,4-triazines have only been demonstrated to provide products with aryl substituents at this position.[14,16,17] By providing access to primary and secondary alkyl substituents at the C6 positions this methodology is complementary to many of the existing methods for preparing C6-substituted 1,2,4-triazines.

A possible mechanistic pathway leading to the formation of the 1,2,4-triazine product is highlighted in Scheme 4. Because the rate of the reaction is highly sensitive to the steric environment adjacent to the ketone, the mechanism likely involves initial condensation of hydrazine with the ketone as the rate-limiting step to give hydrazone **23**. Intermediate **24**, produced by cyclization of hydrazone **23** onto the adjacent acyl sulfonamide, likely undergoes direct dehydration and elimination of sulfinate to give the 1,2,4-triazine product (**10**). In order to test for the possible intermediacy of **25**, ketone **18** and acyl hydrazine **26** were exposed to *p*-TsOH in ethanol at 50 °C. The corresponding 1,2,4-triazine product was not detected by ^{1}H NMR analysis of the crude reaction mixture. This result suggests that intermediate **25**, if produced during the course of the reaction, is not an intermediate leading to the 1,2,4-triazine product.

Scheme 4. Possible mechanistic pathways.



In summary, a strategy for preparing 3,6-disubstituted-1,2,4-triazines through the cyclodehydration of N-acylsulfonamides of type **11** is reported. Unlike many existing methods for preparing this heterocycle, this approach is suitable for preparing 1,2,4-triazines with a variety of sp^3-linked substituents at both the C3 and C6 positions, which is highlighted by the fact that twenty out of the twenty-one triazine products shown in Schemes 2 and 3 were unknown in the chemical literature prior to this disclosure.

Experimental Section

General. Sulfonamide **18** was purchased from ChemBridge. tert-Butyl 3-(chlorocarbonyl)-1H-indole-1-carboxylate was prepared using a literature procedure.[23] 6-Methoxy-2-pyridinecarbonyl chloride was prepared using a literature procedure.[24] 3-Isoxazolecarbonyl chloride was prepared using a literature procedure.[25] 5-Cyanopentanoyl chloride was prepared using a literature procedure.[26] 6-Heptanoyl chloride was prepared using a literature procedure.[27] 2-(7-Bromo-6-oxoheptyl)-1H-isoindole-1,3(2H)-dione was prepared using a literature procedure.[28] All other chemicals and reagents were purchased from commercial sources and used without further purification. Reactions were monitored by thin layer chromatography (TLC) using pre-coated 250 μm silica gel plates and visualized by fluorescence quenching under UV light or staining with iodine, *p*-anisaldehyde or potassium permanganate. Unless otherwise indicated, yields refer to isolated compounds. ^{1}H NMR spectra were recorded at 25 °C with a

spectrometer equipped with an AutoX ID 600-5 probe at 600 MHz or an AVIII spectrometer at 400 MHz. ^{13}C NMR spectra were recorded at 25 °C with a spectrometer equipped with a 5 mm BBO cryoprobe equipped with a Z-axis gradient at 100 MHz. Chemical shifts are reported in part per million (PPM) using the internal solvent residual of CD_3OD or $CDCl_3$ as an internal standard. Signals are listed as follows: chemical shift in ppm (multiplicity identified as s = singlet, br = broad, d = doublet, t = triplet, q = quartet, p = pentet, sx = sextet, m = multiplet; integration; coupling constants in Hz). The HRMS analysis was conducted on a hybrid quadrupole-orbitrap mass spectrometer in positive electrospray mode. The sample was separated on a UPLC system prior to mass spectrometric analysis. The resulting spectra was automatically lockmass corrected and the target mass ions and the confirming adduct (H^+) were extracted and combined as a chromatogram. The mass accuracy was calculated for all observed isotopes against the theoretical mass ions derived from the chemical formula. Melting points are reported in °C and were uncorrected.

N-(Methylsulfonyl)-N-(2-oxobutyl)benzamide (16). A mixture of N,N-diisopropylethylamine (1.97 mL, 11.3 mmol) and N-acylsulfonamide **14**[29] (1.5 g, 7.5 mmol) in DMF (10 mL) was stirred at rt for 5 min then treated with 1-bromo-2-butanone **15** (1.54 mL, 15.1 mmol) and stirred at 45 ^oC for 18 h. The reaction mixture was concentrated under reduced pressure. Heptane (40 mL) was added to the crude reaction mixture and evaporated under reduced pressure. The residue was dissolved in dichloromethane (150 mL) and washed with 1N HCl (50 ml). The aqueous phase was back-extracted with dichloromethane (2 x 100 mL) and the combined organic layers were dried over sodium sulfate, filtered and evaporated. The residue was purified using column chromatography, eluting with heptane/ethyl acetate (100:0 to 1:1) to give **16** (1.42 g, 70%) as a white solid. mp = 102-104 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41-7.52 (m, 5H), 4.62 (s, 2H), 3.50 (s, 3H), 2.27 (q, 2H, J = 7.3), 0.98 (t, 3H, J = 7.3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.1, 171.4, 133.9, 131.5, 128.7, 127.1, 56.1, 42.3, 32.8, 7.3; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{12}H_{16}NO_4S$ 270.0795; Found 270.0793.

6-Ethyl-3-phenyl-1,2,4-triazine (**17**). A suspension of **16** (300 mg, 1.11 mmol) in ethanol (5.5 mL) was treated with hydrazine monohydrochoride (95.5 mg, 1.39 mmol) and hydrazine dihydrochloride (29.3 mg, 0.28 mmol). The vial was sealed, evacuated and backfilled three times with nitrogen. The suspension was stirred at 45 °C for 39 h. The reaction mixture was concentrated under reduced pressure, and the residue was poured into half-diluted saturated sodium bicarbonate solution (7 mL) and extracted with ethyl acetate (5 x 10 mL). The combined organic layers were dried over sodium sulfate, filtered and evaporated. The crude product was purified using column chromatography (100:0 to 9:1 heptane/ethyl acetate) to give triazine **17** (144 mg, 70%) as a light amber oil. ^{1}H NMR (600 MHz, CD_3OD) δ 8.78 (d, 1H, *J* = 2.9), 8.47 (d, 2H, *J* = 7.0), 7.53-7.60 (m, 3H), 3.07 (qd, 2H, *J* = 7.6, 1.7), 1.44 (t, 3H, *J* = 7.6); ^{13}C NMR (100 MHz, CD_3OD) δ 163.7, 162.5, 151.5, 136.3, 132.7, 130.0, 129.0, 27.6, 13.5; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{11}H_{12}N_3$ 186.1026; Found 186.1024.

N-(Methylsulfonyl)-N-(2-oxopropyl)tetrahydro-2H-pyran-4-carboxamide (**19a**). A solution of sulfonamide **18** (300 mg, 1.98 mmol), DMAP (24.2 mg, 0.19 mmol) and triethylamine (0.554 mL, 3.97 mmol) in dichloromethane (6 mL) was treated with the tetrahydro-2*H*-pyran-4-carbonyl chloride (324 mg, 2.18 mmol) dropwise at rt. The reaction mixture was stirred at rt for 16 h. The reaction mixture was diluted with dichloromethane (30 mL) and washed with 1N HCl (2 x 15 mL) and brine (15 mL). The organic layer was dried over sodium sulfate, filtered and evaporated. The crude product was purified using column chromatography (100:0 to 1:1 petroleum ether/ethyl acetate) to afford **19a** (380 mg, 73%) as a white solid. mp = 103-107 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.66 (s, 2H), 3.99-4.09 (m, 2H), 3.45 (td, 2H, *J* = 11.7, 2.3), 3.37 (s, 3H), 3.12-3.21 (m, 1H), 2.23 (s, 3H), 1.90 (qd, 2H, *J* = 11.7, 4.3), 1.78 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.8, 174.8, 66.8, 54.8, 43.0, 41.2, 29.3, 26.9; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{10}H_{17}NO_5S$ 264.0900; Found 264.0898.

N-(Methylsulfonyl)-N-(2-oxopropyl)-3-phenylpropanamide (**19b**). A solution of sulfonamide **18** (300 mg, 1.98 mmol), DMAP (24.2 mg, 0.19 mmol) and triethylamine (0.533 mL, 3.97 mmol) in dichloromethane (6 mL) was treated with benzenepropanoyl chloride (368 mg, 2.18 mmol) dropwise at 0

°C. The reaction mixture was stirred at rt for 16h. The reaction mixture was diluted with dichloromethane (30 mL) and washed with 1N HCl (2 x 15 mL) followed by brine (15 mL). The combined organic layers were dried over sodium sulfate, filtered and evaporated. The crude product was purified using column chromatography (100:0 to 1:1 petroleum ether/ethyl acetate) to afford **19b** (441 mg, 78%) as a colorless gum. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (t, 2H, J = 7.5), 7.19-7.25 (m, 3H), 4.64 (s, 2H), 3.33 (s, 3H), 2.98-3.04 (m, 2H), 2.92-2.98 (m, 2H), 2.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.8, 172.1, 140.1, 128.6, 128.4, 126.5, 54.8, 42.5, 37.6, 30.7, 26.9; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{13}H_{18}NO_4S$ 284.0951; Found 284.0949.

tert-Butyl 4-[(methylsulfonyl)(2-oxopropyl)carbamoyl]piperidine-1-carboxylate (**19c**). A solution of sulfonamide **18** (250 mg, 1.65 mmol), DMAP (20.2 mg, 0.16 mmol) and triethylamine (0.46 mL, 3.31 mmol) in dichloromethane (5 mL) was cooled to 0 °C and treated with a solution of tert-butyl-4-(chlorocarbonyl)piperidine-1-carboxylate (492 mg, 1.98 mmol) in dichloromethane (1 mL) dropwise at 0 °C. The reaction mixture was stirred at rt for 16 h. The reaction mixture was diluted with 1N HCl (30 mL) and extracted with dichloromethane (30 mL). The organic layer was washed with brine (15 mL), dried over sodium sulfate, filtered and evaporated. The crude product was purified using column chromatography (petroleum ether/ethyl acetate, 1:1) to give **19c** (360 mg, 74%) as a yellow gum. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.66 (s, 2H), 4.16 (br. s, 2H), 3.36 (s, 3H), 3.02-3.10 (br. m, 1H), 2.71-2.85 (br. m, 2H), 2.22 (s, 3H), 1.85 (br. d, 2H, J = 12.4), 1.71 (qd, 2H, J = 12.4, 3.9), 1.47 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.8, 175.0, 154.6, 79.8, 54.8, 43.1, 42.8, 42.1, 28.7, 28.4, 27.0; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{15}H_{26}N_2O_6S$ 363.1584; Found 363.1577.

4-Methoxy-N-(methylsulfonyl)-N-(2-oxopropyl)benzamide (**19d**). A solution of sulfonamide **18** (250 mg, 1.65 mmol), DMAP (20.2 mg, 0.16 mmol) and triethylamine (0.461 mL, 3.31 mmol) in dichloromethane (5 mL) was treated with a solution of 4-methoxybenzoyl chloride (492 mg, 1.98 mmol) in dichloromethane (1 mL) dropwise at 0 °C. The reaction mixture was stirred at rt for 16h. The reaction mixture was diluted with dichloromethane (30 mL) and washed with 1N HCl (2 x 15 mL) and brine (15

mL). The combined organic layers were dried over sodium sulfate, filtered and evaporated. The crude product was purified using column chromatography (100:0 to 1:1 petroleum ether/ethyl acetate) to afford **19d** (350 mg, 74%) as a yellow gum. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, 2H, *J* = 8.6), 6.93 (d, 2H, *J* = 8.6), 4.68 (s, 2H), 3.86 (s, 3H), 3.51 (s, 3H), 2.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.0, 171.1, 162.3, 129.7, 125.6, 114.0, 57.2, 55.4, 42.6, 26.7; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{12}H_{16}NO_5S$ 286.0744; Found 286.0741.

tert-Butyl 3-[(methylsulfonyl)(2-oxopropyl)carbamoyl]-1H-indole-1-carboxylate (**19e**). A solution of sulfonamide **18** (150 mg, 1.00 mmol), DMAP (12.1 mg, 0.09 mmol) and triethylamine (0.29 mL, 1.98 mmol) in dichloromethane (5 mL) was cooled to 0 °C and treated with a solution of tert-butyl 3-(chlorocarbonyl)-1H-indole-1-carboxylate (280 mg, 1.00 mmol) in dichloromethane (5 mL) dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 1h. The reaction mixture was diluted with water (2 mL) and 2N HCl (1 mL) and stirred for 5 min. The organic layer was separated and the aqueous layer was back-extracted with dichloromethane (3 x 20 mL). The combined organic layers were washed with brine (5 mL), dried over sodium sulfate, filtered and evaporated. The crude product was purified using column chromatography (DCM) to give **19e** (288 mg, 74%) as a white solid. mp = 132-136 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, 1H, *J* = 7.4), 8.05 (s, 1H), 7.77 (d, 1H, *J* = 7.4), 7.42 (t, 1H, *J* = 7.4), 7.36 (t, 1H, *J* = 7.4), 4.83 (s, 2H), 3.56 (s, 3H), 2.12 (s, 3H), 1.67 (s, 9H); ^{13}C NMR (100 MHz, CD_3OD) δ 202.2, 165.9, 148.7, 134.9, 129.7, 127.1, 125.8, 124.3, 120.5, 115.5, 113.6, 85.5, 56.7, 42.7, 28.1, 26.9; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{18}H_{22}N_2O_6S$ 395.1271; Found 395.1268.

Ethyl 4-[(methylsulfonyl)(2-oxopropyl)amino]-4-oxobutanoate (**19f**). A solution of sulfonamide **18** (200 mg, 1.32 mmol), DMAP (16.2 mg, 0.13 mmol) and triethylamine (0.38 mL, 2.65 mmol) in dichloromethane (10 mL) was treated with a solution of ethyl succinyl chloride (261 mg, 1.59 mmol) in dichloromethane (2 mL) dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 2h. The reaction mixture was diluted with water (2 mL) and 2N HCl (1 mL) and stirred for 5 min. The organic layer was separated and the aqueous layer was back-extracted with dichloromethane (3 x 15 mL). The combined

organic layers were washed with brine (5 mL), dried over sodium sulfate, filtered and evaporated. The crude product was purified using column chromatography (100:0 to 1:1 petroleum ether/ethyl acetate) to afford **19f** (317 mg, 86%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.7 (s, 2H), 4.15 (q, 2H, *J* = 7.0), 3.44 (s, 3H), 2.98 (t, 2H, *J* = 6.2), 2.70 (t, 2H, *J* = 6.2), 2.22 (s, 3H), 1.26 (t, 3H, *J* = 7.0); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.4, 172.2, 171.8, 60.9, 54.8, 42.5, 31.0, 28.9, 26.8, 14.1; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{10}H_{18}NO_6S$ 280.0849; Found 280.0845.

N-(Methylsulfonyl)-4-nitro-N-(2-oxopropyl)benzamide (**19g**). A solution of sulfonamide **18** (400 mg, 2.64 mmol), DMAP (32.3 mg, 0.26 mmol) and triethylamine (0.46 mL, 3.30 mmol) in dichloromethane (15 mL) was cooled to 0 °C and treated with 4-nitrobenzoyl chloride (589 mg, 3.17 mmol) dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 1.5h. The reaction mixture was diluted with water (2 mL) and 2N HCl (1 mL) and stirred for 5 min. The organic layer was separated and the aqueous layer was back-extracted with dichloromethane (3 x 15 mL). The combined organic layers were washed with brine (5 mL), dried over sodium sulfate, filtered and evaporated. The crude product was purified using column chromatography (100:0 to 1:1 petroleum ether/ethyl acetate). The crude product was suspended in petroleum ether/ethyl acetate (1:1, 15 mL), stirred for 15 min, and the resulting solids were collected by filtration and dried under reduced pressure to give **19g** (370 mg, 47%) as a white solid. mp = 185-187 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, 2H, *J* = 8.2), 7.68 (d, 2H, *J* = 8.2), 4.65 (s, 2H), 3.43 (s, 3H), 2.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.5, 169.3, 149.2, 139.8, 128.2, 123.9, 56.4, 42.5, 26.8; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{11}H_{13}N_2O_6S$ 301.0489; Found 301.0489.

N-(Methylsulfonyl)-N-(2-oxopropyl)benzamide (**19h**). A solution of sulfonamide **18** (300 mg, 1.98 mmol), DMAP (24.2 mg, 0.19 mmol) and triethylamine (0.533 mL, 3.97 mmol) in dichloromethane (6 mL) was treated with benzoyl chloride (335 mg, 2.38 mmol) dropwise at rt. The reaction mixture was stirred at rt for 16 h. The reaction mixture was diluted with dichloromethane (30 mL) and washed with 1N HCl (2 x 15 mL). The organic layer was dried over sodium sulfate, filtered and evaporated. The crude product was purified using column chromatography (100:0 to 1:1 petroleum ether/ethyl acetate) to

afford **19h** (371 mg, 73%) as a white solid. mp = 110-113 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.56 (m, 5H), 4.64 (s, 2H), 3.51 (s, 3H), 2.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.9, 171.4, 133.8, 131.5, 128.7, 127.0, 57.0, 42.4, 26.7; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{11}H_{14}NO_4S$ 256.0638; Found 256.0636.

1-Methyl-N-(methylsulfonyl)-N-(2-oxopropyl)-1H-pyrazole-3-carboxamide (**19i**). A solution of sulfonamide **18** (2.89 g, 19.1 mmol), DMAP (234 mg, 1.91 mmol) and 1-methyl-1*H*-pyrazole-3-carbonyl chloride (3.90 g, 26.9 mmol) in dichloromethane (47.8 mL) was treated with triethylamine (7.97 mL, 57.3 mmol) dropwise and stirred at rt for 18h. The reaction mixture was diluted with water (5 mL) and saturated ammonium chloride solution (5 mL) and extracted with dichloromethane (3 x 120 mL). The combined organic layers were dried over sodium sulfate, filtered and evaporated. The crude product was purified using column chromatography (100:0 to 90:10 dichloromethane/methanol) to afford **19i** (3.15 g, 63%) as a white solid. mp = 115-117 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, 1H, J = 2.3), 6.89 (d, 1H, J = 2.3), 5.29 (s, 2H), 3.89 (s, 3H), 3.54 (s, 3H), 2.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.6, 162.7, 145.4, 131.2, 111.4, 56.0, 41.8, 39.6, 26.3; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_9H_{14}N_3O_4S$ 260.0700; Found 260.0695.

6-Methoxy-N-(methylsulfonyl)-N-(2-oxopropyl)pyridine-2-carboxamide (**19j**). A solution of sulfonamide **18** (200 mg, 1.32 mmol), DMAP (16.2 mg, 0.13 mmol) and 6-methoxy-2-pyridinecarbonyl chloride (617 mg, 4.27 mmol) in dichloromethane (7.5 mL) was treated with triethylamine (0.552 mL, 3.97 mmol) dropwise at rt. The reaction mixture was stirred at rt for 16h. The reaction mixture was diluted with water (5 mL) and saturated ammonium chloride (5 mL) and the product was extracted with ethyl acetate (4 x 15 mL). The combined organic layers were dried over sodium sulfate, filtered and evaporated. The crude product was purified using column chromatography (100:0 to 1:1 petroleum ether/ethyl acetate) to afford **19j** (225 mg, 60%) as a white solid. mp = 109-111 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (t, 1H, J = 7.4), 7.46 (d, 1H, J = 7.4), 6.89 (d, 1H, J = 7.4), 5.13 (s, 2H), 3.91 (s, 3H), 3.58

(s, 3H), 2.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.0, 167.8, 162.5, 148.8, 139.8, 118.6, 114.4, 56.2, 53.9, 42.4, 26.7; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{11}H_{14}N_2O_5S$ 287.0696; Found 287.0690.

N-(Methylsulfonyl)-N-(2-oxopropyl)-1,2-oxazole-3-carboxamide (**19k**). A solution of sulfonamide **18** (170 mg, 1.12 mmol), DMAP (13.7 mg, 0.11 mmol) and 3-isoxazolecarbonyl chloride (222 mg, 1.69 mmol) in dichloromethane (7.5 mL) was treated with triethylamine (0.47 mL, 3.37 mmol) dropwise and stirred at rt for 18h. The reaction mixture was diluted with water (5 mL) and saturated ammonium chloride solution (5 mL) and extracted with ethyl acetate (4 x 15 mL). The combined organic layers were dried over sodium sulfate, filtered and evaporated. The crude product was purified using column chromatography (100:0 to 1:1 heptane/ethyl acetate) to afford **19k** (231 mg, 83%) as a white solid. mp = dec 150 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (s, 1H), 6.86 (s, 1H), 5.20 (s, 2H), 3.57 (s, 3H), 2.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.7, 160.7, 159.2, 157.6, 106.7, 55.7, 42.1, 26.5; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_8H_{11}N_2O_5S$ 247.0383; Found 247.0383.

N-(Methylsulfonyl)-N-(2-oxopropyl)hept-6-ynamide (**19l**). A solution of sulfonamide **18** (380 mg, 2.51 mmol), DMAP (30.7 mg, 0.25 mmol) and triethylamine (0.73 mL, 5.00 mmol) in dichloromethane (10 mL) was cooled to 0 °C and treated with a solution of 6-heptanoyl chloride (363 mg, 2.51 mmol) in dichloromethane (4 mL) dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 1.5h. The reaction mixture was diluted with water (2 mL) and 2N HCl (1 mL) and stirred for 5 min. The organic layer was separated and the aqueous layer was back-extracted with dichloromethane (3 x 10 mL). The combined organic layers were washed with brine (5 mL), dried over sodium sulfate, filtered and evaporated. The crude product was purified using column chromatography (100:0 to 1:1 petroleum ether/ethyl acetate) to give **19l** (320 mg, 49%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.70 (s, 2H), 3.40 (s, 3H), 2.68 (t, 2H, J = 7.0), 2.19-2.26 (m, 5H), 1.96 (t, 1H, J = 2.7), 1.77-1.86 (m, 2H), 1.55-1.63 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.9, 172.5, 83.8, 68.8, 54.8, 42.5, 35.1, 27.5, 26.9, 23.6, 18.2; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{11}H_{18}NO_4S$ 260.0951; Found 260.0948.

5-Cyano-N-(methylsulfonyl)-N-(2-oxopropyl)pentanamide (**19m**). A solution of sulfonamide **18** (431 mg, 2.85 mmol), DMAP (34.8 mg, 0.28 mmol) and triethylamine (0.79 mL, 5.70 mmol) in dichloromethane (10 mL) was cooled to 0 °C and treated with a solution of 5-cyanopentanoyl chloride (415 mg, 2.85 mmol) in dichloromethane (5 mL) dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 1.5h. The reaction mixture was diluted with water (10 mL) and stirred for 5 min. The organic layer was separated and the aqueous layer was back-extracted with dichloromethane (3 x 10 mL). The combined organic layers were washed with brine (5 mL), dried over sodium sulfate, filtered and evaporated. The crude product was purified using column chromatography (100:0 to 1:1 petroleum ether/ethyl acetate) to give **19m** (500 mg, 67%) as an off-white solid. mp = 90-96 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.66 (s, 2H), 3.34 (s, 3H), 2.72 (t, 2H, *J* = 7.0), 2.37 (t, 2H, *J* = 7.0), 2.23 (s, 3H), 1.80-1.88 (m, 2H), 1.68-1.76 (m, 2H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.8, 172.0, 119.3, 54.8, 42.5, 34.6, 26.9, 24.5, 23.6, 17.0; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{10}H_{17}N_2O_4S$ 261.0904; Found 261.0901.

General procedure for the cyclodehydration of N-acylsulfonamides (**19a-19m**) to give 1,2,4-triazines (**20a-20m**) from Scheme 2.

In a vial a mixture of the β-keto-N-acylsulfonamide **19** (1 equiv.), hydrazine monohydrochloride (1.25 equiv.) and hydrazine dihydrochloride (0.25 equiv.) in ethanol (0.2 M) is sealed, evacuated and back-filled with nitrogen three times. The reaction mixture is stirred for 18 h at 45 °C. The reaction mixture is then poured into saturated sodium bicarbonate (5 mL) and extracted with ethyl acetate (5 x 15 mL). The combined organic layers are dried over sodium sulfate, filtered and evaporated. The crude product is purified using column chromatography (100:0 to 4:1 heptane/ethyl acetate) to give the triazine product.

6-Methyl-3-(tetrahydro-2H-pyran-4-yl)-1,2,4-triazine (**20a**). General procedure performed on 0.532 mmol scale to give **20a** (74 mg, 78%) as a light yellow solid. mp = 73-75 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 8.70 (s, 1H), 4.06-4.12 (m, 2H), 3.60-3.68 (m, 2H), 3.29-3.39, (m, 1H), 2.71 (s, 3H), 1.95-2.07

(m, 4H); ^{13}C NMR (100 MHz, CD_3OD) δ 170.6, 158.4, 152.3, 68.7, 43.3, 32.3, 19.2; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_9H_{14}N_3O$ 180.1131; Found 180.1130.

6-Methyl-3-(2-phenylethyl)-1,2,4-triazine (**20b**). General procedure performed on 0.529 mmol scale to give **20b** (87 mg, 82%) as a light yellow solid. mp = 128-130 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 8.65 (s, 1H), 7.13-7.27 (m, 5H), 3.40 (t, 2H, J = 7.4), 3.17 (t, 2H, J = 7.4), 2.66 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 168.4, 158.1, 152.2, 142.1, 129.61, 129.57, 127.3, 39.4, 35.3, 19.2; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{12}H_{14}N_3$ 200.1182; Found 200.1180.

tert-Butyl 4-(6-methyl-1,2,4-triazin-3-yl)piperidine-1-carboxylate (**20c**). General procedure performed on 0.497 mmol scale to give **20c** (72 mg, 52%) as a light red solid. mp = 57-60 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 8.69 (s, 1H), 4.21 (br. d, 2H, J = 13.2), 3.27 (tt, 1H, J = 11.7, 3.9), 2.93-3.07 (br. m, 2H), 2.68 (s, 3H), 2.04 (br d, 2H, J = 10.9), 1.83 (qd, 2H, J = 12.1, 4.3), 1.50 (s, 9H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 158.4, 156.6, 152.3, 81.2, 45.1, 44.3, 31.6, 28.9, 19.2; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{14}H_{23}N_4O_2$ 279.1816; Found 279.1813.

3-(4-Methoxyphenyl)-6-methyl-1,2,4-triazine (**20d**). General procedure performed on 0.526 mmol scale to give **20d** (87 mg, 82%) as a light yellow solid. mp = 98-100 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 8.68 (s, 1H), 8.39 (d, 2H, J = 9.0), 7.07 (d, 2H, J = 9.0), 3.90 (s, 3H), 2.69 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 164.2, 163.3, 157.4, 152.0, 130.7, 128.5, 115.4, 56.1, 19.2; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{11}H_{12}N_3O$ 202.0975; Found 202.0973.

tert-Butyl 3-(6-methyl-1,2,4-triazin-3-yl)-1H-indole-1-carboxylate (**20e**). General procedure performed on 0.355 mmol scale to give **20e** (61 mg, 55%) as a yellow solid. mp = 132-133 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66-8.69 (m, 1H), 8.62 (s, 1H), 8.51 (s, 1H), 8.26-8.28 (m, 1H), 7.37-7.45 (m, 2H), 2.75 (s, 3H), 1.72 (s, 9H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.9, 155.1, 149.2, 148.9, 136.3, 129.3, 127.6, 125.1, 123.7, 122.9, 117.0, 115.1, 84.6, 28.2, 19.5; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{17}H_{19}N_4O_2$ 311.1503; Found 311.1498.

Ethyl 3-(6-methyl-1,2,4-triazin-3-yl)propanoate (**20f**). General procedure performed on 0.537 mmol scale to give **20f** (89 mg, 85%) as a light yellow oil. ^{1}H NMR (400 MHz, CD_3OD) δ 8.70 (s, 1H), 4.13 (q, 2H, J = 7.0), 3.39 (t, 2H, J = 7.0), 2.95 (t, 2H, J = 7.0), 2.69 (s, 3H), 1.24 (t, 3H, J = 7.0); ^{13}C NMR (100 MHz, CD_3OD) δ 174.3, 167.7, 158.2, 152.0, 61.8, 32.4, 32.3, 19.2, 14.6; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_9H_{14}N_3O_2$ 196.1081; Found 196.1080.

6-Methyl-3-(4-nitrophenyl)-1,2,4-triazine (**20g**). General procedure performed on 0.450 mmol scale to give **20g** (67 mg, 69%) as an off-white solid. mp = dec. 201 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (d, 2H, J = 8.9), 8.62 (s, 1H), 8.39 (d, 2H, J = 8.9), 2.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.5, 157.4, 149.8, 149.4, 140.6, 128.9, 124.0, 19.6; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{10}H_9N_4O_2$ 217.0720; Found 217.0718.

6-Methyl-3-phenyl-1,2,4-triazine[15,30] (**20h**). General procedure performed on 0.548 mmol scale to give **20h** (69 mg, 73%) as a light yellow solid. mp = 68-70 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 8.73 (s, 1H), 8.41-8.47 (m, 2H), 7.51-7.57 (m, 3H), 2.72 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 163.5, 158.3, 152.1, 136.2, 132.7, 130.0, 129.0, 19.3; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{10}H_{10}N_3$ 172.0869; Found 172.0867.

6-Methyl-3-(1-methyl-1H-pyrazol-3-yl)-1,2,4-triazine (**20i**). General procedure performed on 9.52 mmol scale to give **20i** (1.33 g, 82%) as a yellow solid. General produced performed on 0.791 mmol scale to give **20i** (112 mg, 81%) as a yellow solid. mp 143-148 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 8.71 (s, 1H), 7.74 (d, 1H, J = 2.3), 7.08 (d, 1H, J = 2.3), 4.03 (s, 3H), 2.72 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 159.7, 158.7, 152.1, 149.0, 134.1, 108.0, 39.7, 19.4; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_8H_{10}N_5$ 176.0931; Found 176.0931.

3-(6-Methoxypyridin-2-yl)-6-methyl-1,2,4-triazine (**20j**). General procedure performed on 0.310 mmol scale to give **20j** (44 mg, 69%) as a light yellow solid. mp 74-78 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 8.81 (s, 1H), 8.10 (d, 1H, J = 7.4), 7.87 (t, 1H, J = 7.4), 6.98 (d, 1H, J = 7.4), 4.08 (s, 3H), 2.78 (s, 3H); ^{13}C

NMR (100 MHz, CD_3OD) δ 166.1, 162.6, 159.5, 152.1, 151.5, 141.0, 118.2, 114.6, 54.5, 19.5; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{10}H_{11}N_4O$ 203.0927; Found 203.0925.

6-Methyl-3-(1,2-oxazol-3-yl)-1,2,4-triazine (**20k**). General procedure performed on 0.487 mmol scale to give **20k** (42 mg, 53%) as an off-white solid. mp = dec. 163 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.95 (s, 1H), 8.85 (s, 1H), 7.25 (s, 1H), 2.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 159.6, 158.6, 156.4, 149.8, 104.4, 19.7; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_7H_7N_4O$ 163.0614; Found 163.0613.

3-(Hex-5-yn-1-yl)-6-methyl-1,2,4-triazine (**20l**). General procedure performed on 1.06 mmol scale to give **20l** (149 mg, 80%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (s, 1H), 3.11 (t, 2H, J = 7.6), 2.69 (s, 3H), 2.22-2.28 (m, 2H), 1.92-1.04 (m, 3H), 1.58-1.68 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 156.0, 149.2, 84.0, 68.5, 36.2, 27.9, 27.3, 19.2, 18.2; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{10}H_{14}N_3$ 176.1182; Found 176.1181.

5-(6-Methyl-1,2,4-triazin-3-yl)pentanenitrile (**20m**). General procedure performed on 1.27 mmol scale to give **20m** (160 mg, 71%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (s, 1H), 3.15 (t, 2H, J = 7.4), 2.70 (s, 3H), 2.42 (t, 2H, J = 7.4), 2.00-2.08 (m, 2H), 1.73-1.82 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 156.3, 149.3, 119.4, 35.6, 26.9, 24.7, 19.2, 17.0; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_9H_{13}N_4$ 177.1135; Found 177.1135.

N-(3-Methyl-2-oxobutyl)-N-(methylsulfonyl)benzamide (**21a**). A mixture of N,N-diisopropylethylamine (0.59 mL, 3.39 mmol) and N-acylsulfonamide **14** (450 mg, 2.26 mmol) in DMF (3.01 mL) was stirred at rt for 5 min, then treated with 1-bromo-3-methylbutan-2-one (615 mg, 3.61 mmol) and stirred at 45 °C for 24 h. Additional 1-bromo-3-methylbutan-2-one (200 mg, 1.2 mmol) was added and the reaction was stirred for an additional 18 h at 45 °C. The reaction mixture was poured into 0.5 N HCl (20 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried over sodium sulfate, filtered and evaporated. The crude product was purified using column chromatography (100:0 to 1:1 heptane/ethyl acetate) to give **21a** (450 mg, 70%) as a white solid. mp = 119-121 °C; ^{1}H NMR (400 MHz,

$CDCl_3$) δ 7.48-7.53 (m, 1H), 7.40-7.47 (m, 4H), 4.70 (s, 2H), 3.53 (s, 3H), 2.46 (sx, 1H, *J* = 7.0), 0.93 (d, 6H, *J* = 7.0); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.2, 171.5, 134.0, 131.5, 128.7, 127.1, 55.2, 42.3, 38.0, 17.7; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{13}H_{18}NO_4S$ 284.0951; Found 284.0948.

N-(2-Cyclopropyl-2-oxoethyl)-N-(methylsulfonyl)benzamide (**21b**). A mixture of N,N-diisopropylethylamine (0.65 mL, 3.76 mmol), and N-acylsulfonamide **14** (500 mg, 2.51 mmol) in DMF (3.3 mL) was stirred at rt for 5 min then treated with 2-bromo-1-cyclopropylethan-1-one (614 mg, 3.76 mmol) and stirred at 45 ^oC for 18 h. The reaction mixture was concentrated under reduced pressure. Heptane (40 mL) was added to the crude reaction mixture and evaporated under reduced pressure. The residue was dissolved in ethyl acetate (40 mL) and washed with 1N HCl (20 ml). The aqueous phase was back-extracted with dichloromethane (2 x 20 mL) and the combined organic layers were dried over sodium sulfate, filtered and evaporated. The residue was purified using column chromatography, eluting with heptane/ethyl acetate (100:0 to 1:1) to give **21b** (440 mg, 62%) as a white solid. mp = 149-152 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.49-7.54 (m, 1H), 7.41-7.48 (m, 4H), 4.81 (s, 2H), 3.50 (s, 3H), 1.70-1.77 (m, 1H), 0.96-1.03 (m, 2H), 0.88-0.94 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.3, 171.5, 134.0, 131.4, 128.7, 127.1, 57.0, 42.2, 18.1, 11.5; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{13}H_{16}NO_4S$ 282.0795; Found 282.0790.

N-[4-(4-Bromophenyl)-3-methyl-2-oxobutyl]-N-(methylsulfonyl)benzamide (**21c**). A solution of N-acylsulfonamide **14** (200 mg, 1.00 mmol) in 1,4-dioxane (3.01 mL) was treated with N,N-diisopropylethylamine (0.262 mL, 1.51 mmol) and stirred at rt for 5 min. 1-Bromo-4-(4-bromophenyl)-3-methylbutan-2-one (482 mg, 1.51 mmol) was added to the reaction mixture and the reaction was stirred at 60 °C for 18h. The cooled reaction mixture was poured into 1N HCl (5 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic layers were dried over sodium sulfate, filtered and evaporated. The crude product was purified using column chromatography (100:0 to 1:1 heptane/ethyl acetate) to give **21c** (225 mg, 51%) as an off-white solid. mp = 117-120 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.48-7.52 (m, 1H), 7.37-7.40 (m, 4H), 7.33 (d, 2H, *J* = 8.2), 6.88 (d, 2H, *J* = 8.2), 4.71 (d, 1H, *J* = 19.3),

4.44 (d, 1H, *J* = 19.3), 3.48 (s, 3H), 2.78 (dd, 1H, *J* = 13.5, 7.0), 2.67 (sx, 1H, *J* = 7.0), 2.46 (dd, 1H, *J* = 13.5, 7.0) 0.94 (d, 3H, *J* = 7.0); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.3, 171.4, 137.6, 133.7, 131.6, 131.5, 130.4, 128.7, 127.0, 120.4, 56.1, 45.1, 42.3, 37.6, 16.2; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{19}H_{21}BrNO_4S$ 438.0369; Found 438.0370.

N-(Methylsulfonyl)-N-(2-oxo-4-phenylbutyl)benzamide (**21d**). A solution of N-acyl sulfonamide **14** (450 mg, 2.26 mmol) in DMF (3.0 mL) was treated with N,N-diisopropylethylamine (0.59 mL, 3.39 mmol) and stirred at rt for 5 min. The reaction mixture was treated with 1-bromo-4-phenylbutan-2-one (821 mg, 3.61 mmol) and stirred at 45 °C for 18 h. The reaction mixture was evaporated under reduced pressure and suspended in 0.5N HCl (5 mL). The product was extracted with ethyl acetate (5 x 7 mL) and the combined organic layers were dried over sodium sulfate, filtered and evaporated. The crude product was purified on the isco combiflash (100:0 to 4:1 heptane/ethyl acetate) to give **21d** (461 mg, 64%) as a white solid. mp = 118-122 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74-7.53 (m, 1H), 7.37-7.45 (m, 4H), 7.17-7.27 (m, 3H), 7.08 (d, 2H, *J* = 7.1), 4.65 (s, 2H), 3.49 (s, 3H), 2.82 (t, 2H, *J* = 7.4), 2.60 (t, 2H, *J* = 7.4); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.6, 171.4, 139.9, 133.8, 131.5, 128.7, 128.6, 128.1, 127.0, 126.4, 56.5, 42.3, 41.0, 29.1; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{18}H_{20}NO_4S$ 346.1108; Found 346.1102.

N-(Methylsulfonyl)-N-[2-oxo-2-(tetrahydro-2H-pyran-4-yl)ethyl]benzamide (**21e**). A solution of N-acylsulfonamide **14** (300 mg, 1.51 mmol) in 1,4-dioxane (3.01 mL) was treated with N,N-diisopropylethylamine (0.446 mL, 2.56 mmol) and stirred at rt for 5 min. 2-Bromo-1-(tetrahydro-2H-pyran-4-yl)ethanone (530 mg, 2.56 mmol) was added and the reaction mixture was stirred at 60 °C for 18h. The cooled reaction mixture was poured into 1N HCl (8 mL) and extracted with dichloromethane (3 x 15 mL). The combined organic layers were washed with saturated sodium bicarbonate (8 mL), dried over sodium sulfate, filtered and evaporated. The crude product was purified using column chromatography (100:0 to 1:1 heptane/ethyl acetate) to give **21e** (295 mg, 60%) as a white solid. mp = 149-150 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49-7.54 (m, 1H), 7.41-7.48 (m, 4H), 4.71 (s, 2H), 3.90 (dt, 2H, *J* = 11.7, 3.5), 3.51 (s, 3H), 3.30-3.38 (m, 2H), 2.43-2.51 (m, 1H), 1.49-1.55 (m, 4H); ^{13}C NMR (100

MHz, $CDCl_3$) δ 205.6, 171.3, 133.9, 131.5, 128.7, 127.1, 66.7, 55.0, 44.7, 42.3, 27.4; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{15}H_{20}NO_5S$ 326.1057; Found 326.1053.

N-[7-(1,3-Dioxo-1,3-dihydro-2H-isoindol-2-yl)-2-oxoheptyl]-N-(methylsulfonyl)benzamide (**21f**). A mixture of N-acylsulfonamide **14** (150 mg, 0.753 mmol), 2-(7-bromo-6-oxoheptyl)-1H-isoindole-1,3(2H)-dione (764 mg, 2.26 mmol) and N,N-diisopropylethylamine (0.197 mL, 1.13 mmol) in 1,4-dioxane (2.0 mL) was stirred at 50 °C for 18h. The reaction mixture was diluted with 1N HCl (10 mL) and extracted with ethyl acetate (2 x 10 mL). The combined organic layers were dried over sodium sulfate, filtered and evaporated. The crude product was purified using column chromatography (100:0 to 1:1 heptane/ethyl acetate) to give **21f** (270 mg, 78%) as an off white solid. mp = 141-143 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82-7.86 (m, 2H), 7.70-7.74 (m, 2H), 7.49-7.53 (m, 1H), 7.41-7.47 (m, 4H), 4.61 (s, 2H), 3.63 (t, 2H, *J* = 7.4), 3.49 (s, 3H), 2.24 (t, 2H, *J* = 7.6), 1.61 (p, 2H, *J* = 7.4), 1.49 (p, 2H, *J* = 7.6), 1.21 (p, 2H, *J* = 7.6); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.3, 171.4, 168.4, 134.1, 133.8, 132.1, 131.5, 128.7, 127.1, 123.2, 56.5, 42.3, 39.2, 37.5, 28.2, 26.0, 22.8; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{23}H_{25}N_2O_6S$ 457.1413; Found 457.1428.

N-[4-(1,3-Dioxo-1,3-dihydro-2H-isoindol-2-yl)-2-oxobutyl]-N-(methylsulfonyl)benzamide (**21g**). A solution of N-acylsulfonamide **14** (300 mg, 1.51 mmol) in 1,4-dioxane (3.01 mL) was treated with N,N-diisopropylethylamine (0.393 mL, 2.26 mmol) and stirred at rt for 5 min. 1-Bromo-4-N-phthalimido-2-butanone (669 mg, 2.26 mmol) was added to the reaction mixture and the reaction was stirred at 50 °C for 18h. The reaction mixture was treated with additional 1-bromo-4-N-phthalimido-2-butanone (200 mg, 0.67 mmol) and stirred at 60 °C for an additional 3h. The cooled reaction mixture was then poured into 1N HCl (7 mL) and extracted with dichloromethane (3 x 15 mL). The combined organic layers were washed with water (8 mL), dried over sodium sulfate, filtered and evaporated. The crude product was purified using column chromatography (100:0 to 1:1 heptane/ethyl acetate) to give **21g** (280 mg, 45%) as a white solid. mp = 189-191 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.82-7.86 (m, 2H), 7.72-7.76 (m, 2H), 7.37-7.51 (m, 5H), 4.65 (s, 2H), 3.91 (t, 2H, *J* = 7.0), 3.49 (s, 3H), 2.73 (t, 2H, *J* = 7.0); ^{13}C NMR (100

MHz, $CDCl_3$) δ 201.8, 171.3, 167.9, 134.1, 133.7, 131.9, 131.6, 128.7, 127.1, 123.4, 56.4, 42.4, 37.6, 32.3; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{20}H_{19}N_2O_6S$ 415.0958; Found 415.0950.

NH_2NH_2·1.16 TsOH. A solution of *p*-toluenesulfonic acid monohydrate (2.22 g, 11.7 mmol) in methanol (20 mL) was treated with hydrazine monohydrate (500 mg, 9.99 mmol) and stirred at rt for 5 min. The reaction mixture was concentrated under reduced pressure and the residue was azeotroped from toluene (3 x 20 mL) and dried under high vacuum to give NH_2NH_2·1.16 TsOH (2.1 g, 90%) as a white solid that was used directly in the reactions described below.

3-Phenyl-6-(propan-2-yl)-1,2,4-triazine (**22a**). A vial containing a mixture of **21a** (178 mg, 0.62 mmol), NH_2NH_2·1.16 TsOH (505 mg, 2.47 mmol) and 4Å molecular sieves (150 mg) in ethanol (3.0 mL) was evacuated and back-filled with nitrogen, then heated at 60 °C for 88h. The cooled reaction mixture was poured into half-diluted saturated sodium bicarbonate (4 mL) and extracted with ethyl acetate (5 x 15 mL). The combined organic layers were dried over sodium sulfate, filtered and evaporated. The crude product was purified using column chromatography (100:0 to 4:1 heptane/ethyl acetate) to give triazine **22a** (74 mg, 59%) as an amber oil. ^{1}H NMR (400 MHz, CD_3OD) δ 8.80 (s, 1H), 8.45-8.49 (m, 2H), 7.53-7.62 (m, 3H), 3.36 (sx, 1H, J = 7.0), 1.47 (d, 6H, J = 7.0); ^{13}C NMR (100 MHz, CD_3OD) δ 165.8, 163.9, 150.7, 136.6, 132.7, 130.1, 129.1, 33.9, 22.2; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{12}H_{14}N_3$ 200.1182; Found 200.1179.

6-Cyclopropyl-3-phenyl-1,2,4-triazine (**22b**). A suspension of NH_2NH_2·1.16 TsOH (331 mg, 1.42 mmol), **21b** (100 mg, 0.35 mmol) and 4Å molecular sieves (100 mg) in ethanol (1.78 mL) was evacuated and back-filled with nitrogen, then stirred at 60 °C for 66h. The reaction mixture was poured into half-diluted saturated sodium bicarbonate (4 mL) and extracted with ethyl acetate (5 x 15 mL). The combined organic layers were dried over sodium sulfate, filtered and evaporated. The crude product was purified using column chromatography (100:0 to 4:1, heptane/EtOAc) to give **22b** (44 mg, 63%) as an oil. ^{1}H NMR (400 MHz, CD_3OD) δ 8.70 (s, 1H), 8.40-8.50 (m, 2H), 7.51-7.58 (m, 3H), 2.30 (p, 1H, J = 6.3), 1.25-1.31 (m,

4H); ^{13}C NMR (100 MHz, CD_3OD) δ 163.3, 162.8, 150.2, 136.4, 132.4, 130.0, 128.9, 14.3, 11.6; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{12}H_{12}N_3$ 198.1025; Found 198.1023.

6-[1-(4-Bromophenyl)propan-2-yl]-3-phenyl-1,2,4-triazine (**22c**). A suspension of $NH_2NH_2 \cdot 1.16$ TsOH (280 mg, 1.37 mmol), **21c** (150 mg, 0.342 mmol) and 4Å molecular sieves (150 mg) in ethanol (1.71 mL) was evacuated and back-filled with nitrogen, then stirred at 60 °C for 115h. The cooled reaction mixture was poured into half-diluted saturated sodium bicarbonate (3 mL) and extracted with ethyl acetate (5 x 20 mL). The combined organic layers were dried over sodium sulfate, filtered and evaporated. The crude product was purified using column chromatography (100:0 to 4:1, heptane/EtOAc) to give **22c** (28 mg, 23%) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49-8.55 (m, 2H), 8.30 (s, 1H), 7.51-7.57 (m, 3H), 7.37 (d, 2H, *J* = 8.2), 6.99 (d, 2H, *J* = 8.2), 3.40 (sx, 1H, *J* = 7.0), 3.19 (dd, 1H, *J* = 13.6, 7.8), 3.03 (dd, 1H, *J* = 13.6, 7.8), 1.48 (d, 3H, *J* = 6.6); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.5, 162.2, 148.4, 138.1, 134.7, 131.6, 131.5, 130.8, 128.9, 128.0, 120.3, 42.0, 39.9, 19.8; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{18}H_{17}BrN_3$ 354.0600; Found 354.0598.

3-Phenyl-6-(2-phenylethyl)-1,2,4-triazine (**22d**). A mixture of hydrazine dihydrochloride (9.12 mg, 0.08 mmol), hydrazine hydrochloride (65.4 mg, 0.955) and **21d** (120 mg, 0.347 mmol) was suspended in 1,2-dichloroethane (0.2 mL) and ethanol (1.6 mL) was evacuated and back-filled with nitrogen, then stirred at 50 °C for 48 h. The cooled reaction mixture was poured into saturated sodium bicarbonate (10 mL) and extracted with ethyl acetate (5 x 10 mL). The combined organic layers were dried over sodium sulfate, filtered and evaporated. The crude product was purified using column chromatography (100:0 to 9:1 heptane/EtOAc) to give **22d** (55 mg, 61%) as a white solid. mp = 85-88 °C. ^{1}H NMR (600 MHz, CD_3OD) δ 8.67 (s, 1H), 8.44-8.47 (m, 2H), 7.53-7.60 (m, 3H), 7.29 (t, 2H, *J* = 7.0), 7.18-7.25 (m, 3H), 3.36 (t, 2H, *J* = 7.0), 3.18 (t, 2H, *J* = 7.0); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.3, 158.8, 149.0, 140.0, 134.8, 131.4, 128.8, 128.7, 128.5, 128.0, 126.5, 35.1, 35.0; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{17}H_{16}N_3$ 262.1339; Found 262.1333.

3-Phenyl-6-(tetrahydro-2H-pyran-4-yl)-1,2,4-triazine (**22e**). A suspension of $NH_2NH_2 \cdot 1.16$ TsOH (440 mg, 2.15 mmol), **21e** (175 mg, 0.618 mmol) and 4Å molecular sieves (150 mg) in ethanol (2.69 mL) was evacuated and back-filled with nitrogen, then stirred at 60 °C for 88h. The cooled reaction mixture was poured into half-diluted saturated sodium bicarbonate (4 mL) and extracted with ethyl acetate (5 x 15 mL). The combined organic layers were dried over sodium sulfate, filtered and evaporated. The crude product was purified using column chromatography (100:0 to 4:1, heptane/EtOAc) to give **22e** (67 mg, 52%) as a white solid. mp = 117-118 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.58 (s, 1H), 8.50-8.56 (m, 2H), 7.52-7.58 (m, 3H), 4.17 (dd, 2H, *J* = 11.7, 3.5), 3.63 (td, 2H, *J* = 11.7, 2.3), 3.26 (tt, 1H, *J* = 11.7, 3.9), 2.08 (qd, 2H, *J* = 11.3, 3.9), 1.96-2.03 (m, 2H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.7, 161.4, 147.9, 134.7, 131.5, 128.9, 128.0, 67.7, 39.5, 31.5; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{14}H_{16}N_3O$ 242.1288; Found 242.1285.

2-[5-(3-Phenyl-1,2,4-triazin-6-yl)pentyl]-1H-isoindole-1,3(2H)-dione (**22f**). A mixture of N-acylsulfonamide **21f** (150 mg, 0.329 mmol), hydrazine hydrochloride (90 mg, 1.31 mmol) and hydrazine dihydrochloride (8.6 mg, 0.08 mmol) in ethanol (1.3 mL) and 1,2-dichloroethane (0.3 mL) was stirred at 50 °C for 66h. The cooled reaction mixture was poured into saturated sodium bicarbonate (5 mL) and extracted with ethyl acetate (5 x 15 mL). The combined organic layers were dried over sodium sulfate, filtered and evaporated. The crude product was purified using column chromatography (100:0 to 9:1 heptane/ethyl acetate) to give triazine **22f** (74 mg, 60%) as a yellow solid. mp = 128-131 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (s, 1H), 8.49-8.53 (m, 2H), 7.81-7.86 (m, 2H), 7.68-7.73 (m, 2H), 7.51-7.57 (m, 3H), 3.72 (t, 2H, *J* = 7.0), 3.02 (t, 2H, *J* = 7.4), 1.92 (p, 2H, *J* = 7.4), 1.78 (p, 2H, *J* = 7.4), 1.50 (p, 2H, *J* = 7.4); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 162.5, 159.4, 149.0, 134.8, 133.9, 132.1, 131.4, 128.8, 128.0, 123.2, 37.6, 33.1, 28.4, 28.2, 26.3; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{22}H_{21}N_4O_2$ 373.1659; Found 373.1652.

2-[2-(3-Phenyl-1,2,4-triazin-6-yl)ethyl]-1H-isoindole-1,3(2H)-dione (**22g**). A mixture of N-acylsulfonamide **21g** (100 mg, 0.241 mmol) and $NH_2NH_2 \cdot 1.16$ TsOH (168 mg, 0.724 mmol) in ethanol

(1.5 mL) and 1,4-dioxane (1.5 mL) was stirred at 60 °C for 18h. The reaction mixture was then treated with additional $NH_2NH_2 \cdot 1.16$ TsOH (60 mg, 0.26 mmol) and stirred at 60 °C for an additional 24h. The cooled reaction mixture was poured into saturated sodium bicarbonate (5 mL) and extracted with ethyl acetate (5 x 15 mL). The combined organic layers were dried over sodium sulfate, filtered and evaporated. The crude product was purified using column chromatography (100:0 to 9:1 heptane/ethyl acetate) to give triazine **22g** (34 mg, 43%) as a yellow solid. mp = 174-175 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (s, 1H), 8.47-8.53 (m, 2H), 7.80-7.85 (m, 2H), 7.69-7.74 (m, 2H), 7.49-7.56 (m, 3H), 4.24 (t, 2H, J = 7.0), 3.41 (t, 2H, J = 7.0); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.0, 162.6, 156.4, 149.1, 134.6, 134.1, 131.9, 131.6, 128.8, 128.1, 123.4, 36.7, 32.2; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{19}H_{15}N_4O_2$ 331.1190; Found 331.1183.

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^{1}H and ^{13}C NMR spectra for all new compounds.

Table S1. Optimization of the synthesis of **22a** from **21a**

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Notes

The authors declare no competing financial interest.

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