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S$_N$Ar Reactions

Synthesis of 3-(Alkylamino)-, 3-(Alkoxy)-, 3-(Aryloxy)-, 3-(Alkylthio)-, and 3-(Arylthio)-1,2,4-triazines by Using a Unified Route with 3-(Methylsulfonyl)-1,2,4-triazine

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Abstract: In our attempts to synthesize 3-(alkylthio)- and 3-(alkoxy)-1,2,4-triazines without substituents at the 5- or 6-position, the synthesis of their anticipated precursor 3-(methylsulfonyl)-1,2,4 triazine was also optimized. The reactivity of 3-(methylsulfonyl)-1,2,4-triazine towards alkyl and aryl thiols, primary and secondary alkylamines, phenols, and alcohols was explored, and the reactions were optimized to maximize the isolation of the corresponding 3-substituted 1,2,4-triazine. Good yields were obtained for the products of the reactions with all of the aforementioned nucleophiles, with the exception of alcohols, by using alkali metal carbonates. Higher yields of 3-(alkoxy)-1,2,4-triazines were obtained by using the appropriate magnesium alkoxide as the nucleophile.

Introduction

3-Substituted 1,2,4-triazines **1** (Figure 1) have been used as precursors in the syntheses of furo-, dihydrofuro-, thieno-, thiopyrano-, pyrrolo-, and dihydropyrano[2,3-*b*]pyridines by intramolecular Diels–Alder reactions.[1–3] A number of these heterocyclic cores are found in antibiotics and herbicides that have pharmacological activity.[1–3] In the context of medicinal chemistry, 3-substituted 1,2,4-triazines **1** have drawn attention as mGluR5 antagonists, which are targets in the development of pharmacotherapies to treat drug and alcohol addictions.[4–6] Some 3-substituted 1,2,4-triazines have been found to inhibit SCD-1, an enzyme linked to obesity and hepatocarcinogenesis,[7] whereas others have been identified as selective serotonin 5-HT$_7$ ligands.[8] A very recent report describes their potential as compounds that are capable of modulating skeletal muscle contractility.[9] Our group has identified some 3,3′-disubstituted 5,5′-bi-1,2,4-triazines, which are conveniently derived from 3-substituted 1,2,4-triazines by a cyanide-induced oxidative coupling reaction (Scheme 1) and have low nanomolar levels of activity against *Plasmodium falciparum* with low cytotoxicity.[10]

A literature survey of 3-substituted 1,2,4-triazines indicates that 3-halo-, 3-methylthio-, and 3-methylsulfonyl-1,2,4-triazines (i.e., **2**–**5**) are the most frequently employed precursors for their synthesis (Figure 1). As described in a recent report, the substitution of a bromo group at the 3-position of 1,2,4-triazines with

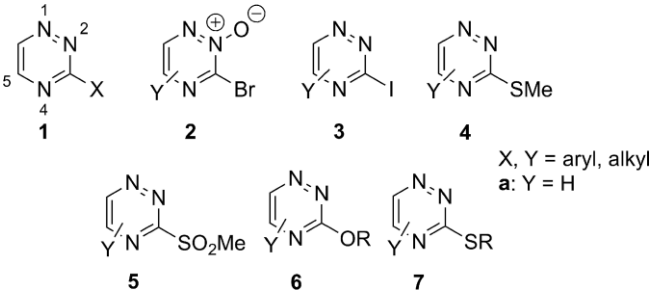
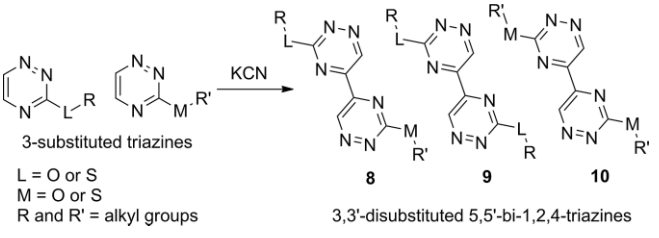


Figure 1. Some 3-substituted 1,2,4-triazines **1** that have reported biological activity and potential synthetic precursors (i.e., **2**–**5**) to related compounds.



Scheme 1. The synthesis of 3,3′-disubstituted 5,5′-bi-1,2,4-triazines by a cyanide ion mediated dimerization reaction.[10]

other nucleophiles is known to occur through precursor **2**, which has an *N*-oxide functionality at the 2-position.[9] The substitution of an iodo group at the 3-position is also known but is less appealing, as synthetic procedures that lead to the synthesis of 3-iodo-1,2,4-triazines **3** are poor-yielding and only known to give triazines that have a substituent in either the 5- or 6-position.[4] The 3-methylthio-substituted 1,2,4-triazine **4** has been used as a precursor of choice for Cu^{I}/Pd^{0}- or Pd^{II}-mediated Suzuki,[11,12] Stille,[12,13] and Buchwald-type[14] coupling reactions, which lead to C–C bond formation at the 3-position of 1,2,4-triazines. The substituted 3-(methylsulfonyl)-

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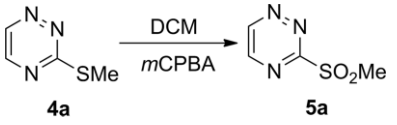
1,2,4-triazines **5** are reported as preferred precursors for the syntheses of 3-(alkoxy)- and 3-(alkylthio)-1,2,4-triazines **6** and **7**.[3,10] However, we were specifically interested in synthetic routes to access 3-(alkoxy)- and 3-(alkylthio)-1,2,4-triazines **6a** and **7a**, which do not have substituents at the 5- and 6-positions. Our interest is related to their use as precursors in the synthesis of the corresponding 3,3′-disubstituted 5,5′-bi-1,2,4-triazines **8**, **9**, and **10**, for the purposes of exploring their antimalarial structure–activity relationships (SARs). Our preliminary SAR studies suggest that compounds such as **8**, **9** and **10** lose activity against *P. falciparum* when a substituent is present at the 6-position.[10]

Although the reactivities of compounds that contain the core structure **5** have been explored with mercaptans, alcohols, and amines, these reactions are carried out under a variety of conditions that can differ significantly with regards to the strength of the base. For example, some reports describe the use of milder bases such as lutidine or triethylamine for the reaction of **5** with mercaptans,[8,15] whereas others use much harsher conditions such as employing NaH as the base for the reaction.[16] Similarly, the reactions of alcohols with **5** have been carried out with a stronger base, including BuLi according to some reports.[17,18] NaH, however, appears to be the most common base used for these reactions.[1] Likewise, some reports suggest **5** to be very reactive towards amines at high temperature without any catalyst,[7] while others have preferred to use phosphazides for the synthesis of 1,2,4-triazin-3-amines.[1,19] Furthermore, reported experimental protocols to obtain **5a** vary considerably.[1–4,7,20]

Herein, we describe the optimization of the synthesis of **5a** and its applications towards the synthesis of 3-substituted 1,2,4-triazines by employing a variety of sulfur-, nitrogen- and oxygen-containing nucleophiles. Our studies are aimed at the development of general and reliable procedures that are high-yielding, preferably use mild reagents and conditions, and offer a convenient workup and isolation procedure.

Results and Discussion

A number of reports describe the synthesis of 3-(methylsulfonyl)-1,2,4-triazines **5** to require the oxidation of the corresponding methylthio compounds **4** with *meta*-chloroperoxybenzoic acid (*m*CPBA; Scheme 2).[1–4,7,20] In general, for reasons that are not apparent, the yields of 3-(methylsulfonyl)-1,2,4-triazines **5** obtained by this oxidation method are significantly higher for triazines that have substituents at the 5- or 6-position. Although a number of reports describe the synthesis of 3-(methylsulfonyl)-1,2,4-triazine (**5a**; Scheme 2) by using *m*CPBA, the synthetic procedures, workup, and isolated yields (from 18 to 90 %) vary considerably.[1–4,7,20] Some of these reports describe the use of anhydrous reaction conditions, workup procedures, and chromatographic separations, whereas others do not.[1,7,20] We sought to clarify the literature by investigating this reaction and developing optimized approaches for the synthesis and separation procedure (Scheme 2) to allow for the isolation of multigram quantities of **5a**. Triazine **4a** was first synthesized by applying the procedure outlined in the Experimental Section.



Scheme 2. Synthesis of 3-(methylsulfonyl)-1,2,4-triazine **5a** by using *m*CPBA as an oxidant (DCM = dichloromethane).

After substantial experimentation, we concluded that the best method to oxidize thioether **4a** was indeed under anhydrous conditions and by using dry solvents both during the reaction and workup. Thus, the optimized procedure begins by dissolving commercially obtained *m*CPBA in DCM and drying the mixture with anhydrous $MgSO_4$. After filtration, this solution was gradually added to **4a** at –10 °C. Once the reaction reached completion, we found that the byproduct *meta*-chlorobenzoic acid (*m*CBA) was easily removed by filtration because of its poor solubility in DCM. Our repeated attempts to isolate **5a** by using column chromatography as suggested in the reported procedure did not come to fruition.[1,7,20] We observed that when the DCM solution of the crude oxidized product was treated with Bu_4NI, the solution turned brown, which suggests the presence of the I_3^- anion, presumably from the presence of unreacted *m*CPBA or another oxidizing agent in the solution with the I^- ions. We believe that the addition of Bu_4NI is necessary, as it provides a nonaqueous alternative to remove the oxidizing agent and to enable the efficient recovery of **5a**. We found an improved method to involve the direct treatment of the crude reaction mixture with Bu_4NI followed by concentration and loading of the resulting residue onto a silica gel column for chromatography. This had a profoundly positive effect on the chromatographic recovery of **5a**, and besides the improvement of the yields over those of the reported procedure, this modification was also synthetically reliable with reproducible yields. For the isolation process, commercial silica gel and solvents were used as received. We were also able to obtain X-ray quality crystals of **5a**, which were used to ascertain its crystal structure (ORTEP plot can be found in the Supporting Information, pp. 131–133).[21]

We then investigated the utility of **5a** in the synthesis of 3-substituted 1,2,4-triazines. Although we were specifically interested in the use of **5a** for the synthesis of 3-(alkylthio)-1,2,4-triazines **11** and 3-(alkoxy)-1,2,4-triazines **13**, we decided to broaden our study to include the reactivity of S-, O-, and N-nucleophiles towards **5a**.

When **5a** was treated with a slight excess amount of an alkylthiol or thiophenol in acetonitrile in the presence of Na_2CO_3 (which served as a base to quench the methanesulfinic acid, which was formed as a byproduct during the reaction), we obtained high yields of the corresponding 3-(alkylthio)- and 3-(arylthio)-1,2,4-triazines **11** (Table 1). High yields of the substitution product **11c** were also obtained when the corresponding sterically hindered tertiary thiol was used as a substrate (Table 1). We found that the reaction conditions that were used for thiols could be easily extended to reactions with primary and secondary amines as nucleophiles (Table 2). The yields of 1,2,4-triazin-3-amines **12**, which resulted from these reactions, were good in most cases. Some amines, however, afforded rela-

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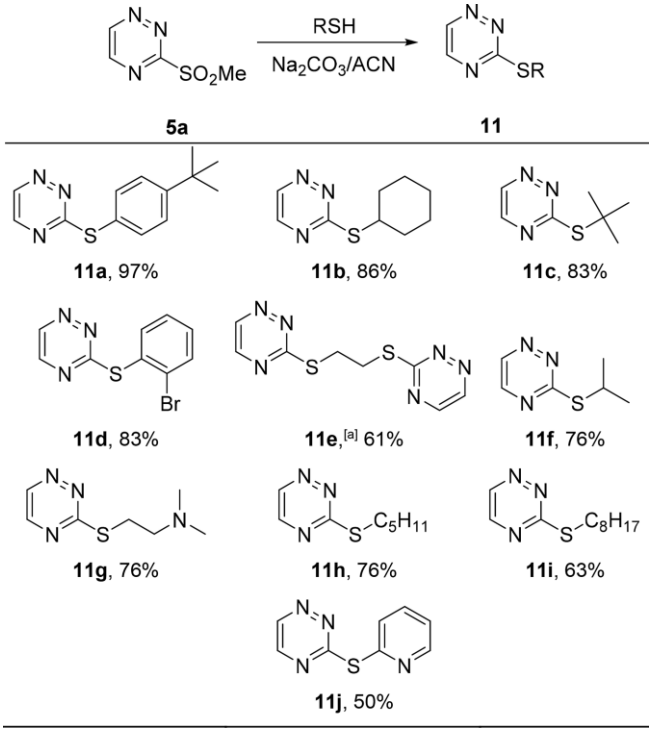
tively low yields of the product (Table 2, compounds **12i** and **12j**). In both of these cases, the formation of a byproduct was apparent by TLC analysis, which helped to account for the poor yields of the desired product. However, our attempts to identify the byproducts were unsuccessful. Na_2CO_3 was used in the reactions of **5a** with the amines to be sure that the 1,2,4-triazin-3-amines **12** were isolated as the free base after chromatographic separation. The reaction of aniline in the presence of Na_2CO_3 showed negligible conversion by TLC and LC–MS analyses. To compare this method with that reported in the literature, the reaction of sulfone **5a** with 3 equiv. of piperazine in acetonitrile at room temperature was attempted. This reaction provided 74 % yield of the product **12k**, which is slightly better than that obtained by the published method that used the less active thioether **4a** and 3 equiv. of piperazine in butanol under harsh conditions, including heating of the reaction mixture at 120 °C for 24 h.[7]

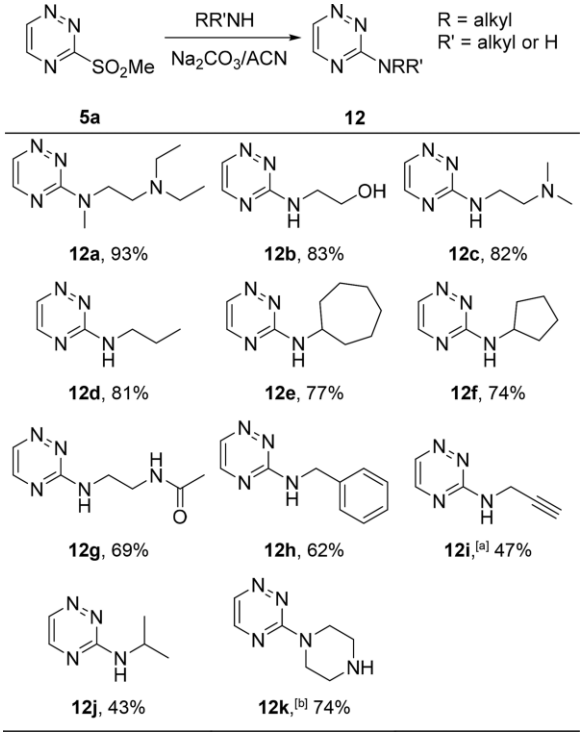
Table 1. Synthesis of 3-(alkylthio)- and 3-(arylthio)-1,2,4-triazines **11** (ACN = acetonitrile).



[a] The ratio of thiol/**5a**/Na_2CO_3 was 1:2:2.

We were particularly interested in investigating alcohols as nucleophiles in these substitution reactions. The use of NaH to completely ionize alcohols for nucleophilic substitution reactions with **5a** has been documented in the literature.[3] However, we were interested in studying the reactivity of sulfone **5a** towards an alcohol under more benign and convenient reaction conditions, in which a relatively weaker base such as Cs_2CO_3 was used. As shown in Table 3, we found that Cs_2CO_3 successfully mediated the reaction of **5a** with alcohols. Although a modest yield of 29 % was obtained when *n*-propanol was used to synthesize 3-(*n*-propoxy)-1,2,4-triazine (**13a**; Table 3, Entry 2), the yields considerably improved when more acidic alcohols

Table 2. Synthesis of *N*,*N*-dialkyl- and *N*-alkyl-1,2,4-triazin-3-amines **12**.



[a] Hydrochloride salt of the amine used during the reaction. [b] Piperazine (300 mol-%) was used without Na_2CO_3.

(Table 3, Entries 3 and 4) and phenols (Table 3, Entries 5–7) were used as the nucleophiles.[22,23] Notably, the employment of Cs_2CO_3 as a mild and efficient base in the reaction of phenols with **5a** is more desirable than using a strong, moisture-sensitive base such as NaH, which is the preference of the literature procedure.[16,24] In contrast, when a weaker base such as Na_2CO_3 was used for the reaction of **5a** with *n*-propanol, we did not observe any formation of **13a** (Table 3, Entry 1). To investigate the effect of switching to NaH as the base, we used *n*-propanol and benzyl alcohol in the synthesis of **13a** and **13g**, respectively. These products were isolated in modest yields of 37 and 55 % (Table 3, Entries 8 and 9), respectively, which is an improvement in the reaction yield.

To obtain more acceptable yields from the reactions with less acidic alcohols, we broadened our use of bases. Specifically, we treated *n*-propanol with MeMgI to obtain its magnesium alkoxide salt, which was dissolved in dry DMF and then treated with 3-(methylsulfonyl)-1,2,4-triazine (**5a**) under cold conditions. It is worth mentioning that magnesium salts are less soluble then their corresponding sodium counterparts, and the more polar solvent DMF was preferred to attain a solution. Gratifyingly, we obtained 72 % yield of the corresponding substitution product **13a** (Table 3, Entry 12). An equally good yield (80 %) was achieved for the synthesis of benzyl alcohol **13g** under the same reaction conditions (Table 3, Entry 13). To determine the effect of changing the solvent, the reactions of *n*-propanol and benzyl alcohol with **5a** and NaH in DMF were also attempted. These reactions afforded products **13a** and **13g** in 20 and 42 % yield (Table 3, Entries 10 and 11), respectively,

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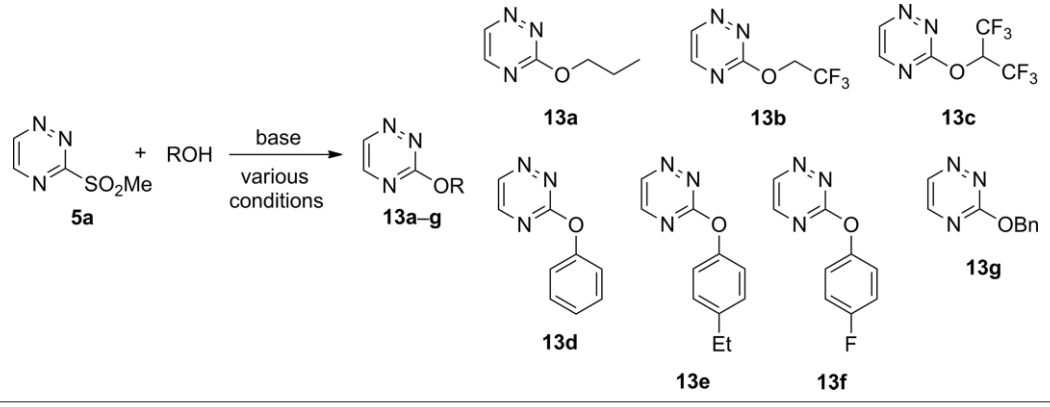
Table 3. Reactions of alkyl and aryl alcohols.

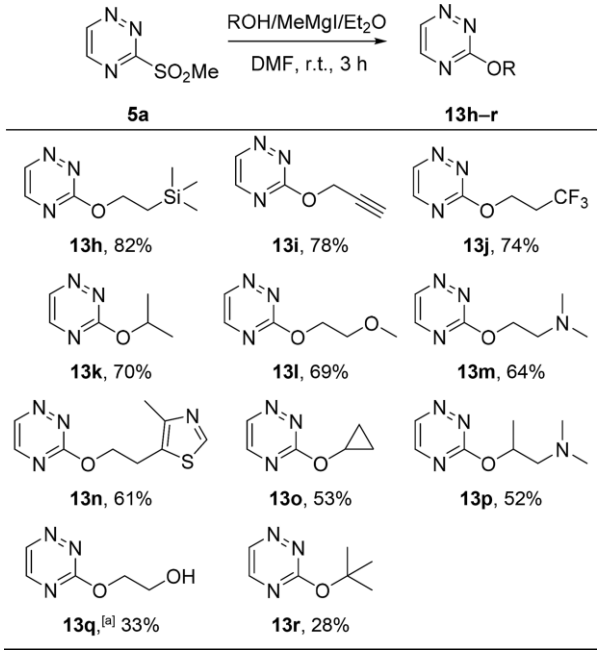


Entry	Conditions	ROH	Product	Yield
1	Na_2CO_3, ACN, r.t., 16 h	PrOH	**13a**	n.r.[a]
2	Cs_2CO_3, ACN, r.t., 16 h	PrOH	**13a**	29 %
3	Cs_2CO_3, ACN, r.t., 16 h	CF_3CH_2OH	**13b**	62 %
4	Cs_2CO_3, ACN, r.t., 16 h	$(CF_3)_2CHOH$	**13c**	55 %
5	Cs_2CO_3, ACN, r.t., 16 h	PhOH	**13d**	62 %
6	Cs_2CO_3, ACN, r.t., 16 h	4-EtC_6H_4OH	**13e**	81 %
7	Cs_2CO_3, ACN, r.t., 16 h	4-FC_6H_4OH	**13f**	78 %
8	NaH, THF,[a] –40 °C then r.t., 16 h	PrOH	**13a**	37 %
9	NaH, THF, –40 °C then r.t., 16 h	BnOH	**13g**	55 %
10	NaH, DMF,[a] –40 °C then r.t., 16 h	PrOH	**13a**	20 %
11	NaH, DMF, –40 °C then r.t., 16 h	BnOH	**13g**	42 %
12	MeMgI, DMF, –40 °C then r.t., 16 h	PrOH	**13a**	72 %
13	MeMgI, DMF, –40 °C then r.t., 16 h	BnOH	**13g**	80 %

[a] n.r. = no reaction, THF = tetrahydrofuran, DMF = *N*,*N*-dimethylformamide.

which indicates that the good product yields obtained by using the magnesium alkoxides were not a result of the change in solvent from THF to DMF.

Table 4. Synthesis of 3-(alkoxy)-1,2,4-triazines **13** by using 3-(methylsulfonyl)-1,2,4-triazine (**5a**), alcohols, and MeMgI.



[a] Significant amount of disubstituted product observed.

A variety of alcohols were then employed to assess the scope of the magnesium alkoxides as nucleophiles in these substitution reactions (Table 4). Good yields were obtained in most of the reactions, with the exception of those that involved hindered secondary and tertiary alcohols (i.e., alcohols used in the preparation of **13o**, **13p**, and **13r**).

Conclusions

The substitution of the methylsulfonyl group of 3-(methylsulfonyl)-1,2,4-triazine by using S-, N-, and O-nucleophiles was investigated. Facile methods that allow for the substitution of the $–SO_2Me$ group by aliphatic and aromatic thiols, aliphatic amines, phenols, and alcohols were developed and assessed for their scope and generalizability. In each method, we observed good tolerance to structural variation and generally good isolated yields of the products. Considering the applicability of 3-substituted 1,2,4-triazines, we believe that these methods will allow for easy access to the synthesis of a variety of 3-(alkoxy)-, 3-(aryloxy)-, 3-(alkylthio)-, 3-(arylthio)-, and 3-(alkylamino)-1,2,4-triazines. We are currently utilizing these facile procedures to elaborate a variety of 3,3′-disubstituted 5,5′-bi-1,2,4-triazines and study the impact of structural variation on the activity against *P. falciparum*.

Experimental Section

General Methods: Commercially available reagents were used without further purification. Column chromatography was per-

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formed using silica gel 60 (40–60 μm). The solvents for chromatography were used without further purification. The reactions were monitored by TLC analysis on Silica Gel 60F-254 plates with detection by UV light and/or $KMnO_4$ stain [$KMnO_4$ (1.50 g), K_2CO_3 (10.0 g), and 10 % NaOH (1.25 mL) in water (200 mL)]. Melting points were measured with a Mettler Toledo MP50 melting point system. Attenuated total reflection Fourier transform infrared spectroscopy (ATR-FTIR) measurements were performed with a Shimazu IRTracer-100 Fourier transform spectrometer by averaging 128 scans with a resolution of 4 cm^{-1}. The ^1H and ^{13}C NMR spectroscopic data were recorded at 400.13 and 100.62 MHz, respectively, with a Bruker Avance III Nanobay spectrometer with a Bruker automatic sample changer (BACS-60). The resonances for the ^1H NMR data are reported as chemical shift (δ), multiplicity [s (singlet), d (doublet), and m (multiplet)], coupling constant (J) in Hz, and the number of protons. HRMS was performed with an Agilent 6224 TOF liquid chromatography mass spectrometry (LC–MS) system coupled to an Agilent 1290 Infinity LC.

Synthesis of *S*-Methylthiosemicarbazide Iodohydrate: Iodomethane (17.04 g, 7.47 mL, 0.12 mol) was added to a mixture of thiosemicarbazide (10.01 g, 0.11 mol) and EtOH (200 mL). The resultant mixture was stirred and heated at reflux for 18 h. During this quaternization reaction, the thiosemicarbazide slowly dissolved into the solution, and subsequently a white solid (presumably the quaternary salt) precipitated from the solution within a few hours. The reaction mixture was cooled to room temperature. The solvent was evaporated under reduced pressure to give a white residual solid. Diethyl ether (200 mL) was added to the solid, and the mixture was stirred at room temperature for a few minutes. The suspended quaternary salt was removed by filtration, washed with diethyl ether (100 mL), and dried under reduced pressure to yield the practically pure quaternary salt (25.24 g, 98 % yield); m.p. 137–139 °C. IR (neat): $\tilde{\nu}$ = 961, 1161, 1300, 1381, 1447, 1605, 1640, 3136, 3194, 3291, 3333 cm^{-1}. ^1H NMR [400 MHz, [D_6]dimethyl sulfoxide ([D_6]DMSO)]: δ = 10.48 (s, 1 H), 8.98 (s, 2 H), 5.19 (s, 2 H), 2.56 (s, 3 H) ppm. ^{13}C NMR (101 MHz, [D_6]DMSO): δ = 167.9, 13.1 ppm. HRMS (EI): calcd. for $C_2H_7N_3S$ $[M + H]^+$ 106.0433; found 106.0433.

Synthesis of 3-(Methylthio)-1,2,4-triazine (4a): Water (150 mL) and glyoxal (40 wt.-% aqueous solution, 12.48 mL, 4.99 g, 86 mmol) were added to *S*-methylthiosemicarbazide iodohydrate (10.00 g, 43 mmol) to obtain an aqueous solution. This solution was cooled externally with ice to 0 °C. $NaHCO_3$ (7.22 g, 86 mmol) was added in small portions, as the solution was stirred so that the evolution of CO_2 remained under control. The stirring was continued at 0 °C for 6 h, whereupon the evolution of the CO_2 gas had completely subsided. The temperature of the reaction mixture was maintained at 0 °C for 12 h. DCM (3 × 100 mL) was then used to extract the product from the aqueous reaction mixture. The combined DCM layers were dried with anhydrous $MgSO_4$ and concentrated under reduced pressure to yield practically pure product **4a** (5.08 g, 93 % yield) as a low-melting solid, which was used in the next step without further purification. IR (neat): $\tilde{\nu}$ = 868, 961, 991, 1034, 1084, 1123, 1153, 1200, 1223, 1312, 1331, 1370, 1420, 1516, 1535, 2928, 3021, 3086 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.92 (d, J = 2.4 Hz, 1 H), 8.36 (d, J = 2.4 Hz, 1 H), 2.65 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 174.7, 148.2, 145.4, 13.9 ppm. HRMS (EI): calcd. for $C_4H_5N_3S$ $[M + H]^+$ 128.0277; found 128.0278.

Synthesis of 3-(Methylsulfonyl)-1,2,4-triazine (5a): DCM (200 mL) was added to wet technical grade *m*CPBA (75 wt.-%; 24.77 g, 108 mmol), and the mixture was stirred to obtain a turbid solution. Anhydrous $MgSO_4$ (20 g) was added, as the stirring was continued for 10 min to ensure that the water suspended in the DCM was removed. This solution was vacuum-filtered to remove the $MgSO_4$, and DCM (3 × 20 mL) was used to wash the filtered $MgSO_4$. These washings and the filtrate were combined and then used for the oxidation of 3-(methylthio)-1,2,4-triazine (**4a**). The solution of *m*CPBA in DCM (obtained above) was slowly added dropwise over 1 h to the cold solution of **4a** (4.95 g, 39 mmol) in DCM (20 mL), which was stirred and maintained at –10 °C. After the addition was complete, the solution was allowed to slowly warm to room temperature, and the stirring was continued for an additional 3 h. The solution was vacuum-filtered, and the insoluble residue was washed with DCM (50 mL). The filtrate and the washings were combined and treated with Bu_4NI (0.500 g, 1.36 mmol), and the resulting mixture was stirred at room temperature for 5 min. The solvent was evaporated under reduced pressure to obtain a concentrated solution, to which silica gel (20 g) was added. The mixture was further dried under reduced pressure to give the crude product absorbed onto the silica gel. Purification by column chromatography (75 % ethyl acetate in hexanes) gave analytically pure **5a** (2.20 g, 36 % yield) as a white solid; m.p. 84–85 °C. ^1H NMR (400 MHz, [D_6]DMSO): δ = 9.74 (d, J = 2.5 Hz, 1 H), 9.18 (d, J = 2.5 Hz, 1 H), 3.55 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 167.4, 151.8, 150.8, 39.8 ppm. IR (neat): $\tilde{\nu}$ = 841, 1038, 1099, 1146, 1254, 1327, 1427, 1458, 1524, 1562, 1647, 2114, 2782, 2824, 2947, 2978, 3260 cm^{-1}. HRMS (EI): calcd. for $C_4H_5N_3O_2S$ $[M + H]^+$ 160.0175; found 160.0175.

General Procedure for the Synthesis of 3-(Alkylthio)- and 3-(Arylthio)-1,2,4-triazines 11 from 3-(Methylsulfonyl)-1,2,4-triazine (5a): Na_2CO_3 (0.367 g, 3.46 mmol) was added to a solution of **5a** (0.500 g, 3.14 mmol) in acetonitrile (5 mL). The corresponding mercaptan (3.46 mmol) was added, and the reaction mixture was stirred at room temperature for 16 h, whereupon the starting material was consumed, as indicated by TLC analysis. The reaction mixture was vacuum-filtered, and the filtrate was concentrated under reduced pressure to obtain the crude product. Analytically pure 3-(alkylthio)-1,2,4-triazine **11** was isolated from the crude product by column chromatography.

General Procedure for the Synthesis of *N*,*N*-Dialkyl- or *N*-Alkyl-1,2,4-triazin-3-amines 12 from 3-(Methylsulfonyl)-1,2,4-triazine (5a): Na_2CO_3 (0.367 g, 3.46 mmol) was added to a solution of **5a** (0.500 g, 3.14 mmol) in acetonitrile (5 mL). The corresponding amine (3.46 mmol) was added, and the reaction mixture was stirred at room temperature for 16 h, whereupon the starting material was consumed, as indicated by TLC analysis. The reaction mixture was vacuum-filtered, and the filtrate was concentrated under reduced pressure to obtain the crude product. Analytically pure **12** was isolated from the crude product by column chromatography.

General Procedure for the Synthesis of 3-(Alkoxy)- and 3-(Aryloxy)-1,2,4-triazines 13b–13f: The procedure that was used for the synthesis of 3-(alkylthio)-1,2,4-triazines **11a**–**11j** was applied for the preparation of **13b**–**13f**. However, the mercaptans were replaced with the corresponding phenol/alcohol, and Cs_2CO_3 was used as a base.

General Procedure for the Synthesis of 3-(Alkoxy)-1,2,4-triazine 13h–13r from 3-(Methylsulfonyl)-1,2,4-triazine (5a): The corresponding alcohol (4.1 mmol) was added dropwise to a cold diethyl ether solution of methylmagnesium iodide (1.34 M solution; 2.81 mL, 3.77 mmol) as the mixture was stirred and maintained at –10 °C under nitrogen. Provisions were made to compensate for the buildup of excess pressure, as a result of the gas evolution, and at the same time maintain an inert atmosphere. The solution was slowly warmed to room temperature and then stirred for 30 min. The diethyl ether was evaporated under reduced pressure to obtain the practically diethyl ether free magnesium alkoxide, which was

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dissolved in DMF (3 mL). This solution was cooled to –40 °C, and **5a** (0.500 g, 3.14 mmol) was added in small portions, as the mixture was stirred. The reaction mixture was then allowed to slowly warm, as the stirring was continued at room temperature for 3 h. Completion of the reaction was determined by TLC analysis. The DMF was evaporated under reduced pressure, and then water (5 mL) was added to the resulting viscous material. The mixture was extracted with EtOAc (3 × 15 mL), and the combined organic extracts were dried with anhydrous $MgSO_4$ and concentrated under reduced pressure to yield the crude product. Analytically pure 3-(alkoxy)-1,2,4-triazine **13** was isolated from the crude product by column chromatography.

3-{[4-(*tert*-Butyl)phenyl]thio}-1,2,4-triazine (11a): Column chromatography (20 % ethyl acetate in hexanes) afforded **11a** (0.749 g, 97 % yield) as a yellow solid; m.p. 67–69 °C. IR (neat): $\tilde{\nu}$ = 826, 860, 968, 1011, 1034, 1088, 1115, 1153, 1196, 1265, 1331, 1373, 1462, 1485, 1516, 1535, 1593, 1659, 2866, 2901, 2959, 3017, 3075 cm^{-1}. ^1H NMR (400 MHz, [D$_6$]DMSO): δ = 9.18 (d, J = 2.4 Hz, 1 H), 8.63 (d, J = 2.4 Hz, 1 H), 7.63–7.55 (m, 2 H), 7.55–7.47 (m, 2 H), 1.31 (s, 9 H) ppm. ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 173.4, 152.6, 150.1, 147.0, 135.0, 126.6, 123.8, 34.6, 31.0 ppm. HRMS (EI): calcd. for $C_{13}H_{15}N_3S$ $[M + H]^+$ 246.1059; found 246.1070.

3-(Cyclohexylthio)-1,2,4-triazine (11b): Column chromatography (20 % ethyl acetate in hexanes) afforded **11b** (0.525 g, 86 % yield) as a yellow solid; m.p. 50–52 °C. IR (neat): $\tilde{\nu}$ = 818, 872, 891, 918, 964, 999, 1030, 1150, 1192, 1258, 1319, 1362, 1439, 1508, 1535, 2851, 2928 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.88 (d, J = 2.4 Hz, 1 H), 8.34 (d, J = 2.3 Hz, 1 H), 3.95–3.89 (m, 1 H), 2.14–2.11 (m, 2 H), 1.79–1.75 (m, 2 H), 1.65–1.41 (m, 5 H), 1.36–1.30 (m, 1 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 174.7, 148.3, 145.2, 53.6, 43.6, 32.8, 26.0, 25.7 ppm. HRMS (EI): calcd. for $C_9H_{13}N_3S$ $[M + H]^+$ 196.0903; found 196.0903.

3-(*tert*-Butylthio)-1,2,4-triazine (11c): Column chromatography (50 % ethyl acetate in hexanes) afforded **11c** (0.440 g, 83 % yield) as a yellow liquid. IR (neat): $\tilde{\nu}$ = 856, 930, 968, 991, 1030, 1080, 1111, 1150, 1204, 1312, 1362, 1454, 1474, 1508, 1535, 2862, 2920, 2963, 3078 cm^{-1}. ^1H NMR (400 MHz, [D$_6$]DMSO): δ = 9.14–9.13 (d, J = 2.4 Hz, 1 H), 8.65–8.64 (d, J = 2.4 Hz, 1 H), 1.61 (s, 9 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 175.3, 147.9, 145.2, 48.5, 29.9 ppm. HRMS (EI): calcd. for $C_7H_{11}N_3S$ $[M + H]^+$ 170.0746; found 170.0744.

3-[(2-Bromophenyl)thio]-1,2,4-triazine (11d): Column chromatography (15 % ethyl acetate in hexanes) afforded **11d** (0.695 g, 83 % yield) as a yellow liquid. IR (neat): $\tilde{\nu}$ = 853, 949, 988, 1018, 1115, 1150, 1204, 1227, 1250, 1319, 1381, 1427, 1447, 1508 cm^{-1}. ^1H NMR (400 MHz, [D$_6$]DMSO): δ = 9.22–9.21 (d, J = 2.4 Hz, 1 H), 8.67–8.66 (d, J = 2.4 Hz, 1 H), 7.87–7.85 (m, 2 H), 7.54–7.45 (m, 2 H) ppm. ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 172.0, 150.2, 147.2, 137.9, 133.7, 132.2, 130.0, 128.8, 128.5 ppm. HRMS (EI): calcd. for $C_9H_6BrN_3S$ $[M + H]^+$ 267.9539; found 267.9547.

1,2-Bis[(1,2,4-triazin-3-yl)thio]ethane (11e): Column chromatography (50 % ethyl acetate in hexanes) afforded **11e** (0.218 g, 61 % yield) as a yellow solid; m.p. 118–120 °C. IR (neat): $\tilde{\nu}$ = 856, 876, 991, 1030, 1115, 1150, 1192, 1231, 1323, 1385, 1512, 1535, 3001, 3075 cm^{-1}. ^1H NMR (400 MHz, [D$_6$]DMSO): δ = 9.19 (d, J = 2.4 Hz, 2 H), 8.67 (d, J = 2.4 Hz, 2 H), 3.63 (s, 4 H) ppm. ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 172.2, 149.8, 146.8, 29.4 ppm. HRMS (EI): calcd. for $C_8H_8N_6S_2$ $[M + H]^+$ 253.0325; found 253.0332.

3-(Isopropylthio)-1,2,4-triazine (11f): Column chromatography (50 % ethyl acetate in hexanes) afforded **11f** (0.372 g, 76 % yield) as a yellow solid; m.p. 49–51 °C. IR (neat): $\tilde{\nu}$ = 853, 930, 972, 1030, 1057, 1119, 1153, 1204, 1246, 1319, 1370, 1458, 1512, 1562, 2866, 2928, 2967, 3078, 3256 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.46 (d, J = 1.8 Hz, 1 H), 8.06 (d, J = 1.8 Hz, 1 H), 4.17 (s, 1 H), 1.25–1.24 (d, J = 6.5 Hz, 6 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 161.6, 149.3, 140.4, 42.9, 22.6 ppm. HRMS (EI): calcd. for $C_6H_9N_3S$ $[M + H]^+$ 156.0590; found 156.0590.

2-[(1,2,4-Triazin-3-yl)thio]-*N*,*N*-dimethylethan-1-amine (11g): Column chromatography (10 % methanol in dichloromethane) afforded **11g** (0.441 g, 76 % yield) as a yellow liquid. IR: $\tilde{\nu}$ = 853, 1034, 1119, 1153, 1200, 1323, 1373, 1458, 1512, 1535, 1670, 2770, 2820, 2859, 2943, 2970 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.91 (d, J = 2.4 Hz, 1 H), 8.35 (d, J = 2.4 Hz, 1 H), 3.39–3.36 (t, J = 7.2 Hz, 2 H), 2.70–2.66 (t, J = 7.2 Hz, 2 H), 2.30 (s, 6 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 174.5, 148.3, 145.5, 58.0, 45.4, 28.8 ppm. HRMS (EI): calcd. for $C_7H_{12}N_4S$ $[M + H]^+$ 185.0855; found 185.0852.

3-(Pentylthio)-1,2,4-triazine (11h): Column chromatography (20 % ethyl acetate in hexanes) afforded **11h** (0.435 g, 76 % yield) as a yellow liquid. IR (neat): $\tilde{\nu}$ = 856, 972, 991, 1030, 1115, 1153, 1200, 1319, 1373, 1462, 1512, 1535, 2855, 2928, 2955 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.88 (d, J = 2.3 Hz, 1 H), 8.33 (d, J = 2.3 Hz, 1 H), 3.21–3.18 (t, J = 7.2 Hz, 2 H), 1.76–1.69 (m, 2 H), 1.44–1.29 (m, 4 H), 0.88–0.84 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 174.6, 148.2, 145.3, 31.0, 30.7, 28.6, 22.2, 14.0 ppm. HRMS (EI): calcd. for $C_8H_{13}N_3S$ $[M + H]^+$ 184.0903; found 184.0903.

3-(Octylthio)-1,2,4-triazine (11i): Column chromatography (10 % ethyl acetate in hexanes) afforded **11i** (0.445 g, 63 % yield) as a yellow liquid. IR (neat): $\tilde{\nu}$ = 853, 972, 991, 1030, 1115, 1153, 1200, 1323, 1373, 1408, 1458, 1512, 1535, 2851, 2920, 2951 cm^{-1}. ^1H NMR (400 MHz, [D$_6$]DMSO): δ = 9.14 (d, J = 2.4 Hz, 1 H), 8.64 (d, J = 2.4 Hz, 1 H), 3.21–3.17 (t, J = 7.4 Hz, 2 H), 1.72–1.64 (m, 2 H), 1.43–1.36 (m, 2 H), 1.27–1.23 (m, 8 H), 0.85–0.82 (t, J = 6.6 Hz, 3 H) ppm. ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 172.9, 149.6, 146.4, 31.2, 29.8, 28.6, 28.5, 28.2, 22.1, 13.9 ppm. HRMS (EI): calcd. for $C_{11}H_{19}N_3S$ $[M + H]^+$ 226.1372; found 226.1381.

3-(Pyridin-2-ylthio)-1,2,4-triazine (11j): Column chromatography (ethyl acetate) afforded **11j** (0.301 g, 50 % yield) as a yellow solid; m.p. 61–63 °C. IR (neat): $\tilde{\nu}$ = 876, 969, 988, 1034, 1084, 1107, 1150, 1200, 1231, 1323, 1377, 1420, 1454, 1516, 1570, 3005, 3071 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.97–8.96 (d, J = 2.3 Hz, 1 H), 8.65–8.64 (m, 1 H), 8.37–8.38 (d, J = 2.3 Hz, 1 H), 7.78–7.73 (m, 2 H), 7.34–7.31 (m, 1 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 174.1, 151.6, 150.9, 148.7, 146.3, 137.7, 130.2, 123.9 ppm. HRMS (EI): calcd. for $C_8H_6N_4S$ $[M + H]^+$ 191.0386; found 191.0386.

***N*^{1},*N*^{1}-Diethyl-*N*^{2}-methyl-*N*^{2}-(1,2,4-triazin-3-yl)ethane-1,2-diamine (12a):** Column chromatography (4 % methanol in dichloromethane) afforded **12a** (0.609 g, 93 % yield) as a yellow liquid. IR (neat): $\tilde{\nu}$ = 837, 964, 1011, 1042, 1099, 1200, 1238, 1289, 1339, 1408, 1435, 1528, 1555, 2801, 2870, 2932, 2967 cm^{-1}. ^1H NMR (400 MHz, [D$_6$]DMSO): δ = 8.55 (d, J = 2.2 Hz, 1 H), 8.27 (d, J = 2.3 Hz, 1 H), 3.69 (br. s, 2 H), 3.16 (br. s, 3 H), 2.58–2.54 (t, J = 6.7 Hz, 2 H), 2.49–2.43 (q, J = 7.1 Hz, 4 H), 0.91–0.88 (t, J = 7.1 Hz, 6 H) ppm. ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 160.8, 149.1, 139.5, 54.9, 49.4, 46.8, 35.3, 12.0 ppm. HRMS (EI): calcd. for $C_{10}H_{19}N_5$ $[M + H]^+$ 210.1713; found 210.1712.

2-[(1,2,4-Triazin-3-yl)amino]ethan-1-ol (12b): Column chromatography (10 % methanol in dichloromethane) afforded **12b** (0.365 g, 83 % yield) as a yellow solid; m.p. 65–67 °C. IR (neat): $\tilde{\nu}$ = 833, 853, 868, 918, 926, 1011, 1042, 1099, 1126, 1157, 1231, 1319, 1339, 1427, 1512, 1524, 1582, 1601, 2870, 2928, 2947, 3113, 3248, 3372 cm^{-1}. ^1H NMR (400 MHz, [D$_6$]DMSO): δ = 8.54 (d, J = 2.0 Hz, 1 H), 8.23 (d, J = 2.1 Hz, 1 H), 7.63 (br. s, 1 H), 4.75–4.72 (t, J = 5.4 Hz, 1 H), 3.55–3.53 (m, 2 H), 3.39 (br. s, 2 H) ppm. ^{13}C NMR (101 MHz,

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[D$_6$]DMSO): δ = 162.0, 149.8, 140.5, 59.3, 43.2 ppm. HRMS (EI): calcd. for $C_5H_8N_4O$ [M + H]$^+$ 141.0771; found 141.0770.

***N*^{1},*N*^{1}-Dimethyl-*N*^{2}-(1,2,4-triazin-3-yl)ethane-1,2-diamine (12c):** Column chromatography (10 % methanol in dichloromethane) afforded **12c** (0.429 g, 82 % yield) as a yellow liquid. IR (neat): $\tilde{\nu}$ = 841, 1038, 1099, 1146, 1254, 1327, 1427, 1458, 1524, 1562, 1647, 2114, 2781, 2824, 2947, 2978, 3260 cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.55–8.54 (d, J = 2.2 Hz, 1 H), 8.24–8.23 (d, J = 2.2 Hz, 1 H), 7.51 (br. s, 1 H), 3.42 (br. s, 2 H), 2.46–2.43 (t, J = 6.7 Hz, 2 H), 2.19 (s, 6 H) ppm. ^{13}C NMR (101 MHz, CDCl$_3$): δ = 162.1, 149.4, 140.9, 57.8, 45.3, 38.7 ppm. HRMS (EI): calcd. for $C_7H_{13}N_5$ [M + H]$^+$ 168.1244; found 168.1241.

***N*-Propyl-1,2,4-triazin-3-amine (12d):** Column chromatography (5 % methanol in dichloromethane) afforded **12d** (0.351 g, 81 % yield) as a yellow liquid. IR (neat): $\tilde{\nu}$ = 837, 991, 1038, 1107, 1126, 1169, 1250, 1323, 1362, 1427, 1458, 1524, 1562, 2874, 2963, 3094, 3260 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.46 (d, J = 2.0 Hz, 1 H), 8.06 (d, J = 1.8 Hz, 1 H), 3.40 (s, 2 H), 1.68–1.58 (m, 2 H), 0.95–0.91 (t, J = 7.4 Hz, 3 H) ppm. ^{13}C NMR (101 MHz, CDCl$_3$): δ = 162.2, 149.3, 140.4, 43.0, 22.6, 11.4 ppm. HRMS (EI): calcd. for $C_6H_{10}N_4$ [M + H]$^+$ 139.0978; found 139.0976.

***N*-Cycloheptyl-1,2,4-triazin-3-amine (12e):** Column chromatography (50 % ethyl acetate in hexanes) afforded **12e** (0.465 g, 77 % yield) as a yellow solid; m.p. 102–104 °C. IR (neat): $\tilde{\nu}$ = 829, 1034, 1061, 1088, 1153, 1196, 1277, 1327, 1350, 1377, 1454, 1520, 1589, 2855, 2924, 3024, 3086, 3140, 3225 cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.50 (s, 1 H), 8.21 (s, 1 H), 7.64 (s, 1 H), 3.94 (br. s, 1 H), 1.88 (br. s, 2 H), 1.63–1.40 (m, 10 H) ppm. ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 160.8, 149.7, 140.1, 51.2, 33.9, 27.9, 23.7 ppm. HRMS (EI): calcd. for $C_{10}H_{16}N_4$ [M + H]$^+$ 193.1448; found 193.1444.

***N*-Cyclopentyl-1,2,4-triazin-3-amine (12f):** Column chromatography (50 % ethyl acetate in hexanes) afforded **12f** (0.381 g, 74 % yield) as a yellow solid; m.p. 89–91 °C. IR (neat): $\tilde{\nu}$ = 849, 876, 941, 1022, 1042, 1099, 1150, 1192, 1319, 1346, 1366, 1454, 1520, 1578, 2866, 2943, 3013, 3082, 3136, 3225 cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.53 (d, J = 2.3 Hz, 1 H), 8.22 (d, J = 2.3 Hz, 1 H), 7.73 (br. s, 1 H), 4.18 (br. s, 1 H), 1.92–1.88 (m, 2 H), 1.71–1.65 (m, 2 H), 1.58–1.47 (m, 4 H) ppm. ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 161.4, 149.5, 140.2, 52.0, 32.0, 23.4 ppm. HRMS (EI): calcd. for $C_8H_{12}N_4$ [M + H]$^+$ 165.1135; found 165.1136.

***N*-{2-[(1,2,4-Triazin-3-yl)amino]ethyl}acetamide (12g):** Column chromatography (5 % methanol in dichloromethane) afforded **12g** (0.395 g, 69 % yield) as a yellow solid; m.p. 128–130 °C. IR (neat): $\tilde{\nu}$ = 856, 1034, 1111, 1169, 1231, 1281, 1327, 1370, 1431, 1451, 1524, 1559, 1601, 1647, 2882, 2936, 3021, 3098, 3233, 3302 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.50 (d, J = 2.0 Hz, 1 H), 8.18 (d, J = 1.8 Hz, 1 H), 7.09 (br. s, 1 H), 3.63 (br. s, 2 H), 3.56–3.52 (m, 2 H), 1.95 (s, 3 H) ppm. ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 169.5, 161.6, 149.8, 140.6, 40.3, 37.9, 22.7 ppm. HRMS (EI): calcd. for $C_7H_{11}N_5O$ [M + H]$^+$ 182.1036; found 182.1040.

***N*-Benzyl-1,2,4-triazin-3-amine (12h):** Column chromatography (75 % ethyl acetate in hexanes) afforded **12h** (0.361 g, 62 % yield) as a yellow solid; m.p. 87–89 °C. IR (neat): $\tilde{\nu}$ = 841, 1038, 1084, 1103, 1161, 1196, 1269, 1304, 1331, 1346, 1362, 1416, 1451, 1493, 1528, 1597, 2859, 2924, 3024, 3090, 3148, 3237 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.57 (s, 1 H), 8.09 (s, 1 H), 7.38–7.27 (m, 5 H), 5.92 (br. s, 1 H), 4.72–4.71 (d, J = 5.0 Hz, 2 H) ppm. ^{13}C NMR (101 MHz, CDCl$_3$): δ = 162.1, 149.4, 141.1, 138.3, 128.7, 127.8, 127.6, 45.3 ppm. HRMS (EI): calcd. for $C_{10}H_{10}N_4$ [M + H]$^+$ 187.0978; found 187.0979.

***N*-(Prop-2-yn-1-yl)-1,2,4-triazin-3-amine (12i):** Column chromatography (80 % ethyl acetate in hexanes) afforded **12i** (0.198 g, 47 % yield) as a yellow liquid. IR (neat): $\tilde{\nu}$ = 829, 841, 914, 972, 1034, 1092, 1115, 1161, 1262, 1343, 1412, 1454, 1528, 1597, 2114, 2917, 3229 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.63–8.62 (d, J = 2.2 Hz, 1 H), 8.20–8.19 (d, J = 2.1 Hz, 1 H), 6.16 (br. s, 1 H), 4.31 (s, 2 H), 2.26–2.25 (t, J = 2.4 Hz, 1 H) ppm. ^{13}C NMR (101 MHz, CDCl$_3$): δ = 161.4, 149.5, 141.7, 79.9, 71.6, 31.2 ppm. HRMS (EI): calcd. for $C_6H_6N_4$ [M + H]$^+$ 135.0665; found 135.0664.

***N*-Isopropyl-1,2,4-triazin-3-amine (12j):** Column chromatography (5 % methanol in dichloromethane) afforded **12j** (0.186 g, 43 % yield) as a yellow solid; m.p. 53–55 °C. IR (neat): $\tilde{\nu}$ = 845, 976, 1018, 1057, 1092, 1126, 1188, 1292, 1323, 1362, 1454, 1520, 1582, 2870, 2905, 2963, 3017, 3090, 3140, 3217 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.49 (d, J = 2.3 Hz, 1 H), 8.09 (d, J = 2.2 Hz, 1 H), 5.74 (br. s, 1 H), 4.20–4.18 (m, 1 H), 1.28–1.26 (d, J = 6.5 Hz, 6 H) ppm. ^{13}C NMR (101 MHz, CDCl$_3$): δ = 161.6, 149.4, 140.5, 43.0, 22.7 ppm. HRMS (EI): calcd. for $C_6H_{10}N_4$ [M + H]$^+$ 139.0978; found 139.0978.

3-(Piperazin-1-yl)-1,2,4-triazine (12k): Column chromatography (15 % methanol in ethyl acetate) afforded **12k** (0.383 g, 74 % yield) as a yellow liquid. IR (neat): $\tilde{\nu}$ = 837, 918, 1003, 1034, 1057, 1119, 1169, 1262, 1335, 1443, 1512, 1555, 1655, 2851, 2913, 3291, 3387 cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.59–8.58 (d, J = 2.2 Hz, 1 H), 8.30–8.29 (d, J = 2.2 Hz, 1 H), 3.73–3.70 (m, 4 H), 3.07 (br. s, 2 H), 2.78–2.75 (m, 4 H) ppm. ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 160.8, 149.4, 140.2, 45.1, 44.0 ppm. HRMS (EI): calcd. for $C_7H_{11}N_5$ [M + H]$^+$ 166.1087; found 166.1087.

3-*n*-Propoxy-1,2,4-triazine (13a): Column chromatography (50 % ethyl acetate in hexanes) afforded **13a** (0.313 g, 72 % yield) as a yellow liquid. IR: $\tilde{\nu}$ = 860, 964, 988, 1022, 1045, 1065, 1100, 1153, 1300, 1335, 1354, 1427, 1470, 1520, 1551, 2878, 2936, 2967 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.88–8.87 (d, J = 1.9 Hz, 1 H), 8.37–8.36 (d, J = 2.0 Hz, 1 H), 4.42–4.38 (t, J = 6.7 Hz, 2 H), 1.83–1.77 (m, 2 H), 0.98–0.95 (t, J = 7.4 Hz, 3 H) ppm. ^{13}C NMR (101 MHz, CDCl$_3$): δ = 165.4, 150.8, 144.6, 70.2, 21.9, 10.2 ppm. HRMS (EI): calcd. for $C_6H_9N_3O$ [M + H]$^+$ 140.0818; found 140.0813.

3-(2,2,2-Trifluoroethoxy)-1,2,4-triazine (13b): Column chromatography (50 % ethyl acetate in hexanes) afforded **13b** (0.348 g, 62 % yield) as a yellow liquid. IR (neat): $\tilde{\nu}$ = 841, 880, 957, 999, 1045, 1072, 1103, 1153, 1262, 1331, 1381, 1404, 1435, 1539 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 9.07 (d, J = 2.2 Hz, 1 H), 8.51 (d, J = 2.2 Hz, 1 H), 4.98–4.92 (qd, J = 8.1, 0.9 Hz, 2 H) ppm. ^{13}C NMR (101 MHz, CDCl$_3$): δ = 164.4, 151.4, 146.2, 122.9, 64.2 ppm. ^{19}F NMR (376 MHz, CDCl$_3$): δ = –73.7 (s) ppm. HRMS (EI): calcd. for $C_5H_4F_3N_3O$ [M + H]$^+$ 180.0379; found 180.038.

3-[(1,1,1,3,3,3-Hexafluoropropan-2-yl)oxy]-1,2,4-triazine (13c): Column chromatography (50 % ethyl acetate in hexanes) afforded **13c** (0.423 g, 55 % yield) as a yellow liquid. IR (neat): $\tilde{\nu}$ = 872, 891, 1007, 1045, 1099, 1200, 1273, 1319, 1377, 1412, 1539, 1555, 1736, 2963 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 9.18 (d, J = 2.3 Hz, 1 H), 8.58 (d, J = 2.3 Hz, 1 H), 6.56–6.48 (hept, J = 5.9 Hz, 1 H) ppm. ^{13}C NMR (101 MHz, CDCl$_3$): δ = 163.8, 151.6, 147.3, 117.8, 70.0 ppm. ^{19}F NMR (376 MHz, CDCl$_3$): δ = –73.4 (s) ppm. HRMS (EI): calcd. for $C_6H_3F_6N_3O$ [M + H]$^+$ 248.0253; found 248.0249.

3-Phenoxy-1,2,4-triazine (13d): Column chromatography (50 % ethyl acetate in hexanes) afforded **13d** (0.336 g, 62 % yield) as a yellow solid; m.p. 52–54 °C. IR (neat): $\tilde{\nu}$ = 814, 872, 910, 1045, 1072, 1157, 1200, 1304, 1358, 1404, 1485, 1520, 1551, 1589 cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 9.26 (d, J = 2.3 Hz, 1 H), 8.73 (d, J = 2.3 Hz, 1 H), 7.50–7.46 (m, 2 H), 7.33–7.29 (m, 3 H) ppm. ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 165.8, 152.3, 152.3, 146.7, 129.9, 125.8, 121.4 ppm. HRMS (EI): calcd. for $C_9H_7N_3O$ [M + H]$^+$ 174.0662; found 174.0654.

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3-(4-Ethylphenoxy)-1,2,4-triazine (13e): Column chromatography (50 % ethyl acetate in hexanes) afforded **13e** (0.511 g, 81 % yield) as a yellow liquid. IR (neat): $\tilde{\nu}$ = 810, 845, 891, 1015, 1045, 1107, 1165, 1196, 1312, 1358, 1400, 1458, 1505, 1551, 2870, 2928, 2963 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.05 (d, J = 2.3 Hz, 1 H), 8.45 (d, J = 2.3 Hz, 1 H), 7.29–7.26 (m, 2 H), 7.16–7.13 (m, 2 H), 2.73–2.66 (q, J = 7.6 Hz, 2 H), 1.28–1.25 (t, J = 7.6 Hz, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.6, 150.9, 150.3, 145.7, 142.2, 129.3, 121.2, 28.4, 15.6 ppm. HRMS (EI): calcd. for $C_{11}H_{11}N_3O$ $[M + H]^+$ 202.0975; found 202.0969.

3-(4-Fluorophenoxy)-1,2,4-triazine (13f): Column chromatography (50 % ethyl acetate in hexanes) afforded **13f** (0.467 g, 78 % yield) as a yellow solid; m.p. 59–61 °C. IR (neat): $\tilde{\nu}$ = 823, 841, 868, 899, 1007, 1053, 1092, 1180, 1323, 1370, 1404, 1501, 1535, 1555, 3078 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.08–9.07 (d, J = 2.3 Hz, 1 H), 8.47–8.46 (d, J = 2.3 Hz, 1 H), 7.23–7.18 (m, 2 H), 7.16–7.10 (m, 2 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 116.7, 123.0, 146.0, 148.2, 151.0, 160.5, 166.4 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –116.4 (s) ppm. HRMS (EI): calcd. for $C_9H_6FN_3O$ $[M + H]^+$ 192.0568; found 192.0563.

3-(Benzyloxy)-1,2,4-triazine (13g): Column chromatography (50 % ethyl acetate in hexanes) afforded **13g** (0.470 g, 80 % yield) as a yellow solid; m.p. 67–69 °C. IR (neat): $\tilde{\nu}$ = 880, 988, 1026, 1103, 1165, 1231, 1323, 1359, 1381, 1416, 1454, 1493, 1543, 2886, 2955, 3024, 3086 cm^{-1}. ^1H NMR (400 MHz, $[D_6]$DMSO): δ = 9.17 (d, J = 2.3 Hz, 1 H), 8.71 (d, J = 2.3 Hz, 1 H), 7.52–7.50 (m, 2 H), 7.43–7.34 (m, 3 H), 5.54 (s, 2 H) ppm. ^{13}C NMR (101 MHz, $[D_6]$DMSO): δ = 165.0, 152.2, 145.8, 135.9, 128.5, 128.3, 128.3, 69.3 ppm. HRMS (EI): calcd. for $C_{10}H_9N_3O$ $[M + H]^+$ 188.0818; found 188.0816.

3-[2-(Trimethylsilyl)ethoxy]-1,2,4-triazine (13h): Column chromatography (50 % ethyl acetate in hexanes) afforded **13h** (0.507 g, 82 % yield) as a yellow liquid. IR (neat): $\tilde{\nu}$ = 833, 937, 961, 1015, 1038, 1099, 1153, 1177, 1246, 1319, 1343, 1378, 1431, 1470, 1520, 1551, 1697, 2897, 2951 cm^{-1}. ^1H NMR (400 MHz, $[D_6]$DMSO): δ = 9.11 (d, J = 2.3 Hz, 1 H), 8.65 (d, J = 2.3 Hz, 1 H), 4.57–4.53 (m, 2 H), 1.19–1.15 (m, 2 H), 0.06 (s, 9 H) ppm. ^{13}C NMR (101 MHz, $[D_6]$DMSO): δ = 165.0, 151.9, 145.4, 66.0, 16.8, 2.0, –1.5 ppm. HRMS (EI): calcd. for $C_8H_{15}N_3OSi$ $[M + H]^+$ 198.1057; found 198.1062.

3-(Prop-2-yn-1-yloxy)-1,2,4-triazine (13i): Column chromatography (50 % ethyl acetate in hexanes) afforded **13i** (0.332 g, 78 % yield) as a yellow solid; m.p. 51–53 °C. IR (neat): $\tilde{\nu}$ = 876, 964, 988, 1018, 1053, 1103, 1157, 1316, 1346, 1366, 1424, 1474, 1539, 1555, 2129, 2943, 2963, 3051, 3094, 3240 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.03–9.02 (d, J = 2.3 Hz, 1 H), 8.49–8.48 (d, J = 2.3 Hz, 1 H), 5.20–5.19 (d, J = 2.4 Hz, 2 H), 2.54–2.53 (t, J = 2.4 Hz, 1 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.8, 151.1, 145.6, 77.4, 75.9, 56.2 ppm. HRMS (EI): calcd. for $C_6H_5N_3O$ $[M + H]^+$ 136.0505; found 136.0502.

3-(3,3,3-Trifluoropropoxy)-1,2,4-triazine (13j): Column chromatography (50 % ethyl acetate in hexanes) afforded **13j** (0.451 g, 74 % yield) as a yellow liquid. IR (neat): $\tilde{\nu}$ = 826, 864, 910, 991, 1030, 1045, 1072, 1130, 1150, 1250, 1296, 1323, 1362, 1389, 1431, 1470, 1524, 1535, 1555, 2920, 2974 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.01 (d, J = 2.2 Hz, 1 H), 8.46 (d, J = 2.2 Hz, 1 H), 4.79–4.76 (t, J = 6.5 Hz, 2 H), 2.79–2.68 (qt, J = 10.4, 6.5 Hz, 2 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 165.0, 151.3, 145.5, 124.8, 61.6, 33.6 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –64.8 ppm. HRMS (EI): calcd. for $C_6H_6F_3N_3O$ $[M + H]^+$ 194.0536; found 194.0531.

3-Isopropoxy-1,2,4-triazine (13k): Column chromatography (50 % ethyl acetate in hexanes) afforded **13k** (0.307 g, 70 % yield) as a yellow liquid. IR (neat): $\tilde{\nu}$ = 864, 949, 1015, 1049, 1103, 1153, 1180, 1316, 1335, 1373, 1420, 1466, 1520, 1551, 2874, 2940, 2982 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.90–8.89 (d, J = 2.2 Hz, 1 H), 8.40–8.39 (d, J = 2.2 Hz, 1 H), 5.49–5.42 (sept, J = 6.2 Hz, 1 H), 1.44–1.43 (d, J = 6.2 Hz, 7 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 165.2, 151.0, 144.5, 72.1, 21.8 ppm. HRMS (EI): calcd. for $C_6H_9N_3O$ $[M + H]^+$ 140.0818; found 140.0818.

3-(2-Methoxyethoxy)-1,2,4-triazine (13l): Column chromatography (ethyl acetate) afforded **13l** (0.337 g, 69 % yield) as a yellow solid; m.p. 68–70 °C. IR (neat): $\tilde{\nu}$ = 853, 880, 930, 1007, 1042, 1057, 1099, 1126, 1157, 1192, 1238, 1281, 1327, 1346, 1373, 1400, 1431, 1454, 1539, 1555, 2816, 2839, 2905, 2936, 2997, 3051, 3094 cm^{-1}. ^1H NMR (400 MHz, $[D_6]$DMSO): δ = 9.15 (d, J = 2.3 Hz, 1 H), 8.68 (d, J = 2.3 Hz, 1 H), 4.59–4.56 (m, 2 H), 3.74–3.71 (m, 2 H), 3.31 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $[D_6]$DMSO): δ = 165.1, 152.1, 145.7, 69.7, 67.0, 58.1 ppm. HRMS (EI): calcd. for $C_6H_9N_3O_2$ $[M + H]^+$ 156.0768; found 156.0760.

2-[(1,2,4-Triazin-3-yl)oxy]-*N*,*N*-dimethylethan-1-amine (13m): Column chromatography (5 % methanol in dichloromethane) afforded **13m** (0.337 g, 64 % yield) as a yellow liquid. IR (neat): $\tilde{\nu}$ = 833, 864, 918, 953, 991, 1026, 1099, 1153, 1192, 1319, 1339, 1373, 1424, 1458, 1520, 1551, 1670, 2770, 2820, 2947, 3414 cm^{-1}. ^1H NMR (400 MHz, $[D_6]$DMSO): δ = 9.13–9.12 (d, J = 2.3 Hz, 1 H), 8.67–8.66 (d, J = 2.3 Hz, 1 H), 4.53–4.51 (t, J = 5.8 Hz, 2 H), 2.68–2.65 (t, J = 5.8 Hz, 2 H), 2.20 (s, 6 H) ppm. ^{13}C NMR (101 MHz, $[D_6]$DMSO): δ = 165.1, 152.0, 145.5, 65.7, 57.2, 45.4 ppm. HRMS (EI): calcd. for $C_7H_{12}N_4O$ $[M + H]^+$ 169.1084; found 169.1086.

5-{2-[(1,2,4-Triazin-3-yl)oxy]ethyl}-4-methylthiazole (13n): Column chromatography (ethyl acetate) afforded **13n** (0.428 g, 61 % yield) as a yellow solid; m.p. 103–105 °C. IR (neat): $\tilde{\nu}$ = 837, 876, 918, 988, 1011, 1042, 1107, 1161, 1188, 1297, 1316, 1350, 1408, 1435, 1458, 1532, 1555, 3040 cm^{-1}. ^1H NMR (400 MHz, $[D_6]$DMSO): δ = 9.15–9.14 (d, J = 2.3 Hz, 1 H), 8.84 (s, 1 H), 8.68–8.67 (d, J = 2.3 Hz, 1 H), 4.64–4.61 (t, J = 6.4 Hz, 2 H), 3.33–3.30 (t, J = 6.4 Hz, 2 H), 2.34 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $[D_6]$DMSO): δ = 164.9, 152.2, 150.9, 149.6, 145.8, 127.0, 67.8, 25.2, 14.7 ppm. HRMS (EI): calcd. for $C_9H_{10}N_4OS$ $[M + H]^+$ 223.0648; found 223.0653.

3-Cyclopropoxy-1,2,4-triazine (13o): Column chromatography (50 % ethyl acetate in hexanes) afforded **13o** (0.227 g, 53 % yield) as a yellow liquid. IR (neat): $\tilde{\nu}$ = 826, 860, 964, 1026, 1045, 1096, 1146, 1165, 1211, 1335, 1373, 1412, 1451, 1532, 1551, 1593, 3017, 3098 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.98 (d, J = 2.2 Hz, 1 H), 8.42 (d, J = 2.2 Hz, 1 H), 4.51–4.46 (m, 1 H), 0.89–0.86 (m, 4 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.6, 150.8, 145.2, 52.8, 6.0 ppm. HRMS (EI): calcd. for $C_6H_7N_3O$ $[M + H]^+$ 138.0662; found 138.0659.

2-[(1,2,4-Triazin-3-yl)oxy]-*N*,*N*-dimethylpropan-1-amine (13p): Column chromatography (5 % methanol in dichloromethane) afforded **13p** (0.296 g, 52 % yield) as a yellow liquid. IR (neat): $\tilde{\nu}$ = 837, 856, 945, 1038, 1099, 1134, 1153, 1207, 1265, 1319, 1331, 1373, 1420, 1520, 1551, 1670, 2770, 2820, 2940, 2978 cm^{-1}. ^1H NMR (400 MHz, $[D_6]$DMSO): δ = 9.10 (d, J = 2.3 Hz, 1 H), 8.65 (d, J = 2.3 Hz, 1 H), 5.45–5.40 (m, 1 H), 2.64–2.59 (dd, J = 12.9, 7.3 Hz, 1 H), 2.43–2.38 (dd, J = 12.9, 4.9 Hz, 1 H), 2.18 (s, 6 H), 1.34–1.32 (d, J = 6.2 Hz, 3 H) ppm. ^{13}C NMR (101 MHz, $[D_6]$DMSO): δ = 164.9, 151.9, 145.3, 72.0, 63.6, 45.8, 18.0 ppm. HRMS (EI): calcd. for $C_8H_{14}N_4O$ $[M + H]^+$ 183.1240; found 183.1237.

2-[(1,2,4-Triazin-3-yl)oxy]ethan-1-ol (13q): Column chromatography (2 % methanol in dichloromethane) afforded **13q** (0.144 g, 33 % yield) as a yellow liquid. IR (neat): $\tilde{\nu}$ = 823, 868, 922, 1030, 1157, 1319, 1339, 1377, 1424, 1462, 1524, 1555, 1690, 2947, 3333 cm^{-1}. ^1H NMR (400 MHz, $[D_6]$DMSO): δ = 9.14–9.13 (d, J = 2.3 Hz, 1 H), 8.68–8.67 (d, J = 2.3 Hz, 1 H), 4.93 (br. s, 1 H), 4.48–4.46 (m, 2 H), 3.79–3.76 (m, 2 H) ppm. ^{13}C NMR (101 MHz, $[D_6]$DMSO): δ = 165.2,

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152.0, 145.5, 69.7, 59.0 ppm. HRMS (EI): calcd. for $C_5H_7N_3O_2$ [M + H]$^+$ 142.0611; found 142.0607.

3-(*tert*-Butoxy)-1,2,4-triazine (13r): Column chromatography (50 % ethyl acetate in hexanes) afforded **13r** (0.133 g, 28 % yield) as a yellow liquid. IR (neat): $\tilde{\nu}$ = 826, 860, 910, 934, 1018, 1045, 1096, 1165, 1250, 1362, 1408, 1478, 1520, 1551, 2870, 2932, 2978 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.85–8.84 (d, J = 2.2 Hz, 1 H), 8.35–8.34 (d, J = 2.2 Hz, 1 H), 1.64 (s, 9 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 165.4, 150.5, 144.1, 83.6, 28.1 ppm. HRMS (EI): calcd. for $C_7H_{11}N_3O$ [M + H]$^+$ 154.0975; found 154.0979.

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[1] E. C. Taylor, J. E. Macor, J. L. Pont, *Tetrahedron* **1987**, *43*, 5145–5158.
[2] E. C. Taylor, J. E. Macor, *J. Org. Chem.* **1987**, *52*, 4280–4287.
[3] Y. Hajbi, F. Suzenet, M. Khouili, S. Lazar, G. Guillaumet, *Synlett* **2009**, *40*, 92–96.
[4] C. F. Ivy, S. V. Kotturi, H. A. Navarro, M. S. Wayne, B. P. Gilmour, F. L. Smith, B. H. Gabra, W. L. Dewey, *J. Med. Chem.* **2007**, *50*, 3388–3391.
[5] J. P. Olson, F. I. Carroll, *Synthesis* **2011**, 409–412.
[6] J. P. Olson, M. G. Gichinga, E. Butala, H. A. Navarro, B. P. Gilmour, F. I. Carroll, *Org. Biomol. Chem.* **2011**, *9*, 4276–4286.
[7] I. Leroy, E. Dupont-Passelaigue, S. Mialhe, D. Junquero, K. Valeille, PCT Int. Patent, WO 2011131593 A1 20111027, **2011**.
[8] E. Badarau, R. Bugno, F. Suzenet, A. J. Bojarski, A.-L. Fînaru, G. Guillaumet, *Bioorg. Med. Chem.* **2010**, *18*, 1958–1967.
[9] L. W. Ashcraft, G. Bergnes, S. Collibee, C. Chuang, J. Gardina, B. P. Morgan, A. R. Muci, X. Qian, A. Romero, J. Warrington, Z. Yang, PCT Int. Patent, WO 2011133920 A1 20111027, **2011**.
[10] K. Ban, S. Duffy, Y. Khakham, V. M. Avery, A. Hughes, O. Montagnat, K. Katneni, E. Ryan, J. B. Baell, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 6024–6029.
[11] F.-A. Alphonse, F. Suzenet, A. Keromnes, B. Lebret, G. Guillaumet, *Synlett* **2002**, 447–450.
[12] F.-A. Alphonse, F. Suzenet, A. Keromnes, B. Lebret, G. Guillaumet, *Synthesis* **2004**, 2893–2899.
[13] F.-A. Alphonse, F. Suzenet, A. Keromnes, B. Lebret, G. Guillaumet, *Org. Lett.* **2003**, *5*, 803–805.
[14] E. Garnier, J. Audoux, E. Pasquinet, F. Suzenet, D. Poullain, B. Lebret, G. Guillaumet, *J. Org. Chem.* **2004**, *69*, 7809–7815.
[15] Y. A. Azev, E. Lork, T. Djul'Ks, D. Gabel', *Pharm. Chem. J.* **2005**, *39*, 375–378.
[16] M. G. Gichinga, J. P. Olson, E. Butala, B. P. Gilmour, H. H. Navarro, F. I. Carroll, *Tetrahedron Lett.* **2011**, *52*, 3345–3346.
[17] Y. Hajbi, F. Suzenet, M. Khouili, S. Lazar, G. Guillaumet, *Synthesis* **2010**, 1349–1355.
[18] E. Badarau, F. Suzenet, A.-L. Fînaru, G. Guillaumet, *Eur. J. Org. Chem.* **2009**, 3619–3627.
[19] E. C. Taylor, J. L. Pont, *Tetrahedron Lett.* **1987**, *28*, 379–382.
[20] S. C. Benson, J. L. Gross, J. K. Snyder, *J. Org. Chem.* **1990**, *55*, 3257–3269.
[21] CCDC 1451306 (for **5a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.
[22] The pK_a of phenol is 9.95 and that of trifluoroethanol is 12.5; see: http://evans.rc.fas.harvard.edu/pdf/evans_pKa_Tablepdf.
[23] The pK_a of *n*-propanol is 16.1; see: http://www.drugbank.ca/drugs/DB03175.
[24] E. C. Taylor, J. L. Pont, J. C. Warner, *Tetrahedron* **1987**, *43*, 5159–5168.

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