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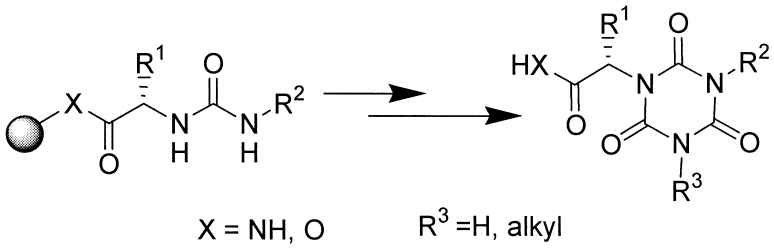

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Efficient Solid-Phase Synthesis of 1,3,5-Trisubstituted 1,3,5-Triazine-2,4,6-triones

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The solid-phase synthesis of 1,3-disubstituted and 1,3,5-trisubstituted 1,3,5-triazine-2,4,6-triones from MBHA and Wang resin is described. Reaction of resin-bound amino acids with isocyanates yield resin-bound ureas, which further react with chlorocarbonyl isocyanate in toluene at 65 °C to selectively afford the resin-bound 1,3-disubstituted 1,3,5-triazine-2,4,6-triones. Selective alkylation at the N-5 position of the resin-bound 1,3-disubstituted 1,3,5-triazine-2,4,6-triones was accomplished by treatment with alkyl halides in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). The desired products were cleaved from their solid support and obtained in good yield and purity. The method can be employed in production of toltrazuril analogue libraries for identification of new anticoccidial agents.

Combinatorial organic synthesis on solid supports has emerged as an important tool in lead structure identification and optimization in drug discovery.[1] Recently, the focus of this field of research, which initially involved the synthesis of peptides and oligonucleotides, is now on the synthesis of small organic molecules on the solid phase.[2] Heterocyclic compounds have received special attention in combinatorial synthesis because of their high degree of structural diversity and biologically interesting properties.[3]

Triazinetriones are an important class of molecules with pharmaceutical[4] and agricultural[5] utility including use as effective herbicides,[5a] as drugs against coccidosis,[5b] and as animal growth stimulators.[6] An example of such biologically interesting triazinetrione derivatives is toltrazuril (Figure 1). It has coccidiocidal action and damages all intracellular developmental stages of the schizogony cycles and of the gametogony phase and is an approved anticoccidial therapeutic.[7] Symmetrically trisubstituted triazinetriones have previously been synthesized in solution from isocyanates using a broad range of catalysts such as Lewis acids,[8] anions,[9] and organometallics.[10] However, most of these conventional methods require severe conditions and are not suitable for solid-phase synthesis. Other approaches to the synthesis of substituted triazinetriones are found in the patent literature,[11] in which they are generated by the cyclocondensation of isocyanate with ureas and diethyl carbonate or by the cyclocondensation of ureas with chlorocarbonyl isocyanate. As part of our ongoing efforts directed toward the solid-phase synthesis of small-molecule and heterocyclic libraries using amino acids and peptides as starting materials,[12] we report here an efficient strategy for the solid-phase synthesis of 1,3-disubstituted and 1,3,5-trisubstituted 1,3,5-triazine-2,4,6-triones from resin-bound amino acids.

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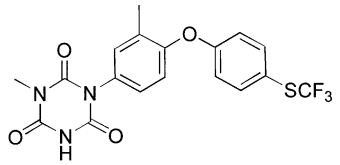

Figure 1. Toltrazuril.

Results and Discussion

1,3-Disubstituted 1,3,5-Triazine-2,4,6-triones (7) from *p*-Methylbenzhydrylamine (MBHA) Resin. The parallel solid-phase synthesis of 1,3-disubstituted 1,3,5-triazine-2,4,6-triones was carried out on the solid phase using the "tea-bag" methodology.[13] To demonstrate the general feasibility of the cyclization, we initially decided to alkylate the amide nitrogen of the linkage and then build the triazinetrione moiety on the support by reaction of chlorocarbonyl isocyanate with resin-bound urea **3**. The reaction sequence is illustrated in Scheme 1. Thus, Boc-protected amino acid was attached to the *p*-methylbenzhydrylamine resin using 1-hydroxybenzotriazole (HOBT) and *N*,*N*-diisopropylcarbodiimide (DIC) as coupling reagents in *N*,*N*-dimethylformamide (DMF) to form resin-bound *N*-*tert*-butyloxycarbonyl (Boc) amino acid **1**. The Boc group was removed using 55% trifluoroacetic acid (TFA) in dichloromethane (DCM). The resulting amine salt was neutralized, and the primary amine was then protected with triphenylmethyl chloride (TrtCl). The secondary amide was then selectively methylated in the presence of lithium *tert*-butoxide and methyl iodide.[14] Upon removal of the trityl group with 2% TFA in DCM, the resin was neutralized and then reacted with isocyanate to yield resin-bound urea **3**. The resin-bound 1,3-disubstituted 1,3,5-triazine-2,4,6-trione **4** was obtained following the treatment of the resin-bound urea **3** with chlorocarbonyl isocyanate. A variety of conditions were studied in order to optimize the cyclization. The conversion of **3** to **4** was completed using chlorocarbonyl isocyanate (6 equiv, 0.1 M) in toluene at 65

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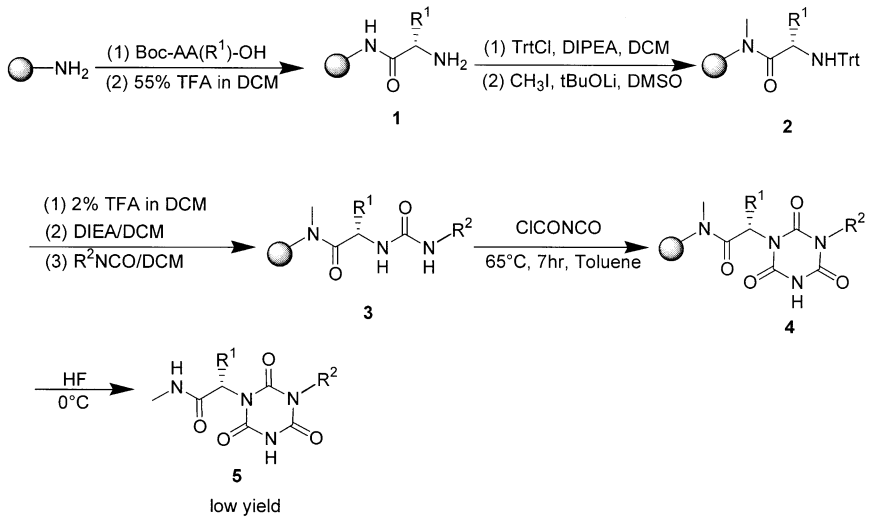
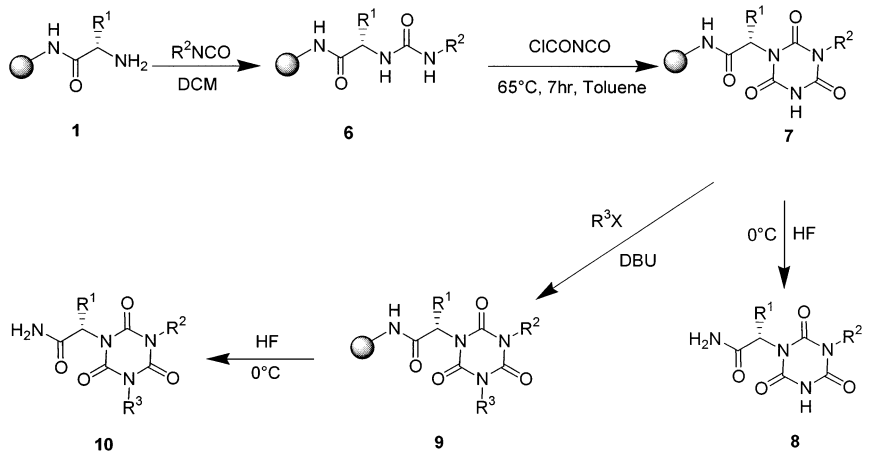
Scheme 1



Scheme 2

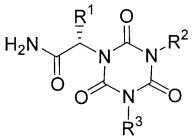


°C for 7 h. Product **5** was obtained following cleavage from the resin with HF. Unfortunately, the yield of crude product was low (<15%). The alkylation of the amide nitrogen of the resin linkage increases the acid sensitivity.[14] When Et_3N or K_2CO_3 was added as a base to the reactions, the yield was improved. However, the purity of the product was decreased. Presumably, the lower yield was caused by premature cleavage during the cyclization reaction due to the generation of HCl.

To overcome this problem, the reaction of chlorocarbonyl isocyanate with resin-bound urea **6**, which was not alkylated at the amide nitrogen and thus was more stable under acidic conditions, was investigated. On the basis of the above results, we reasoned that any byproduct formed with the amide group of the linker, which would increase the acid sensitivity, would be easily cleaved from the resin during the cyclization reaction. The resin-bound triazinetrione **7**, following HF cleavage, would then yield the desired products in good purity. As outlined in Scheme 2, the primary amine of **1** was reacted with an isocyanate in DCM for 3 h at room temperature to provide the resin-bound urea **6**. The reaction was conveniently monitored via the ninhydrin test.[15] The resin-bound urea **6** was reacted with chlorocarbonyl isocyanate in toluene at 65 °C for 7 h to yield the resin-bound 1,3-disubstituted 1,3,5-triazine-2,4,6-triones **7**. The desired products **8** were cleaved from the resin using HF for 1.5 h at 0 °C in moderate yield and good purity. The products were characterized by electrospray LC−MS under ESI conditions and by ^1H and ^{13}C NMR.

Selective Alkylation at the N-5 Position of the Resin-Bound 1,3-Disubstituted 1,3,5-Triazine-2,4,6-triones. Selective alkylation at the N-5 position of the resin-bound 1,3-disubstituted 1,3,5-triazine-2,4,6-triones **7** produced the possibility of alkylation of the linker amide group and O-alkylation. We first examined the reaction of **7** with alcohols under Mitsunobu conditions.[16] However, the purity of product **10** was only between 40% and 60%. Starting materials as well as some byproducts were observed in the LC−MS. We then examined the reaction of **7** with alkyl halides and a range of bases. When Bu^tOLi, Bu^tOK, NaH, or NaOMe was used as the base, the N-5 alkylation product **9** and the dialkylation byproducts were found as determined by LC−MS. Selective alkylation at the N-5 position of **7** was accomplished by treatment with alkyl halides in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (Scheme 2). The desired products **10** were cleaved from the resin using HF for 1.5 h at 0 °C in good purity. The results are listed in Table 1. Interestingly, the benzyl-substituted products were stable under the HF cleavage conditions used. O-alkylation and amide alkylation derivatives were not

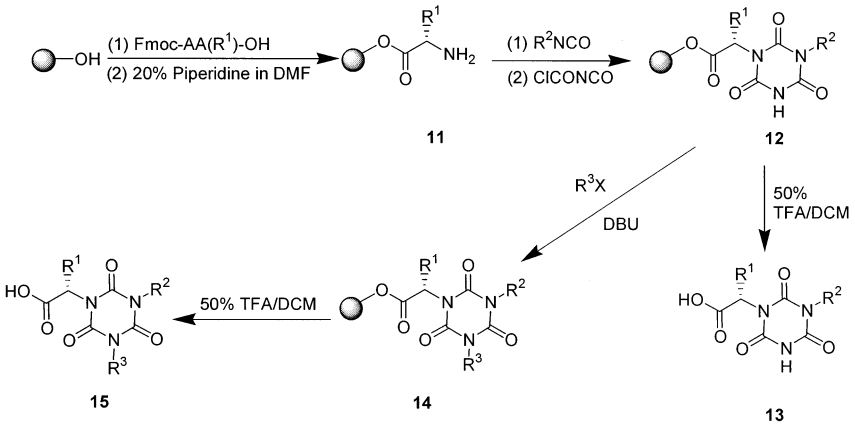
Table 1. Individual 1,3-Disubstituted and 1,3,5-Trisubstituted 1,3,5-Triazine-2,4,6-triones **8** and **10** from MBHA Resin



entry	product	R^1	R^2	R^3 [a]	yield,[b] %	purity,[c] %	MW (found)[d]
1	**8a**	$C_6H_5CH_2$	C_6H_5	H	72	83	352.9 ($[M + H]^+$)
2	**8b**	$C_6H_5CH_2$	*p*-Cl−C_6H_4	H	68	81	387.5 ($[M + H]^+$)
3	**8c**	$C_6H_5CH_2$	*p*-CH_3O−C_6H_4	H	67	85	382.9 ($[M + H]^+$)
4	**10a**	$C_6H_5CH_2$	CH_3CH_2	CH_3	58	76	318.7 ($[M + H]^+$)
5	**10b**	$C_6H_5CH_2$	C_6H_5	CH_3	62	79	366.8 ($[M + H]^+$)
6	**10c**	CH_3	C_6H_5	CH_3	63	82	290.7 ($[M + H]^+$)
7	**10d**	H	C_6H_5	CH_3	65	73	276.8 ($[M + H]^+$)
8	**10e**	CH_3	C_6H_5	CH_3CH_2	62	88	304.7 ($[M + H]^+$)
9	**10f**	CH_3	C_6H_5	$C_6H_5CH_2$	58	93	366.8 ($[M + H]^+$)
10	**10g**	CH_3	C_6H_5	*p*-Br−$C_6H_4CH_2$	61	91	445.2 ($[M + H]^+$)
11	**10h**	CH_3	C_6H_5	2-CH_3−$C_6H_4CH_2$	56	96	381.1 ($[M + H]^+$)
12	**10i**	$C_6H_5CH_2$	C_6H_5	*p*-Br−$C_6H_4CH_2$	67	82	521.8 ($[M + H]^+$)
13	**10j**	$C_6H_5CH_2$	*p*-Cl−C_6H_4	CH_3	71	76	400.8 ($[M + H]^+$)

[a] In the alkylated products, alkyl bromides were used except in the case of methyl, in which methyl iodide was used. [b] Yields are based on the weight of crude material and are relative to the initial loading of the resin. The isolated yields are listed in the Experimental Section. [c] The purity of the crude material was estimated on the basis of analytical traces at $\lambda = 214$ nm. [d] Confirmed by mass spectra (ESI).

Scheme 3



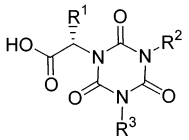
detected from LC−MS and NMR. In addition, no racemization was observed by ^{1}H NMR. It is noteworthy that the nature of the substituents (R^2) of the ureas appeared to have little effect on the cyclization reaction. Both aryl and alkyl (R^2) substituents of the ureas could be used in conjunction with the cyclization to create a variety of 1,3,5-disubstituted 1,3,5-triazine-2,4,6-triones.

1,3-Disubstituted 1,3,5-Triazine-2,4,6-trione and 1,3,5-Trisubstituted 1,3,5-Triazine-2,4,6-trione from Hydroxymethylpolystyrene (Wang) Resin. Our next objective was to synthesize 1,3,5-trisubstituted 1,3,5-triazine-2,4,6-triones bearing a carboxylic acid through the use of Wang resin. By use of the analogous protocol, an Fmoc-protected amino acid was attached to the Wang resin using *N*,*N*-diisopropyldiimide (DIC) and 4-(dimethylamino)pyridine (DMAP) as coupling reagents in DCM/DMF (5:1). The process was repeated twice to give the resin-bound Fmoc-protected amino acid **11**.[17] As outlined in Scheme 3, the Fmoc group was removed using 20% piperidine in DMF. The free amine was reacted with an isocyanate to form a resin-bound urea. Treatment of the resin-bound urea with chlorocarbonyl isocyanate yielded the 1,3-disubstituted 1,3,5-triazine-2,4,6-trione **12**. Product **13** was obtained following cleavage from the resin by treatment with trifluoroacetic acid in methylene chloride. The resin-bound 1,3-disubstituted 1,3-triazine-2,4,6-trione **12** was alkylated with alkyl halides in the presence of DBU to yield 1,3,5-triazine-2,4,6-triones **14**. Upon treatment with trifluoroacetic acid in methylene chloride, the desired product **15** was obtained in good yield and purity (Table 2). From the results obtained, the ester linker of Wang resin was stable under the cyclization and alkylation reaction conditions used.

Conclusion

Using the concept of "libraries from libraries",[18] we have demonstrated that 1,3-disubstituted and 1,3,5-trisubstituted 1,3,5-triazine-2,4,6-triones can be prepared on two different solid supports from common building blocks such as amino acids (R^1), isocyanates (R^2), and alkyl halides (R^3). This approach is a continuation of our efforts directed toward the synthesis of acyclic and heterocyclic compounds from amino acids and short peptides. The current method is well suitable for combinatorial library synthesis of a diverse collection of structurally novel triazinetriones with potential for anti-

Table 2. Individual 1,3-Disubstituted and 1,3,5-Trisubstituted 1,3,5-Triazine-2,4,6-triones **13** and **15** from Wang Resin



entry	product	R^1	R^2	R^3	yield,[a] %	purity,[b] %	MW (found)[c]
1	**13a**	$(CH_3)_2CH$	*p*-Cl−C_6H_4	H	75	81	340.1 ($[M + H]^+$)
2	**13b**	$(CH_3)_2CH$	*p*-CH_3−C_6H_4	H	76	86	320.1 ($[M + H]^+$)
3	**13c**	$C_6H_5CH_2$	*p*-CH_3O−C_6H_4	H	78	88	384.1 ($[M + H]^+$)
4	**15a**	$(CH_3)_2CH$	C_6H_5	$C_6H_5CH_2$	82	87	395.9 ($[M + H]^+$)
5	**15b**	$(CH_3)_2CH$	C_6H_5	2-CH_3−$C_6H_4CH_2$	75	82	410.0 ($[M + H]^+$)
6	**15c**	$C_6H_5CH_2$	CH_3CH_2	CH_3CH_2	75	85	334.0 ($[M + H]^+$)
7	**15d**	$C_6H_5CH_2$	CH_3CH_2	CH_2CHCH_2	78	86	346.0 ($[M + H]^+$)
8	**15e**	$C_6H_5CH_2$	CH_3CH_2	2-CH_3−$C_6H_4CH_2$	72	91	409.9 ($[M + H]^+$)
9	**15f**	$C_6H_5CH_2$	CH_3CH_2	*p*-NO_2−$C_6H_4CH_2$	79	92	440.7 ($[M + H]^+$)

[a] Yields are based on the weight of crude material and are relative to the initial loading of the resin. The isolated yields are listed in the Experimental Section. [b] The purity of the crude material was estimated on the basis of analytical traces at $\lambda = 214$ nm. [c] Confirmed by mass spectra (ESI).

coccidial activity. The preparation of a positional scanning combinatorial library[19] containing 11 200 ($28R^1 \times 20R^2 \times 20R^3$) different triazinetriones and its screening in different assays for the identification of active compounds will be reported in due course.

Experimental Section

p-Methylbenzhydrylamine (MBHA) resin, 1% divinylbenzene (100−200 mesh, 1 mequiv/g substitution), hydroxymethyl polystyrene (Wang) resin (1% divinylbenzene, 100−200 mesh, 0.96 mequiv/g substitution), and *N*,*N*′-diisopropylcarbodiimide (DIC) were purchased from Chem Impex Int. (Wood Dale, IL). Boc-amino acid derivatives and *N*-hydroxybenzotriazole (HOBt) were purchased from Calbiochem-Novabiochem Corp. (San Diego, CA) and Bachem Bioscience Inc. (Philadelphia, PA). Trifluoroacetic acid (TFA) and HF were purchased from Halocarbon (River Edge, NJ) and Air Products (San Marcos, CA), respectively. All other reagents and anhydrous solvents were purchased from Aldrich Chemical Co. (Milwaukee, WI). Analytical RP-HPLC was performed on a Beckman system Gold instrument (Fullerton, CA). Samples were analyzed using a Vydac 218TP54 C18 column (0.46 cm × 25 cm). LC−MS (APCI) data were recorded on a Finnigan Mat LCQ mass spectrometer (ThermoQuest Corporation, CA) at 214 nm using a Betasil C18, 3 μm, 100 Å, 3 mm × 50 mm column. Preparative RP-HPLC was performed on a Waters DeltaPrep preparative HPLC (Millipore) using a Vydac 218TP1022 C18 column (2.2 cm × 25 cm).

Typical Procedure for the Individual Synthesis of 1,3-Disubstituted 1,3,5-Triazine-2,4,6-triones (8) from *p*-Methylbenzhydrylamine (MBHA) Resin. A polypropylene mesh packet was sealed with 100 mg of MBHA resin (1 mequiv/g, 100−200 mesh).[20] Reactions were carried out in polypropylene bottles. The resin was washed with dichloromethane (DCM), neutralized with 5% diisopropylethylamine (DIEA) in DCM, and washed with DCM. The first Boc-L-amino acid (6 equiv, 0.1 M) was coupled using DIC (6 equiv, 0.1 M) and HOBt (6 equiv, 0.1 M) in anhydrous DMF for 2 h. The resin was washed with DMF (three times), DCM (three times), and MeOH (three times), and the Boc was deprotected using 55% TFA in DCM for 30 min, followed by washing with DCM (two times), 2-propanol (IPA) (two times), and DCM (two times). After neutralization, the resin was treated with isocyanate (6 equiv) in anhydrous DCM overnight to yield the ureas. Completeness of the coupling was verified by the ninhydrin test. The resin was washed with DCM (two times), IPA (two times), and DCM (two times). The resin-bound urea was reacted with chlorocarbonyl isocyanate (6 equiv, 0.1 M) in anhydrous toluene at 65 °C for 7 h to yield the resin-bound 1,3-disubstituted 1,3,5-triazine-2,4,6-triones **7**. After being washed with DMF (three times), DCM (three times), and MeOH (three times), the resin was cleaved by anhydrous HF at 0 °C for 1.5 h.[21] The cyclization product was extracted with 95% acetic acid in H_2O and lyophilized. Following purification by RP-HPLC, the product was characterized by electrospray LC−MS and ^1H and ^{13}C NMR.

Selective N-Alkylation of 1,3-Disubstituted 1,3,5-Triazine-2,4,6-triones (10). To the resin **7** in THF was added 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 10 equiv, 0.1 M). After the mixture was shaken for 30 min, excess base was removed by cannulation. The individual alkylating agent (5 equiv, 0.1 M) in DMSO was then added. The solution was vigorously shaken for 4 h at room temperature. After being washed with DMF (three times), DCM (three times), and MeOH (three times), the resin was cleaved by anhydrous HF at 0 °C for 1.5 h and product **10** was extracted with 95% acetic acid in H_2O and lyophilized. Following purification by RP-HPLC, the product was characterized by electrospray LC−MS and ^1H and ^{13}C NMR.

Typical Procedure for the Individual Synthesis of 1,3,5-Trisubstituted 1,3,5-Triazine-2,4,6-triones from Hydroxymethylpolystyrene (Wang) Resin (13, 15). A polypropylene mesh packet was sealed with 100 mg of Wang resin (0.94 mequiv/g, 100−200 mesh). Reactions were carried out in polypropylene bottles. A solution of *N*-Fmoc-L-amino acid (3 equiv, 0.1 M), DMAP (0.3 equiv), and DIC (3 equiv, 0.1 M) in anhydrous DCM/DMF (5:1) was added to the resin. The mixture was shaken at room temperature for 2 h. The

resin was washed with DMF (three times) and CH_2Cl_2 (three times). The loading process was repeated to ensure completion and afforded **11**. The Fmoc deprotection was performed using 20% piperidine in DMF for 30 min, followed by washing with DCM (two times), 2-propanol (IPA) (two times), and DCM (two times). The resin was treated with isocyanate (6 equiv, 0.1 M) in anhydrous DCM overnight to yield the urea. The resin-bound urea was reacted with chlorocarbonyl isocyanate (6 equiv, 0.1 M) in anhydrous toluene at 65 °C for 7 h to yield the resin-bound 1,3-disubstituted 1,3,5-triazine-2,4,6-trione **12**. After being washed with DMF (three times), MeOH (three times), and DCM (three times), the resin was cleaved with 50% TFA/DCM for 1 h. The solution was concentrated to give the cyclization product **13**. To the resin-bound 1,3-disubstituted 1,3,5-triazine-2,4,6-triones **12** was added 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU, 10 equiv, 0.1 M) in THF. The reaction mixture was shaken for 30 min and drained. The individual alkylating agent (5 equiv, 0.1 M) in DMSO was added. The solution was vigorously shaken for 4 h at room temperature. After being washed with DMF (three times), DCM (three times), and MeOH (three times), the resin was cleaved with 50% TFA/DCM for 1 h. The solution was concentrated to give product **15**. Following purification by RP-HPLC, the product was characterized by electrospray LC−MS and ^{1}H and ^{13}C NMR.

(2*S*)-3-Phenyl-2-(2,4,6-trioxo-3-phenyl-1,3,5-triazinan-1-yl)propanamide (8a). Yield: 32%. LC−MS (ESI), *m*/*z*: 352.9 (M + H$^+$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.35−3.40 (m, 2H), 5.5−5.53 (t, J = 7.5 Hz, 1H), 6.43 (s, 1H), 6.69 (s, 1H), 6.97 (s, 2H), 7.14−7.15 (d, J = 6.8 Hz, 2H), 7.26−7.39 (m, 6H), 9.63 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 34.4, 56.9, 127.5, 128.4, 129.2, 129.3, 129.7, 129.8, 133.1, 135.9, 148.3, 148.6, 149.6, 172.6.

(2*S*)-2-[3-(4-Chlorophenyl)-2,4,6-trioxo-1,3,5-triazinan-1-yl]-3-phenylpropanamide (8b). Yield: 28%. LC−MS (ESI) *m*/*z*: 387.5 (M + H$^+$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.32−3.38 (m, 2H), 5.51−5.54 (t, J = 7.5 Hz, 1H), 6.54 (s, 1H), 6.71 (s, 1H), 6.84 (s, 2H), 7.12 (s, 2H), 7.26−7.29 (m, 5H), 10.02 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 34.4, 56.9, 127.7, 129.2, 129.8, 131.5, 135.7, 135.8, 148.2, 148.7, 149.5, 172.5.

(2*S*)-2-[3-(4-Methoxyphenyl)-2,4,6-trioxo-1,3,5-triazinan-1-yl]-3-phenylpropanamide (8c). Yield: 41%. LC−MS (ESI), *m*/*z*: 382.9 (M + H$^+$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.33−3.39 (m, 2H), 3.75 (s, 1H), 5.51−5.55 (t, J = 7.5 Hz, 1H), 6.51 (s, 1H), 6.67 (s, 1H), 6.86 (s, 4H), 7.12−7.27 (m, 5H), 9.77 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 34.3, 55.6, 56.9, 114.9, 125.5, 127.6, 129.1, 129.3, 129.5, 136.1, 148.6, 148.7, 149.8, 160.3, 172.5.

(2*S*)-2-(3-Ethyl-5-methyl-2,4,6-trioxo-1,3,5-triazinan-1-yl)-3-phenylpropanamide (10a). Yield: 38%. LC−MS (ESI), *m*/*z*: 318.7 (M + H$^+$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.09−1.12 (t, J = 7.1 Hz, 3H), 3.25 (s, 3H), 3.44−3.47 (m, 2H), 3.82−3.86 (q, J = 7.1 Hz, 2H), 5.51−5.65 (t, J = 7.5 Hz, 1H), 5.99 (s, 1H), 6.31 (s, 1H), 7.16−7.29 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.0, 29.5, 34.8, 38.7, 57.3,-127.7, 129.1, 129.2, 136.0, 148.7, 149.1, 171.8.

(2*S*)-2-(3-Methyl-2,4,6-trioxo-5-phenyl-1,3,5-triazinan-1-yl)-3-phenylpropanamide (10b). Yield: 41%. LC−MS (ESI), *m*/*z*: 366.8 (M + H$^+$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.31 (s, 3H), 3.48−3.49 (d, J = 8.3 Hz, 2H), 5.67−5.71 (t, J = 7.5 Hz, 1H), 6.03 (s, 1H), 6.45 (s, 1H), 7.07−7.48 (m, 10H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 29.9, 34.8, 57.5, 127.9, 128.4, 129.2, 129.3, 129.7, 133.7, 135.9, 148.8, 148.9, 149.1, 171.9.

(2*S*)-2-(3-Methyl-2,4,6-trioxo-5-phenyl-1,3,5-triazinan-1-yl)propanamide (10c). Yield: 36%. LC−MS (ESI), *m*/*z*: 290.7 (M + H$^+$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.69−1.71 (d, J = 6.9 Hz, 3H), 3.39 (s, 3H), 5.39−5.43 (q, J = 7.1 Hz, 1H), 5.99 (s, 1H), 6.18 (s, 1H), 7.26−7.51 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 15.1, 29.9, 52.6, 128.6, 129.7, 129.8, 133.5, 148.8, 149.1, 172.4.

2-(3-Methyl-2,4,6-trioxo-5-phenyl-1,3,5-triazinan-1-yl)-acetamide (10d). Yield: 33%. LC−MS (ESI), *m*/*z*: 276.8 (M + H$^+$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.39 (s, 3H), 4.58 (s, 2H), 5.84 (brs, 1H), 7.26−7.49 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 29.9, 44.6, 128.6, 129.6, 129.7, 133.9, 149.2, 149.4, 168.5.

(2*S*)-2-(3-Ethyl-2,4,6-trioxo-5-phenyl-1,3,5-triazinan-1-yl)propanamide (10e). Yield: 47%. LC−MS (ESI), *m*/*z*: 304.7 (M + H$^+$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.28−1.31 (t, J = 7.1 Hz, 3H), 1.69−1.71 (d, J = 7.0 Hz, 3H), 3.98−4.02 (q, J = 7.0 Hz, 2H), 5.39−5.43 (q, J = 7.1 Hz, 1H), 5.95 (s, 1H), 6.15 (s, 1H), 7.25−7.50 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.3, 15.1, 39.2, 52.5, 128.6, 129.6, 129.7, 133.8, 148.6, 148.7, 148.9, 172.3.

(2*S*)-2-(3-Benzyl-2,4,6-trioxo-5-phenyl-1,3,5-triazinan-1-yl)propanamide (10f). Yield: 48%. LC−MS (ESI), *m*/*z*: 366.8 (M + H$^+$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.69−1.70 (d, J = 7.0 Hz, 3H), 5.06−5.12 (m, 2H), 5.39−5.43 (q, J = 7.0 Hz, 1H), 5.97 (s, 1H), 6.44 (s, 1H), 7.25−7.50 (m, 10H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 15.0, 46.8, 52.6, 128.6, 128.9, 129.7, 133.7, 135.6, 148.7, 148.9, 149.0, 172.7.

(2*S*)-2-[3-(4-Bromobenzyl)-2,4,6-trioxo-5-phenyl-1,3,5-triazinan-1-yl]propanamide (10g). Yield: 43%. LC−MS (ESI), *m*/*z*: 445.2 (M + H$^+$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.69−1.71 (d, J = 7.0 Hz, 3H), 5.06−5.12 (dd, J = 5.2, 14.1 Hz, 2H), 5.39−5.44 (q, J = 7.0 Hz, 1H), 5.98 (s, 1H), 6.60 (s, 1H), 7.25−7.50 (m, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 15.1, 46.2, 52.7, 122.8, 128.5, 129.7, 131.5, 132.1, 133.6, 134.5, 148.6, 148.8, 148.9, 172.7.

(2*S*)-2-[3-(2-Methylbenzyl)-2,4,6-trioxo-5-phenyl-1,3,5-triazinan-1-yl]propanamide (10h). Yield: 38%. LC−MS (ESI), *m*/*z*: 381.1 (M + H$^+$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.69−1.71 (d, J = 7.0 Hz, 3H), 2.42 (s, 3H), 5.12 (s, 2H), 5.42−5.46 (q, J = 7.0 Hz, 1H), 6.08 (s, 1H), 6.83 (s, 1H), 7.16−7.50 (m, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.9, 19.5, 44.1, 52.6, 126.5, 127.1, 128.1, 128.5, 129.7, 130.8, 133.6, 133.7, 136.4, 148.8, 148.9, 149.1, 173.6.

(2*S*)-2-[3-(4-Bromobenzyl)-2,4,6-trioxo-5-phenyl-1,3,5-triazinan-1-yl]propanamide (10i). Yield: 36%. LC−MS (ESI), *m*/*z*: 521.8 (M + H$^+$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.39−3.48 (m, 2H), 4.86−4.98 (dd, J = 14.2, 33.5 Hz, 2H), 5.65−5.68 (dd, J = 2.6, 7.1 Hz, 1H), 6.14 (s, 1H), 6.74 (s, 1H), 7.05−7.46 (m, 14H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 34.4, 45.9, 57.3, 122.6, 127.7, 128.3, 129.1, 129.7, 131.1, 131.9, 133.5, 134.4, 135.4, 148.6, 148.7, 148.8, 172.5.

(2*S*)-2-[3-(4-Chlorophenyl)-5-methyl-2,4,6-trioxo-1,3,5-triazinan-1-yl]-3-phenylpropanamide (10j). Yield: 31%.

LC−MS (ESI), *m*/*z*: 400.8 ($M + H^+$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.31 (s, 3H), 3.47−3.49 (d, J = 8.3 Hz, 2H), 5.66−5.69 (t, J = 8.4 Hz, 1H), 6.06 (s, 1H), 6.63 (s, 1H), 7.00−7.43 (m, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 29.9, 34.8, 57.4, 127.9, 129.2, 129.3, 129.8, 129.9, 132.1, 135.7, 135.8, 148.6, 148.7, 148.9, 172.2.

(2*S*)-2-[3-(4-Chlorophenyl)-2,4,6-trioxo-1,3,5-triazinan-1-yl]-3-methylbutanoic Acid (13a). Yield: 28%. LC−MS (ESI), *m*/*z*: 340.1 ($M + H^+$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.89 (d, J = 6.9 Hz, 3H), 1.21 (d, J = 6.9 Hz, 3H), 2.66 (m, 1H), 4.93 (d, J = 9.1 Hz, 1H), 7.16−7.18 (d, J = 8.4 Hz, 2H), 7.42−7.44 (d, J = 8.4 Hz, 2H), 9.47 (brs, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 19.3, 21.9, 27.9, 60.8,129.9, 130.0, 131.4, 135.9, 148.1, 148.5, 149.5, 173.0.

(2*S*)-3-Methyl-2-[3-(4-methylphenyl)-2,4,6-trioxo-1,3,5-triazinan-1-yl]butanoic Acid (13b). Yield: 32%. LC−MS (ESI), *m*/*z*: 320.1 ($M + H^+$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.90 (d, J = 6.8 Hz, 3H), 1.21 (d, J = 6.8 Hz, 3H), 2.39 (s, 1H), 2.66 (m, 1H), 4.934 (d, J = 9.2 Hz, 1H), 7.11−7.12 (d, J = 8.2 Hz, 2H), 7.26−7.28 (d, J = 8.2 Hz, 2H), 9.44 (brs, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 19.3, 21.5, 22.0, 27.6, 60.7, 128.2, 130.4, 130.5, 140.0, 148.5, 148.7, 149.8, 173.2.

(2*S*)-2-[3-(4-Methoxyphenyl)-2,4,6-trioxo-1,3,5-triazinan-1-yl]-3-phenylpropanoic Acid (13c). Yield: 35%.LC−MS (ESI), *m*/*z*: 384.1 ($M + H^+$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.40−3.45 (m, 1H), 3.50−3.54 (m, 1H), 3.78 (s, 1H), 5.61−5.64 (dd, J = 5.1, 5.7 Hz, 1H), 6.89 (s, 4H), 7.16−7.31 (m, 4H), 9.32 (brs, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 34.4, 55.7, 56.2, 114.9, 125.4, 127.5, 128.9, 129.4, 129.5, 136.2, 148.3, 148.4, 149.5, 160.3, 172.8.

(2*S*)-2-(3-Benzyl-2,4,6-trioxo-5-phenyl-1,3,5-triazinan-1-yl)-3-methylbutanoic Acid (15a). Yield: 35%. LC−MS (ESI), *m*/*z*: 395.9 ($M + H^+$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.88 (d, J = 6.8 Hz, 3H), 1.23 (d, J = 6.8 Hz, 3H), 2.71 (m, 1H), 5.03 (d, J = 9.2 Hz, 1H), 5.11 (d, J = 7.6 Hz, 2H), 7.23−7.26 (m, 2H), 7.31−7.35 (m, 2H), 7.43−7.49 (m, 4H), 9.44 (brs, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 19.2, 22.1, 27.9, 46.8, 51.1, 128.5, 128.9, 129.3, 129.7, 133.7, 135.7, 148.8, 148.9, 149.3, 173.6.

(2*S*)-3-Methyl-2-[3-(2-methylbenzyl)-2,4,6-trioxo-5-phenyl-1,3,5-triazinan-1-yl]butanoic Acid (15b). Yield: 38%. LC−MS (ESI), *m*/*z*: 410.1 ($M + H^+$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.91 (d, J = 7.0 Hz, 3H), 1.25 (d, J = 7.0 Hz, 3H), 2.42 (s, 3H), 2.73 (m, 1H), 5.04 (d, J = 9.2 Hz, 1H), 5.15 (s, 2H), 7.17−7.25 (m, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 19.3, 19.5, 22.1, 27.9, 29.9, 44.2, 61.2, 126.5, 126.7, 127.9, 128.5, 129.7, 130.8, 133.6, 133.7, 136.3, 148.9, 149.0, 149.4, 173.1.

(2*S*)-2-(3,5-Diethyl-2,4,6-trioxo-1,3,5-triazinan-1-yl)-3-phenylpropanoic acid (15c). Yield: 38%. LC−MS (ESI), *m*/*z*: 334.0 ($M + H^+$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.10 (t, J = 6.9 Hz, 6H), 3.41−3.54 (m, 2H), 3.81−3.86 (dd, J = 7.0, 7.2 Hz, 4H), 5.65−5.68 (dd, J = 4.8, 5.8 Hz, 1H), 7.12−7.25 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.1, 34.4, 38.5, 56.0, 127.3, 128.8, 129.3, 136.3, 148.3, 148.4, 173.9.

(2*S*)-2-(3-Allyl-5-ethyl-2,4,6-trioxo-1,3,5-triazinan-1-yl)-3-phenylpropanoic Acid (15d). Yield: 41%. LC−MS (ESI), *m*/*z*: 346.0 ($M + H^+$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.09 (t, J = 6.9 Hz, 3H), 3.41−3.55 (m, 2H), 3.81−3.86 (dd, J = 7.0, 7.2 Hz, 2H), 4.38 (d, J = 7.0 Hz, 2H), 5.16 (d, J = 10.2 Hz, 1H), 5.65−5.68 (dd, J = 4.8, 5.8 Hz, 1H), 5.71−5.75 (m, 2H), 7.12−7.25 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.1, 34.4, 38.6, 44.9, 56.1, 118.5, 127.3, 128.8, 129.3, 130.7, 136.2, 148.2, 148.4, 148.5, 173.9.

(2*S*)-2-[3-Ethyl-5-(2-methylbenzyl)-2,4,6-trioxo-1,3,5-triazinan-1-yl]-3-phenylpropanoic Acid (15e). Yield: 39%. LC−MS (ESI), *m*/*z*: 409.9 ($M + H^+$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.11 (t, J = 6.9 Hz, 3H), 2.35 (s, 2H), 3.47−3.51 (m 2H), 3.84−3.88 (dd, J = 7.0, 7.2 Hz, 2H), 4.92−5.01 (dd, J = 11.3, 15.4 Hz, 2H), 5.72−5.75 (dd, J = 4.8, 5.8 Hz, 1H), 7.09−7.26 (m, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.1, 19.4, 29.9, 34.3, 38.7, 43.8, 56.1, 125.9, 126.4, 127.3, 127.7, 128.8, 129.3, 130.7, 133.5, 135.9, 136.1, 148.3, 148.5, 148.9, 173.8.

(2*S*)-2-[3-Ethyl-5-(4-nitrobenzyl)-2,4,6-trioxo-1,3,5-triazinan-1-yl]-3-phenylpropanoic Acid (15f). Yield: 42%. LC−MS (ESI), *m*/*z*: 440.7 ($M + H^+$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.11 (t, J = 6.8 Hz, 3H), 3.41−3.55 (m, 2H), 3.41−3.46 (m, 1H), 3.51−3.56 (dd, J = 5.6, 8.5 Hz, 1H), 3.83−3.88 (dd, J = 7.0, 7.2 Hz, 2H), 4.98 (d, J = 14.8 Hz, 2H), 5.06 (d, J = 14.8 Hz, 1H), 5.68−5.71 (dd, J = 4.8, 5.8 Hz, 1H), 7.05−7.32 (m, 7H), 8.15 (d, J = 8.4 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.0, 34.3, 38.9, 45.5, 56.3, 124.1, 127.4, 128.8, 129.2, 129.3, 135.9, 142.7, 147.9, 148.1, 148.4, 148.7, 173.8.

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Supporting Information Available. LC−MS and ^{1}H and ^{13}C NMR spectra of **8a−c**, **10a−j**, **13a−c**, **15b−f** and a listing of building blocks used for the library. This material is available free of charge via the Internet at http://pubs.acs.org.

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