5-Lipoxygenase Inhibitors: Synthesis and Structure−Activity Relationships of a Series of 1-Aryl-2*H*,4*H*-tetrahydro-1,2,4-triazin-3-ones

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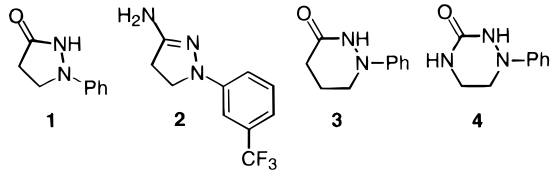
Synthetic routes were developed to access a variety of novel 1-aryl-2*H*,4*H*-tetrahydro-1,2,4-triazin-3-one analogs which were evaluated as 5-lipoxygenase (5-LO) inhibitors. The parent structure, 1-phenylperhydro-1,2,4-triazin-3-one (**4**), was found to be a selective inhibitor of 5-LO in broken cell, intact cell, and human blood assays with IC_{50} values of 5−21 μM. In a rat anaphylaxis model, **4** blocked leukotriene formation with an $ED_{50} = 7$ mg/kg when administered orally. Compound **4** exhibited selectivity for inhibition of 5-LO with little activity against related enzymes: 12-LO from human platelets, 15-LO from soybean, and cyclooxygenase (COX) from sheep seminal vesicle. In pilot subacute toxicity testing, **4** did not produce methemoglobinemia in rats (400 mg/kg po daily for 9 days) or in dogs (200 mg/kg po daily for 28 days). These results indicated that the triazinone structure provided a 5-LO inhibitor template devoid of the toxicity problems observed in the related phenidone (**1**) and pyridazinone (**3**) classes of 5-LO inhibitors. The parent compound **4** is a selective, orally bioavailable 5-LO inhibitor which can serve as a useful reference standard for *in vivo* pharmacological studies involving leukotriene-mediated phenonmena.

Introduction

Selective inhibition of 5-lipoxygenase (5-LO) provides a definitive means to limit the pathological effects of all leukotrienes and their metabolites.[1] The 5-LO inhibitor, zileuton,[2] has demonstrated therapeutic benefit in the treatment of asthma.[3] Over the past decade, we have investigated several structural classes of 5-LO inhibitors with the objective of identifying suitable orally active 5-LO inhibitors for clinical study to evaluate the role of leukotrienes in human diseases.[4] This report describes a series of 1-aryl-2*H*,4*H*-tetrahydro-1,2,4-triazin-3-ones with oral activity as selective 5-LO inhibitors which will be referred to simply as triazinones.

Phenidone (**1**)[5] was one of the earliest orally active inhibitors of 5-LO to be discovered. Animal studies revealed that **1** and several analogs thereof were found to be toxic due to methemoglobin formation upon repeated dosing.[6,7] The related aminopyrazoline series of 5-LO inhibitors, represented by BW-755C (**2**),[8] was also found to cause methemoglobinemia.[9] The Sterling group also investigated 1-phenyl-3-pyrazolidinones and found hematologic toxicity to be a limiting factor.[10] The redox properties of 1-phenyl-3-pyrazolidinones were likely linked to the propensity for causing methemoglobinemia.[11] We tested the hypothesis that the inhibition of 5-LO by 1-phenyl-3-pyrazolidinones was not entirely due to a nonspecific redox interaction by examining the corresponding six-membered analog, 1-phenyl-2*H*-tetrahydropyridazin-3-one (A-53612, **3**).[12]

The cyclic hydrazide, **3** was found to be a selective orally active inhibitor of 5-LO.[13,14] The increased inhibitory selectivity of **3** for 5-LO compared to phenidone supported the hypothesis that by ring expansion the inhibitory component due to nonspecific antioxidant activity observed for the five-membered phenidone



analogs was reduced.[15] In contrast to phenidone, the homolog **3** did not convert hemoglobin to methemoglobin *in vitro* in whole blood from various species including humans. However, in pilot toxicity studies, repeated 400 mg/kg daily oral doses of **3** resulted in the appearance of Heinz bodies in red blood cells and progressive methemoglobinemia. These unexpected results suggested that a metabolite of **3** might be responsible for the toxicity. None of the metabolites identified in the rat, accounting for about 92% of the radioactivity, converted hemoglobin to methemoglobin *in vitro* up to 400 μM. We therefore were left to rationalize that *in vivo* hydrolysis of **3** might form a reactive phenylhydrazide intermediate **3b** (Scheme 1), which was not isolated as it may have formed adducts with macromolecules. A reactive phenylhydrazine intermediate like **3b** might be a likely source of the observed methemoglobinemia since it is known that phenylhydrazine rapidly converts human oxyhemoglobin to methemoglobin.[16] To test this hypothesis, we synthesized the novel heterocycle, 1-phenyl-2*H*,4*H*-tetrahydro-1,2,4-triazin-3-one (**4**), which was predicted to have increased stability toward *in vivo* metabolic hydrolysis due to its cyclic urea functionality. The biological properties and structure−activity relationships of this new series of triazinone 5-LO inhibitors were investigated.

Chemistry

Several synthetic routes were developed to access a variety of novel 1-aryl-2*H*,4*H*-tetrahydro-1,2,4-triazin-3-one analogs. The first synthesis of the parent compound, 1-phenyl-2*H*,4*H*-tetrahydro-1,2,4-triazin-3-one

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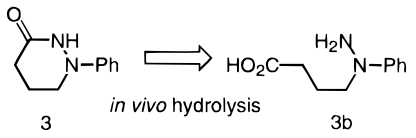
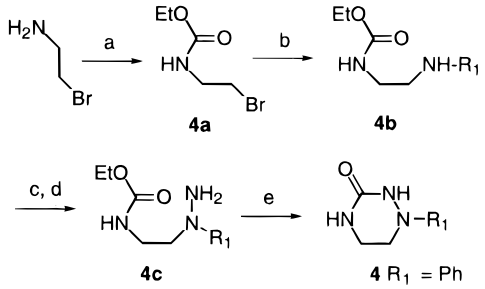
Scheme 1. Hypothetical *in Vivo* Hydrolysis of Pyridazinones to Toxic Phenylhydrazine Intermediates



3 3b

Scheme 2. Method A: Synthesis of Triazinones **4**–**9**, **11**, **12**, and **14**–**17** from 1-Amino-2-haloethanes[a]



[a] Reagents: (a) $ClCO_2Et$, Et_3N, CH_2Cl_2, 0 °C, 1 h; (b) $EtN(iPr)_2$, NH_2-R_1, toluene, 80 °C, 24 h; (c) $NaNO_2$, concentrated HCl, H_2O, 5 °C, 2 h; (d) Zn dust, H_2O, CH_3CO_2H, 5–15 °C, 1 h then room temperature for 1 h; (e) EtMgBr, CH_2Cl_2, −40 °C, 0.5 h then 40 °C, 48 h.

(**4**), was accomplished by the sequence of reactions illustrated in Scheme 2. Bromoethylamine was converted to the corresponding ethoxycarbamate **4a** which was then reacted with aniline to provide the intermediate ethyl *N*-[(phenylamino)ethyl]carbamate **4b**. Standard procedures were used for nitrosation of **4b** followed by reduction, to provide the substituted phenylhydrazine intermediate **4c**. The intramolecular cyclization of the hydrazine, **4c**, proved to be problematic until we applied the urea method reported by Basha.[17] Treatment of **4c** initially at −40 °C with slightly more than 1 equiv of ethylmagnesium bromide followed by warming at 40 °C for 2 days provided the desired phenyltriazinone **4** in 16% overall yield. The procedures shown in Scheme 2 were used for the synthesis of analogs **5**–**9**, **11**, **12**, and **14**–**17** by applying the requisite substituted aniline (Table 1).

A more efficient synthesis of the triazinone heterocycle was devised by changing the order of construction of the ring system as shown in Scheme 3. For example, the synthesis of **10** was accomplished by reaction of 2-chloroethyl isocyanate with (3-fluorophenyl)hydrazine to provide the intermediate **10a** which was cyclized by heating in DMF at 75 °C with 1 equiv of NaI for 2 days to provide **10** in 40% overall yield. The procedures shown in Scheme 3 were used for the preparation of analogs **10**, **13**, **19**, **27**, **29**–**31**, and **33**–**50** (Table 1).

The synthesis of analogs **21**–**26** and **28** from amino alcohols was devised as shown in Scheme 4. For example, the synthesis of 5-methyl-1-phenyl-2*H*,4*H*-tetrahydro-1,2,4-triazin-3-one (**21**) was accomplished by conversion of D,L-2-amino-1-propanol to the corresponding ethyl carbamate followed by a Swern oxidation to provide the aldehyde intermediate **21a**, which was reacted with aniline under conditions of reductive amination with $NaBH_3CN$ to provide the ethyl [(phenylamino)ethyl]carbamate **21b**. This intermediate was then converted to the desired triazinone analog by the procedures of nitrosation, reduction, and cyclization previously described in Scheme 2 to provide **21** in 6% overall yield.

An alternative synthesis from amino acid derivatives was attempted as shown in Scheme 5. For example, the synthesis of 5-(hydroxymethyl)-1-phenyl-2*H*,4*H*-tetrahydro-1,2,4-triazin-3-one (**32**) was accomplished by reaction of D,L-serine methyl ester with aniline to provide the amide **32a**, which was reduced with $LiAlH_4$, and the primary amino group was selectively converted to the corresponding ethyl carbamate intermediate **32b**. The nitrosation and reduction steps provided the corresponding hydrazine intermediate which was difficult to cyclize to the desired compound **32** (less than 1% yield). The unprotected hydroxyl group was likely responsible for the poor yield. Since **32** was found to be a weak 5-LO inhibitor no further attempts to improve this method were made.

The heteroarylphenyl-substituted analogs **51**–**59** were prepared as shown in Scheme 6. The (3-bromophenyl)-triazinone **12** or **29** was used in a Pd-catalyzed coupling reaction[18] with the requisite trimethylstannyl heterocycle, prepared by *n*-butyllithium-mediated metalation of the heterocycle followed by quenching with trimethylstannyl chloride.[19] For example, compound **54** was prepared in 17% yield by the coupling of **29** with 2-(trimethylstannyl)thiophene.

The 4-*N*-substituted analogs **60**–**62** were prepared as shown in Scheme 7. The 4-N substituent was determined by the acyl chloride used to react with *N*-phenylethylenediamine. For example, the synthesis of 4-(phenylmethyl)-1-phenyl-2*H*,4*H*-tetrahydro-1,2,4-triazin-3-one (**62**) was accomplished by reaction of *N*-phenylethylenediamine with benzoyl chloride to provide the intermediate amide **62a**. Reduction of **62a** with $LiAlH_4$ provided the intermediate amine which was directly converted to the methyl carbamate **62b**. The nitrosation, reduction, and cyclization methods of Scheme 1 were applied to **62b** to afford **62** in 24% overall yield.

The 4-*N*-hydroxy analogs **63**–**65** were prepared as shown in Scheme 8. For example, the carbamate **63a** was reacted with chloroacetone oxime in the presence of Na_2CO_3 to provide the adduct **63b**. The oxime group was reduced with borane–pyridine in the presence of 6 N ethanolic HCl to provide the intermediate hydroxylamine, which was cyclized by treating with potassium *tert*-butoxide to provide the 4-*N*-hydroxytriazinone analog **63** in 20% overall yield.

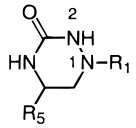
Synthesis of 1-phenyl-3*H*-trihydro-1,3,4-oxadiazin-2-one (**67**) was accomplished by the procedures of Scheme 9. 1-Acetyl-2-phenylhydrazine was reacted with 2-bromoethanol, and the intermediate was subjected to hydrolysis with 6 N HCl at reflux to provide 1-(2-hydroxyethyl)-1-phenylhydrazine which was treated with carbonyldiimidazole to provide **67** in 6% overall yield.

Synthesis of 1-phenyl-2*H*,4*H*-tetrahydro-1,2,4-triazin-3-thione (**68**) in 42% yield was accomplished by treatment of **4** with Lawesson's reagent in toluene at 80 °C for 15 h.

Results and Discussion

Biological Testing. The biological methods used to provide the critical data for inhibitor optimization are described as follows.[2] Direct evaluation of inhibition of 5-LO catalysis was conducted using a crude supernatant from sonicated rat basophilic leukemia cells and measuring 5-HETE product formation. Compounds of in-

Table 1. Structure−Activity Relationships for Selected Triazinones

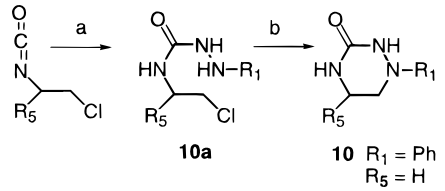


compd	(synth meth)	R_1	R_5	IC_{50}, μM broken cell[a]	IC_{50}, μM HWBL[b]	*in vivo* rat[c] ED_{50}, mg/kg, or (% *I* at 200 μmol/kg)	rat po[d] T_{max}, h; C_{max}, μM
4	(A)	phenyl	H	21	5.8	7	1; 130
5	(A)	2-methylphenyl	H	386		NS[e]	2.1; 78
6	(A)	3-methylphenyl	H	15	2.0	18	1.1; 98
7	(A)	4-methylphenyl	H	NS (300 μM)[e]			1.1; 105
8	(A)	3,5-dimethylphenyl	H	12		(46%)	4; 20
9	(A)	3-ethylphenyl	H	13		24	1.1; 32
10	(B)	3-fluorophenyl	H	19		(38%)	1; 108
11	(A)	3-chlorophenyl	H	5.3	2.1	18	2; 59
12	(A)	3-bromophenyl	H	4.9		(46%)	4.2; 35
13	(B)	3,5-difluorophenyl	H	8.9	4.6	(59%)	2; 64
14	(A)	3-(trifluoromethyl)phenyl	H	17		(40%)	4.1; 24
15	(A)	3-methoxyphenyl	H	47		(44%)	1.2; 72
16	(A)	3-(methylthio)phenyl	H	14	2.2	(73%)	1; 26
17	(A)	3-(phenylmethoxy)phenyl	H	1.1	0.2	(14%)	1; 2.5
18		3-hydroxyphenyl	H	NS (32 μM)[e]			
19	(B)	3-nitrophenyl	H	49		NS[e]	2; 62
20		3-aminophenyl	H	178			1.1; 95
21	(C)	phenyl	CH_3	11	5.8	13	2; 141
22	(C)	phenyl	$(CH_3)_2$	6.8		NS[e]	2.2; 20
23	(C)	phenyl	CH_2CH_3	6.9	3.8	24	1.2; 59
24	(C)	phenyl	*i*-C_3H_7	6.8	20	59	2; 48
25	(C)	phenyl	C_4H_9	1.5		(42%)	1; 8
26	(C)	3-methylphenyl	CH_3	19		(43%)	2.2; 44
27	(B)	3-fluorophenyl	CH_3	6.3	1.8	(60%)	7.2; 70.2
28	(C)	3-chlorophenyl	CH_3	2.7	2.7	(40%)	4; 31
29	(B)	3-bromophenyl	CH_3	2.6	5.2	(54%)	7.2; 26
30	(B)	phenyl	phenoxy		2.6	NS[e]	
31	(B)	phenyl	4-fluorophenoxy		2.6	NS[e]	
32	(D)	phenyl	CH_2OH	40% (32 μM)			
33	(B)	phenyl	$CH_2OCH_2CH_2OCH_3$	14	24		
34	(B)	pyrid-2-yl	H	26	8.6	8	1; 184
35	(B)	pyrid-3-yl	H	NS (32 μM)[e]			
36	(B)	pyrid-4-yl	H	NS (32 μM)[e]			
37	(B)	6-methylpyrid-2-yl	H	5.5	7.9	17	1; 99
38	(B)	6-methylpyrid-2-yl	CH_3	3.8	1.7		1; 125
39	(B)	6-fluoropyrid-2-yl	H	9.1	3		
40	(B)	6-fluoropyrid-2-yl	CH_3	6.6	6.0		
41	(B)	6-chloropyrid-2-yl	H	5.6	4.8	16	2; 122
42	(B)	6-chloropyrid-2-yl	CH_3	3.5	1.6	NS[e]	2; 48
43	(B)	6-bromopyrid-2-yl	H	3.5	4.6	41	1; 79
44	(B)	6-bromopyrid-2-yl	CH_3	2.4	3.1	(57%)	2; 21
45	(B)	6-methoxypyrid-2-yl	H	9.5	3.5	(26%)	1; 101
46	(B)	6-methoxypyrid-2-yl	CH_3	5.5	7.1		1; 85
47	(B)	7-chloroquinol-4-yl	H	NS (32 μM)[e]			4; 85
48	(B)	quinol-3-yl	H	NS (32 μM)[e]			1; 58
49	(B)	benzothiazol-2-yl	H	NS (32 μM)[e]			2; 123
50	(B)	benzoxazol-2-yl	H	NS (32 μM)[e]			
51	(E)	3-pyrid-2-ylphenyl	H	30			
52	(E)	3-pyrid-4-ylphenyl	H	30			
53	(E)	3-thien-2-ylphenyl	H	2.1	8.8		1; 3
54	(E)	3-thien-2-ylphenyl	CH_3	2.8	5.5		4; 1
55	(E)	3-thien-3-ylphenyl	H	4.9	5.3		1; 2
56	(E)	3-fur-2-ylphenyl	CH_3	4.8	8.4	NS[e]	1; 7
57	(E)	3-thiazol-2-ylphenyl	H	35% (32 μM)			
58	(E)	6-thien-2-ylpyrid-2-yl	H	8.2	37		
59	(E)	6-pyrid-2-ylpyrid-2-yl	H	6	>50		

[a] A broken cell 20000*g* supernatant from rat basophilic leukemia (RBL) cells with 5-LO activity. The 95% confidence limits were <±50% of the mean value, and assays were done in duplicate. [b] Human whole blood stimulated with calcium ionophore (A23187) and LTB_4 was measured by enzyme immunoassay. The 95% confidence limits were <±50% of the mean value and assays were done in duplicate. [c] Rat anaphylaxis leukotriene formation with a 1 h inhibitor pretreatment time, an oral dose of 200 μmol/kg was used to screen compounds for *in vivo* activity, and data are reported as the mean of eight rats (percent inhibition of LTE_4 from peritoneal fluids). Dose response studies were conducted for the more promising compounds, the ED_{50} values in mg/kg are the mean of eight rats with 90% confidence limits <±50% of the mean value. [d] Plasma drug levels evaluated in rats dosed by oral gavage with 200 μmol/kg of test compound and blood samples were drawn via the tail vein at approximately 1 h time intervals and analyzed by HPLC. Values are the mean of data from two animals. [e] NS indicates that the activity observed was not significantly different from that of the control group.

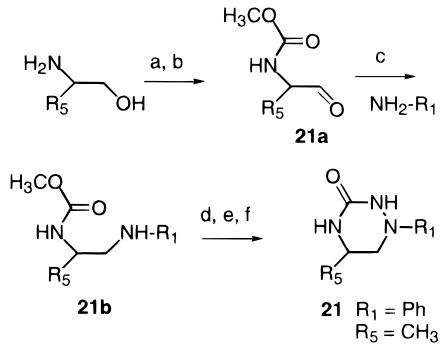
terest from this initial screen of activity were examined further in a human whole blood assay. Stimulation of human blood with calcium ionophore A23187 resulted in leukotriene formation. This assay provided a second

Scheme 3. Method B: Synthesis of Triazinones **10**, **13**, **19**, **27**, **29**−**31**, and **33**−**50** from 2-Chloroethyl Isocyanates[a]



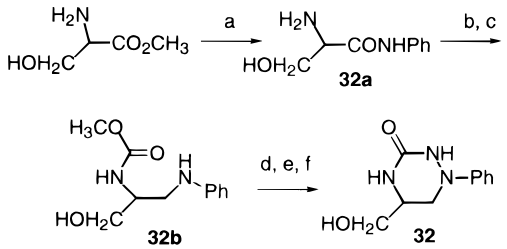
[a] Reagents: (a) Et_3N, H_2NNHR_1, CH_2Cl_2, room temperature for 2 h; (b) NaI, DMF, 75 °C, 48 h.

Scheme 4. Method C: Synthesis of Triazinones **21**−**26** and **28** From 1-Amino-2-hydroxyethanes[a]



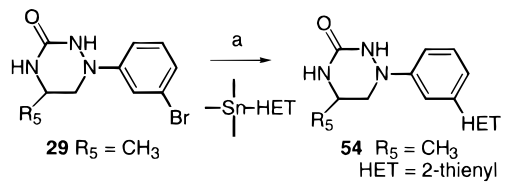
[a] Reagents: (a) $ClCO_2CH_3$, K_2CO_3, CH_3CN, −20 °C for 1 h then room temperature for 16 h; (b) $(COCl)_2$, Et_3N, DMSO, CH_2Cl_2, −78 °C for 0.5 h then room temperature for 1 h; (c) $NaBH_3CN$, CH_3OH, pH 5−6, room temperature for 16 h; (d) $NaNO_2$, 12 N HCl, H_2O, 5 °C, 2 h; (e) Zn dust, H_2O, CH_3CO_2H, 5−15 °C for 1 h then room temperature for 1 h; (f) EtMgBr, CH_2Cl_2, −40 °C for 0.5 h then 40 °C for 48 h.

Scheme 5. Method D: Synthesis of Triazinone **32** from an Amino Acid[a]



[a] Reagents: (a) NH_2R_1, EtMgBr, THF, CH_2Cl_2, 0 °C for 1 h, then reflux for 72 h; (b) $LiAlH_4$, THF, room temperature for 1 h then reflux for 16 h; (c) $ClCO_2CH_3$, Et_3N, THF, −5 °C for 2 h then room temperature for 1 h; (d) $NaNO_2$, 12 N HCl, H_2O, 5 °C, 2 h; (e) Zn dust, H_2O, CH_3CO_2H, 5−15 °C for 1 h then room temperature for 1 h; (f) EtMgBr, CH_2Cl_2, −40 °C for 0.5 h then 40 °C for 48 h.

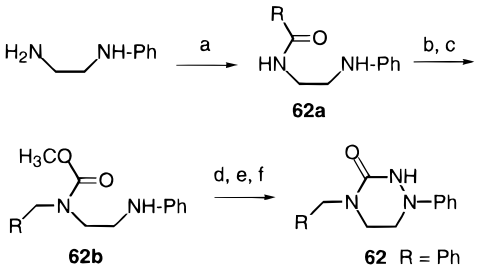
Scheme 6. Method E: Synthesis of Triazinones **51**−**59** by Pd-Catalyzed Coupling with Trimethylstannyl Heterocycles[a]



[a] Reagents: (a) $[(C_6H_5)_3P]_4Pd^0$, toluene, reflux, 4 h.

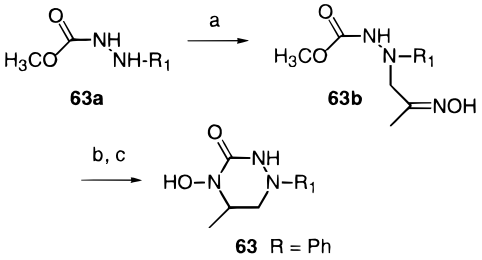
measure of inhibitory activity in the complex medium of whole blood containing intact leukotriene producing cells. In general the triazinone analogs showed similar or better inhibitory activity in human blood than in the broken RBL cell assay. Routine oral dosing of inhibitors

Scheme 7. Method F: Synthesis of 4-*N*-Substituted Triazinones **60**−**62**[a]



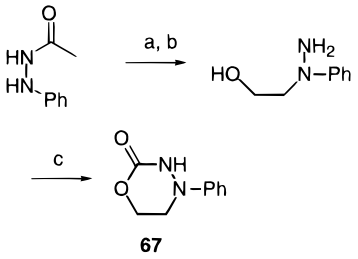
[a] Reagents: (a) RCOCl, Et_3N, CH_2Cl_2, 0 °C for 1 h then room temperature for 16 h; (b) $LiAlH_4$, THF, room temperature for 1 h then reflux for 16 h; (c) $ClCO_2CH_3$, Et_3N, THF, −5 °C, 2 h then room temperature for 16 h; (d) $NaNO_2$, 12 N HCl, H_2O, 5 °C, 2 h; (e) Zn dust, H_2O, CH_3CO_2H, 5−15 °C for 1 h then room temperature for 1 h; (f) EtMgBr, CH_2Cl_2, −40 °C for 0.5 h then 40 °C for 48 h.

Scheme 8. Method G: Synthesis of 4-*N*-Hydroxy-Substituted Triazinones **63**−**65**[a]



[a] Reagents: (a) Na_2CO_3, chloroacetone oxime, CH_2Cl_2, reflux for 18 h; (b) BH_3/pyridine, ethanol, room temperature for 1 h then 0 °C, 6 N ethanolic HCl; (c) $KOtC_4H_9$, THF, room temperature for, 18 h.

Scheme 9. Synthesis of 1-Phenyl-3*H*-trihydro-1,3,4-oxadiazin-2-one (**67**)[a]



[a] Reagents: (a) $EtN(iPr)_2$, $HOCH_2CH_2Br$, toluene, 80 °C, 48 h; (b) 6 N HCl, reflux, 2 h; (c) carbonyldiimidazole, CH_2Cl_2, room temperature, 3 h.

at 200 μmol/kg in rats was conducted with measurement of compound plasma concentrations by HPLC as a preliminary evaluation of pharmacokinetic properties. A rat anaphylaxis assay was used to evaluate the *in vivo* leukotriene inhibitory activity of orally administered compounds. In this *in vivo* assay leukotriene biosynthesis was induced in the peritoneal cavity of rats in response to an antibody−antigen reaction.[20] An oral dose of 200 μmol/kg was selected with a 1 h pretreatment time for the initial screen of 5-LO inhibitors. A dose−response study was conducted on the more potent analogs identified. The most promising inhibitors were evaluated in dog and monkey for *ex vivo* leukotriene inhibition of calcium ionophore stimulated blood samples taken over a 24 h period after oral dosing. The drug plasma levels were also measured by HPLC. Finally, due to the toxicity problems seen with earlier progenitors of this series, a preliminary evaluation of blood

abnormalities was conducted by examining blood samples for Heinz bodies after multiple daily oral doses in rats and dogs.

The design of the parent triazinone **4** evolved as a means to reduce the hypothetical potential for metabolic cleavage of the pyridazinone **3** to form reactive and toxic phenylhydrazine intermediates such as **3b**. Replacing the 4-CH_2 for a 4-NH group in the tranformation of **3** to **4** resulted in a 5-fold loss of inhibitory activity in the broken cell (IC_{50} = 4.3 versus 21 μM) and an 8-fold loss of potency in the human blood 5-LO assay (IC_{50} = 0.7 versus 5.8 μM). However the *in vivo* leukotriene inhibitory activity of the two compounds was similar with ED_{50} values of 6 mg/kg for **3** and 7 mg/kg for **4**. Thus the triazinone **4** represented a promising new 5-LO inhibitor for further optimization.

SAR of Phenyl Substitution. The initial plan was to survey several analogs with the objective of identifying structural modifications which might enhance inhibitory activity. Substituents on the phenyl group of **4** were examined (Table 1). The results were analogous to the previously reported pyridazinone system where inhibitory potency was significantly attenuated by any substituent in the 2- or 4-positions.[13] For example, in the toluene series, *ortho*-substituted **5** and *para*-substituted **7** were inactive below 100 μM, whereas *meta*-substituted **6** (IC_{50} = 15 μM) had similar potency to the parent **4**. The 3,5-dimethyl analog **8** (IC_{50} = 12 μM) maintained potency *in vitro* but had about a 6-fold lower plasma level compared to that of **4** in orally dosed rats which correlated with its weak activity *in vivo*. The 3-ethyl analog **9** (IC_{50} = 13 μM) also demonstrated reduced plasma levels and attenuated *in vivo* activity (ED_{50} = 24 mg/kg). Halogen-substituted analogs **10**−**14** were examined and found to offer no significant advantages. The 3-methoxy analog **15** (IC_{50} = 47 μM) was less potent than the 3-methyl thiol analog **16** (IC_{50} = 14 μM), further supporting the conclusion that inhibitory activity preferred less polar substituents. Increasing the lipophilicity of the *meta* substituent as in the 3-phenylmethoxy analog **17** (IC_{50} = 1.1 μM in the broken cell and 0.2 μM in human blood) provided the most potent *in vitro* inhibitor prepared. Unfortunately, **17** had very low plasma levels after oral dosing in the rat and, as expected from this, poor activity *in vivo*.

It became clear that the optimization of this series would prove challenging in view of opposing phenomena where increased lipophilicity resulted in greater *in vitro* inhibitory potency but reduced oral bioavailability which in turn attenuated *in vivo* activity. Three analogs with polar hydrogen bonding substituents, 3-hydroxy (**18**), 3-nitro (**19**), and 3-amino (**20**), were found to have weak *in vitro* inhibition. It was concluded that lipophilic substituents in the *meta* position of the phenyl group provided enhanced *in vitro* 5-LO inhibitory activity which did not result in improved *in vivo* activity due to diminished oral bioavailability.

SAR of 5-Substituted Triazinones. Alternative sites for modification that might lead to optimized potency were investigated. A series of 5-substituted analogs were evaluated (Table 1). The trend for improved *in vitro* potency with increased liphophilicity of the 5-substituent is supported by comparing the methyl (**21**) (IC_{50} = 11 μM), dimethyl (**22**) (IC_{50} = 6.8 μM), ethyl (**23**) (IC_{50} = 6.9 μM), isopropyl (**24**) (IC_{50} = 6.8 μM), and *n*-butyl (**25**) (IC_{50} = 1.5 μM) analogs. However the opposing trend of reduced activity *in vivo* continued as the plasma levels in rats of these analogs (oral dose of 200 μmol/kg) decreased accordingly: **21** (C_{max} 141 μM), **22** (C_{max} 20 μM), **23** (C_{max} 59 μM), **24** (C_{max} 48 μM), and **25** (C_{max} 8 μM). Several other analogs were examined which did not provide any clues to overcome this dichotomy.

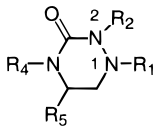
SAR of 1-*N*-Heteroaryltriazinones. The next phase of SAR evaluation was to replace the 1-*N*-phenyl substituent in **4** with heteroaryl substituents to test the idea that the presence of heteroatoms might change the SAR profile. In the pyridyl series the position of the nitrogen atom proved to be critical. The 2-pyridyl analog **34** (IC_{50} = 26 μM) had potency similar to that of **4**, whereas the 3-pyridyl (**35**) and 4-pyridyl (**36**) analogs were inactive at the screening dose of 32 μM. Compound **34** had activity similar to that of **4** in the human whole blood assay (IC_{50} = 8.6 versus 5.8 μM) and *in vivo* in the rat (ED_{50} = 8 versus 7 mg/ kg), and **34** (C_{max} 184 μM) also gave higher plasma levels upon oral dosing in rats compared to **4** (C_{max} 130 μM). The promising properties of **34** stimulated the evaluation of several analogs substituted in the 6-position of the pyridyl group and the 5-position of the triazinone (Table 1). The results were similar to those observed in the phenyl-substituted series, and no unexpectedly superior analogs were identified. Other heteroaryl substituents surveyed, 4-quinolyl (**47**), 3-quinolyl (**48**), 2-benzothiazolyl (**49**), and 2-benzoxazolyl (**50**), were all inactive against 5-LO at 32 μM.

SAR of (Heteroarylphenyl)triazinones. The next phase of the SAR evaluation was to add a heteroaryl substituent to the 1-*N*-phenyl group of **4** in the *meta* position. The 3-pyrid-2-yl (**51**) and 3-pyrid-4-yl (**52**) analogs had similar *in vitro* potency. The thienylphenyl analogs **53**−**55** and furylphenyl analog **56** were at least 10-fold more potent *in vitro* but unfortunately gave very low plasma levels in rats. The 3-thiazol-2-yl analog **57** was a weak inhibitor. Two analogs with heteroaryl combinations were examined for the 2-pyridyl series. The thienylpyridyl analog, **58** and the pyridylpyridyl analog **59** showed much less activity in the human blood assay than in the broken cell assay, which might be attributed to increased interference from plasma protein binding effects. None of these analogs were considered promising enough to conduct *in vivo* testing.

SAR of 4-*N*-Substituted Triazinones. The outcome of 4-N substituents was examined (Table 2). In the series, methyl (**60**), ethyl (**61**), and phenylmethyl (**62**) only the latter showed 5-LO inhibitory activity below the screening dose of 32 μM. In the context of our experience with hydroxamate and *N*-hydroxyureas[4] the corresponding 4-*N*-OH analogs **63**−**65** were evaluated and found to have IC_{50} values in the range of 4−13 μM in both the broken cell and human blood assays. The *N*-methoxy analog **66** had *in vitro* potency similar to that of the parent compound **4**. In the rat anaphylaxis assay, **62** and **63** had 14% and 55% leukotriene inhibition with a single 200 μmol/kg oral dose.

SAR of Miscellaneous Analogs. Replacing 4-CH_2 in **3** for 4-O provided 1-phenyl-3*H*-trihydro-1,3,4-oxadiazin-2-one (**67**) which had an IC_{50} = 21 μM in the broken cell and 5.8 μM in human blood. Transforming **4** into the corresponding thiocarbonyl analog **68** resulted

Table 2. Inhibitory Activity for Selected Triazinone Analogs



compd	(synth meth)	R_1	R_2	R_4	R_5	IC_{50}, μM broken cell[a]	IC_{50}, μM HWBL[b]
60	(F)	phenyl	H	CH_3	H	NS (32 μM)[c]	
61	(F)	phenyl	H	CH_2CH_3	H	NS (32 μM)[c]	
62	(F)	phenyl	H	$CH_2C_6H_5$	H	8.3	
63	(G)	phenyl	H	OH	CH_3	6	13
64	(G)	3-chlorophenyl	H	OH	CH_3	3.9	3.6
65	(G)	3-methylphenyl	H	OH	CH_3	8.4	4.8
66		phenyl	H	OCH_3	CH_3	22	

[a] A broken cell 20000*g* supernatant from rat basophilic leukemia (RBL) cells with 5-LO activity. The 95% confidence limits were <±50% of the mean value, and assays were done in duplicate. [b] HWBL, human whole blood stimulated with calcium ionophore (A23187) and LTB_4 was measured by enzyme immunoassay. The 95% confidence limits were <±50% of the mean value, and assays were done in duplicate. [c] NS indicates that the activity observed was not significantly different from that of the control group.

Table 3. Selectivity of *in Vitro* Inhibition of 5-Lipoxygenase and Related Enzymes

enzyme	IC_{50},[a] μM or (% inhibition) phenidone (**1**)	**3**	**4**
5-LO broken RBL	1.9 (1.5−2.8)	4.3 (4.1−4.5)	21 (18−24)
12-LO human platelet	0.10 (0.09−0.10)	(7% at 100 μM)[b]	(14% at 100 μM)[b]
15-LO soybean	0.42 (0.34−0.51)	(25% at 100 μM)[b]	(14% at 100 μM)[b]
COX sheep seminal vesicle	94 (78−115)	(5% at 300 μM)[b]	(4% at 100 μM)[b]

[a] 95% confidence limits shown in parentheses; assays done in duplicate. [b] Percent inhibition at highest tested concentration.

Table 4. *In Vitro* Inhibition of 5-LO and Cyclooxygenase (COX) in Intact Cells and Human Blood

enzyme (cell type)	IC_{50},[a] μM or (% inhibition) phenidone (**1**)	**3**	**4**
5-LO rat PMNL[c]	0.52 (0.33−0.74)	1.2 (0.8−1.9)	4.6 (4.5−4.8)
COX rat PMNL[d]	13 (11−16)	(3% at 300 μM)[b]	(28% at 100 μM)[b]
5-LO human PMNL[e]	1.3 (1.1−1.6)	1.0 (0.1−2.3)	9.2 (4.7−17.0)
5-LO human blood[f]	0.3 (0.25−0.4)	0.7 (0.1−1.3)	5.8 (4.4−7.4)
COX human blood[g]	12 (4−20)	(13% at 100 μM)[b]	(0% at 100 μM)[b]

[a] 95% confidence limits shown in parentheses, assays done in duplicate. [b] Percent inhibition at highest tested concentration. [c] Rat polymorphonuclear leukocytes stimulated with calcium ionophore (A23187) and LTB_4 was measured by enzyme immunoassay. [d] Rat polymorphonuclear leukocytes stimulated with calcium ionophore (A23187) and thromboxane was measured by enzyme immunoassay. [e] Human polymorphonuclear leukocytes stimulated with calcium ionophore (A23187) and LTB_4 was measured by enzyme immunoassay. [f] Human whole blood stimulated with calcium ionophore (A23187) and LTB_4 was measured by enzyme immunoassay. [g] Human whole blood stimulated with calcium ionophore (A23187) and thromboxane was measured by enzyme immunoassay.

in an inhibitor with similar potency in the broken cell assay (IC_{50} = 17 μM). However, **68** was less active *in vivo*, and toxicity was observed in the rat at oral doses of 200 μmol/kg. Further study of the thiocarbonyl series was discontinued.

Further Biological Evaluation of 4. This survey of SAR did not reveal any compounds with overall properties superior to the parent compound **4**, which had the most consistent *in vivo* inhibition on repeated oral dose response studies. Compound **4** exhibited selectivity for 5-LO inhibition with little activity against related enzymes 12-LO from human platelets, 15-LO from soybean, and cyclooxygenase (COX) from sheep seminal vesicle (Table 3). In both intact cell assays and human blood, compound **4** was a selective inhibitor of calcium ionophore (A23187) stimulated 5-LO activity and did not inhibit COX activity (Table 4). Preliminary pharmacokinetic studies in rat, dog, and monkey showed satisfactory drug plasma levels after oral administration (Table 5). In both dog (Figure 1) and monkey (Figure 2), oral administration of 10 mg/kg of **4** provided greater than 50% *ex vivo* leukotriene inhibition in blood samples taken over the first 4 h. The plasma concentration of **4** was also measured and corresponded to the degree of *ex vivo* inhibition observed in the monkey. However, in the dog the shape of the plasma versus inhibition plots indicated that an active metabolite was being formed (not identified).

Table 5. Plasma Levels of **4** after Oral Dosing[a]

species	oral dose, μmol/kg	T_{max}, h	C_{max}, μM	$T_{1/2}$ est, h
rat	200	1.0	130	3.3
dog	113	0.3	132	0.8
monkey	113	2.0	74	1.0

[a] Values are the mean of data from two animals.

Two analogs were found to have comparable properties to **4**. The 5-methyl analog (**21**) had a longer elimination half-life in dog (4.2 h) compared to that of **4** (0.8 h) but was about 2-fold less active than **4** in the rat anaphylaxis model. The pyridyl analog (**34**) had similar inhibitory activity (Table 1) and pharmacokinetics in rat (n = 2, dose 200 μmol/kg po, T_{max} 1 h, C_{max} 184 μM, $T_{1/2}$ 2.9 h), dog (n = 2, dose 112 μmol/kg po, T_{max} 0.7 h, C_{max} 109 μM, $T_{1/2}$ 1 h), and monkey (n = 2, dose 112 μmol/kg po, T_{max} 1.5 h, C_{max} 37 μM, $T_{1/2}$ 1.1 h) as **4** (Table 5). Oral administration of 10 mg/kg of **34**

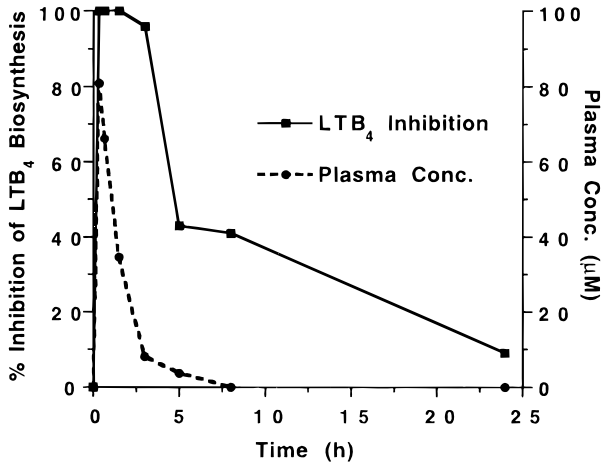


Figure 1. Plasma concentrations of **4** and *ex vivo* inhibition of LTB_4 after a 10 mg/kg oral dose in dog. Plasma concentrations were determined by HPLC. Data presented are the mean from two dogs.

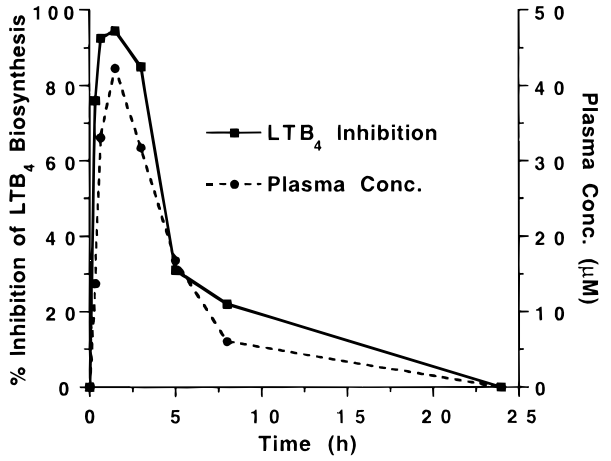


Figure 2. Plasma concentrations of **4** and *ex vivo* inhibition of LTB_4 after a 10 mg/kg oral dose in cynomolgus monkeys. Plasma concentrations were determined by HPLC. Data presented are the mean from two monkeys.

to cynomolgus monkeys ($n = 2$) provided greater than 50% *ex vivo* leukotriene inhibition in blood samples taken over the first 4 h.

In pilot subacute toxicity testing, **4** did not produce methemoglobinemia in rats after repeated oral daily doses of 400 mg/kg for 9 days. In a dog toxicity study, oral daily doses of 200 mg/kg of **4** for 1 month also showed no methemoglobinemia. Therefore, the phenyltriazinone heterocycle represented by **4** provided a 5-LO inhibitor pharmacophore which was devoid of the methemoglobinemia-associated toxicity problem previously observed for the pyridazinone series represented by **3**.[13] The SAR study did not identify triazinone analogs with *in vitro* potency below 1 μM and at the same time exhibit *in vivo* activity with ED_{50} values below 10 mg/kg. Triazinone **4** is an easily synthesized, low molecular weight, selective, orally bioavailable 5-LO inhibitor useful for *in vivo* pharmacologic studies involving biosynthetic products derived from 5-lipoxygenase.

Experimental Section

Chemistry. General. Melting points were determined in open glass capillaries and are uncorrected. ^{1}H NMR spectra were recorded on a GE QE300 spectrometer and chemical shifts are reported in parts per million (ppm, δ) relative to tetramethylsilane as an internal standard. Elemental analysis (C, H, N) were performed by Abbott Laboratories Pharmaceutical Products Division or Robertson Microlit Laboratories, Inc., Madison, NJ. Silica gel 60 (E. Merck, 230−400 mesh) was used for preparative column chromatography. Reactions were performed under dry nitrogen atmosphere unless stated otherwise. THF was freshly distilled from sodium benzophenone ketyl. Other solvents were HPLC grade. Reagents were obtained commercially and used without further purification. Chemical yields reported are unoptimized specific examples of one prepartion. Analytical TLC using E. Merck F254 commercial plates was used to follow the course of reactions.

Method A (Scheme 2). 1-Phenyl-2*H*,4*H*-tetrahydro-1,2,4-triazin-3-one (4). To a stirred 0 °C suspension of bromoethylamine hydrochloride (255 g, 1.25 mol) in dichloromethane (700 mL) was added triethylamine (252 g, 2.5 mol) followed by dropwise addition of ethyl chloroformate (135.3 g, 1.25 mol) in dichloromethane (200 mL) while the reaction termperature was maintained between 0 and 4 °C. The mixture was stirred for 1 h; water (500 mL) was added; and the organic layer was separated and washed with saturated aqueous NaCl, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give ethyl *N*-(2-bromoethyl)carbamate as a colorless oil (218 g, 88%).

A solution of aniline (83.7 g, 0.9 mol), ethyl *N*-(2-bromoethyl)carbamate (190.0 g, 0.92 mol), and diisopropylethylamine (90.3 g, 0.7 mol) in benzene (700 mL) was heated at reflux for 24 h. The reaction mixture was allowed to cool to room temperature, water (500 mL) was added, and the organic layer was separated, washed with saturated aqueous NaCl, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give ethyl *N*-[2-(phenylamino)ethyl]carbamate (118 g, 63%).

To ethyl *N*-[2-(phenylamino)ethyl]carbamate (118 g, 0.57 mol) was added an ice cold solution of concentrated HCl (120 mL) dissolved in water (200 mL). With mechanical stirring at 0 °C, a solution of $NaNO_2$ (41.4 g, 0.6 mol) in water (100 mL) was added dropwise. The mixture was stirred for 2 h at 0 °C, and a solid precipitate formed. The solid was collected by filtration, washed with water (2 × 100 mL), and dried *in vacuo* to provide ethyl *N*-[2-(phenylnitrosoamino)ethyl]carbamate as a greenish yellow solid (115 g, 85%).

To a mechanically stirred suspension of zinc dust (115 g, 0.48 mol) in water (350 mL) was added dropwise a solution of *N*-nitroso intermediate (115 g) dissolved in acetic acid (230 mL). The temperature was controlled between 5−15 °C during the addition after which the cooling bath was removed, and the mixture was stirred at 30 °C for 1 h. Dichloromethane (700 mL) was added, and the mixture was filtered. The organic layer was separated, washed with 10% Na_2CO_3 (2 × 350 mL) and saturated aqueous NaCl, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give *N*-[2-[(ethoxycarbonyl)-amino]ethyl]-*N*-phenylhydrazine (93 g, 87%).

To a stirred solution of the hydrazine intermediate (93 g, 0.42 mol) in dichloromethane (350 mL) cooled to −40 °C was added dropwise ethylmagnesium bromide (225 mL, 2.0 M in tetrahydrofuran) while the temperature was maintained below −30 °C. After the addition, the mixture was allowed to warm to room temperature and then heated at 40 °C for 48 h. Ice chips (500 g) were added, and the mixture was acidified with 3 N HCl to pH 3. The phases were separated, and the aqueous phase was extracted with 5% methanol in dichloromethane (2 × 300 mL). The combined organic extracts were washed with saturated aqueous NaCl, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was suspended in 2% MeOH in dichloromethane (100 mL), and the solids were collected by filtration to provide **4** (28.7 g, 39%): mp 219 °C; ^{1}H NMR (300 MHz, DMSO-d_6) 3.01−3.07 (2 H, m), 3.63 (2 H, t, $J = 5.5$ Hz), 6.64 (1 H, br s), 6.87 (1 H, t, $J = 7.5$ Hz), 7.03 (2 H, d, $J = 8$ Hz), 7.27 (2 H, t, $J = 8$ Hz), 8.42 (1 H, br s). Anal. ($C_9H_{11}N_3O$) C, H, N.

1-(2-Methylphenyl)-2*H*,4*H*-tetrahydro-1,2,4-triazin-3-one (5). Method A: 25% overall yield; mp 230 °C; NMR (300 MHz, DMSO-d_6) 2.23 (3 H, s), 2.99−2.93 (2 H, m), 3.22 (2 H, t, $J = 5$ Hz), 6.78 (1 H, br s), 6.99 (1 H, dt, $J = 6$, 1 Hz), 7.04 (1 H, d, $J = 7$ Hz), 7.16 (2 H, d, $J = 7$ Hz), 8.19 (1 H, br s). Anal. ($C_{10}H_{13}N_3O$) C, H, N.

1-(3-Methylphenyl)-2*H*,4*H*-tetrahydro-1,2,4-triazin-3-one (6). Method A: 18% overall yield; mp 235−236 °C; ^{1}H NMR (300 MHz, DMSO-d_6) 2.26 (3 H, s), 3.05−2.98 (2 H, m), 3.61 (2 H, t, J = 5 Hz), 6.63 (1 H, br s), 6.68 (1 H, d, J = 7.0 Hz), 6.87−6.80 (2 H, m), 7.14 (1 H, t, J = 7.5 Hz), 8.38 (1 H, br s). Anal. ($C_{10}H_{13}N_3O$) C, H, N.

1-(4-Methylphenyl)-2*H*,4*H*-tetrahydro-1,2,4-triazin-3-one (7). Method A: 23% overall yield; mp 218−220 °C; ^{1}H NMR (300 MHz, $CDCl_3$, CD_3OD) 2.22 (3 H, s), 3.14 (2 H, t, J = 5 Hz), 3.52 (2 H, t, J = 5 Hz), 6.87 (2 H, d, J = 9 Hz), 7.03 (2 H, d, J = 9 Hz); MS *m/e* M^+ 191. Anal. ($C_{10}H_{13}N_3O\cdot0.5H_2O$) C, H, N.

1-(3′,5′-Dimethylphenyl)-2*H*,4*H*-tetrahydro-1,2,4-triazin-3-one (8). Method A: 27% overall yield; mp 255−257 °C; ^{1}H NMR (300 MHz, DMSO-d_6) 2.20 (6 H, s), 2.99−3.06 (2 H, m), 3.58 (2 H, t, J = 5 Hz), 6.51 (1 H, s), 6.6 (1 H, br s), 6.65 (2 H, s), 8.33 (1 H, d, J = 1.5 Hz). Anal. ($C_{11}H_{15}N_3O$) C, H, N.

1-(3-Ethylphenyl)-2*H*,4*H*-tetrahydro-1,2,4-triazin-3-one (9). Method A: 22% overall yield; mp 204−205 °C; ^{1}H NMR (300 MHz, DMSO-d_6) 1.16 (3 H, t, J = 7.5 Hz), 2.56 (2 H, q, J = 7 Hz), 3.01−3.07 (2 H, m), 3.62 (2 H, t, J = 5 Hz), 6.63 (1 H, br s), 6.73 (1 H, d, J = 7.5 Hz), 6.82−6.9 (2 H, m), 7.16 (1 H, t, J = 7.5 Hz), 8.38 (1 H, br s). Anal. ($C_{11}H_{15}N_3O$) C, H, N.

Method B (Scheme 3). 1-(3-Fluorophenyl)-2*H*,4*H*-tetrahydro-1,2,4-triazin-3-one (10). To a stirred suspension of (3-fluorophenyl)hydrazine hydrochloride (4.06 g, 25 mmol) in dichloromethane (150 mL) was added triethylamine (2.5 g, 25 mmol), and the mixture was stirred for 15 min, after which 2-chloroethyl isocyanate (2.6 g, 25 mmol) was added dropwise. The mixture was stirred for 2 h, water (100 mL) was added, and the organic layer was separated, washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give *N*-(4-fluorophenyl)-*N*′-[[(2-chloroethyl)amino]carbonyl]hydrazine (5.03 g, 87%).

A mixture of *N*-(4-fluorophenyl)-*N*′-[[(2-chloroethyl)amino]-carbonyl]hydrazine (2.3 g, 10 mmol) in DMF (20 mL) and NaI (2.99 g, 20 mmol) was stirred at 75 °C for 48 h and allowed to cool to room temperature, and water (10 mL) was added followed by dropwise addition of a saturated solution of $NaHSO_3$ to consume the iodine color. The pH of the mixture was adjusted to 8−9 by adding 2 N NaOH and was concentrated *in vacuo* to give an oil which was purified by chromatography (silica gel, 7% methanol in dichloromethane) to provide **10** (0.8 g, 46%): mp 194−196 °C; ^{1}H NMR (300 MHz, DMSO-d_6) 2.17−2.23 (2 H, m), 2.8 (2 H, t, J = 6 Hz), 5.79 (1 H, dt, J = 8, 1.5 Hz), 5.85 (1 H, br s), 5.94−6.04 (2 H, m), 6.36−6.44 (1 H, m), 7.76 (1 H, br s). Anal. ($C_9H_{10}FN_3O$) C, H, N.

1-(3-Chlorophenyl)-2*H*,4*H*-tetrahydro-1,2,4-triazin-3-one (11). Method A: 18% overall yield; mp 244−245 °C; ^{1}H NMR (300 MHz, DMSO-d_6) 3.03−3.09 (2 H, m), 3.67 (2 H, t, J = 5 Hz), 6.72 (1 H, br s), 6.9 (1 H, dd, J = 9, 1.5 Hz), 7.01 (1 H, dd, J = 9, 1.5 Hz), 7.07 (1 H, t, J = 2.5 Hz), 7.27 (1 H, t, J = 8 Hz), 8.53 (1 H, br s). Anal. ($C_9H_{10}ClN_3O$) C, H, N.

1-(3-Bromophenyl)-2*H*,4*H*-tetrahydro-1,2,4-triazin-3-one (12). Method A: 21% overall yield; mp 260−262 °C; ^{1}H NMR (300 MHz, DMSO-d_6) 3.03−3.09 (2 H, m), 3.67 (2 H, t, J = 6 Hz), 6.77 (1 H, br s), 7.01−7.07 (2 H, m), 7.22 (2 H, t, J = 7.5 Hz), 8.54 (1 H, br s). Anal. ($C_9H_{10}BrN_3O\cdot0.25H_2O$) C, H, N.

1-(3,5-Difluorophenyl)-2*H*,4*H*-tetrahydro-1,2,4-triazin-3-one (13). Method B: 39% overall yield; mp 238−240 °C; ^{1}H NMR (300 MHz, DMSO-d_6) 3.07−3.13 (2 H, m), 3.69 (2 H, t, J = 5 Hz), 6.65 (1 H, tt, J = 8, 2 Hz), 6.73 (1 H, d, J = 2 Hz), 6.77 (1 H, d, J = 2 Hz), 6.82 (b, 1 H), 8.62 (br s). Anal. ($C_9H_9F_2N_3O$) C, H, N.

1-[3-(Trifluoromethyl)phenyl]-2*H*,4*H*-tetrahydro-1,2,4-triazin-3-one (14). Method A: 16% overal yield; mp 239−241 °C; ^{1}H NMR (300 MHz, DMSO-d_6) 3.04−3.11 (2 H, m), 3.76 (2 H, t, J = 5.5 Hz), 6.79 (1 H, br s), 7.20 (1 H, d, J = 7 Hz), 7.36 (1 H, d, J = 10 Hz), 7.5 (1 H, t, J = 7.5 Hz), 8.63 (1 H, d, J = 1.5 Hz). Anal. ($C_{10}H_{10}F_3N_3O$) C, H, N.

1-(3-Methoxyphenyl)-2*H*,4*H*-tetrahydro-1,2,4-triazin-3-one (15). Method A: 23% overall yield; mp 183 °C; ^{1}H NMR (300 MHz, DMSO-d_6) 3.01−3.09 (2 H, m), 3.62 (2 H, t, J = 6 Hz), 3.73 (3 H, s), 6.47 (1 H, dd, J = 9, 2 Hz), 6.58 (1 H, t, J = 2.5 Hz), 6.63 (1 H, dd, J = 9, 1 Hz), 6.75 (1 H, br s), 7.16 (1 H, t, J = 8 Hz), 8.46 (1 H, br s). Anal. ($C_{10}H_{13}N_3O_2$) C, H, N.

1-[3-(Methylthio)phenyl]-2*H*,4*H*-tetrahydro-1,2,4-triazin-3-one (16). Method A: 28% overall yield; mp 179−180 °C; ^{1}H NMR (300 MHz, DMSO-d_6) 2.45 (3 H, s), 3.01−3.07 (2 H, m), 3.63 (2 H, t, J = 6 Hz), 6.67 (1 H, br s), 6.76 (1 H, d, J = 7 Hz), 6.82 (1 H, dd, J = 9, 1.5 Hz), 6.9 (1 H, t, J = 1.5 Hz), 7.21 (1 H, t, J = 8 Hz), 8.56 (1 H, br s). Anal. ($C_{10}H_{13}N_3OS\cdot0.25H_2O$) C, H, N.

1-[3-(Phenylmethoxy)phenyl]-2*H*,4*H*-tetrahydro-1,2,4-triazin-3-one (17). Method A: 18% overall yield; mp 169 °C; ^{1}H NMR (300 MHz, DMSO-d_6) 3.01−3.07 (2 H, m), 3.62 (2 H, t, J = 6 Hz), 5.06 (2 H, s), 6.54 (1 H, dd, J = 9, 1.5 Hz), 6.61−6.66 (2 H, m), 6.68 (1 H, t, J = 2 Hz), 7.17 (1 H, t, J = 8 Hz), 7.28−7.47 (5 H, m), 8.42 (1 H, d, J = 1 Hz). Anal. ($C_{16}H_{17}N_3O\cdot0.75H_2O$) C, H, N.

1-(3-Hydroxyphenyl)-2*H*,4*H*-tetrahydro-1,2,4-triazin-3-one (18). A mixture of **17** (0.5 g, 1.8 mmol) in methanol (50 mL) was hydrogenated at 4 atm with 20% Pd/C (0.2 g) at room temperature for 4 h. The mixture was filtered, concentrated *in vacuo*, and crystallized from ethyl acetate to provide **18** (0.22 g, 60%): mp 244 °C; ^{1}H NMR (300 MHz, DMSO-d_6) 3.03 (2 H, m), 3.53 (2 H, t, J = 7 Hz), 6.27 (1 H, m), 6.44 (2 H, m), 6.62 (1 H, br s), 7.03 (1 H, t, J = 7.5 Hz), 8.73 (1 H, br s), 9.28 (1 H, br s). Anal. ($C_9H_{11}N_3O_2$) C, H, N.

1-(3-Nitrophenyl)-2*H*,4*H*-tetrahydro-1,2,4-triazin-3-one (19). Method B: 42% overall yield; mp 205−208 °C; ^{1}H NMR (300 MHz, DMSO-d_6) 3.06−3.14 (2 H, m), 3.79 (2 H, t, J = 5 Hz), 6.82 (1 H, br s), 7.49−7.59 (2 H, m), 7.68−7.74 (1 H, m), 7.83 (1 H, t, J = 7 Hz), 8.73 (1 H, br s). Anal. ($C_9H_{10}N_4O_3$) C, H, N.

1-(3-Aminophenyl)-2*H*,4*H*-tetrahydro-1,2,4-triazin-3-one (20). A solution of **19** in ethyl acetate was hydrogenated at 4 atm with 20% Pd/C at room temperature for 4 h to provide **20** (0.085 g, 40%): mp 214−216 °C; ^{1}H NMR (300 MHz, DMSO-d_6) 3.02 (2 H, m), 3.5 (2 H, t, J = 7 Hz), 4.97 (2 H, s), 6.08 (1 H, dd, J = 9, 1.5 Hz), 6.18 (1 H, dd, J = 9, 1.5 Hz), 6.55 (1 H, br s), 6.88 (1 H, t, J = 7.5 Hz), 8.21 (1 H, br s). Anal. ($C_9H_{12}N_4O$) C, H, N.

Method C (Scheme 4). 5-Methyl-1-phenyl-2*H*,4*H*-tetrahydro-1,2,4-triazin-3-one (21). A solution of D,L-2-amino-1-propanol (7.51 g, 0.10 mol) in acetonitrile (100 mL) and K_2CO_3 (27.6 g, 0.20 mol) was mechanically stirred at −20 °C while a solution of methyl chloroformate (9.45 g, 0.10 mol) in acetonitrile (20 mL) was added over 0.5 h. The reaction mixture was stirred overnight at room temperature, filtered, and concentrated *in vacuo* to give 2-[(methoxycarbonyl)amino]-1-propanol (8.47 g, 64%).

To a stirred solution of oxalyl chloride (4.36 g, 34.0 mmol) in methylene chloride (30 mL) at −78 °C was added, dropwise, a solution of dimethyl sulfoxide (5.28 g, 68.0 mmol) in methylene chloride (10 mL) over 15 min. The mixture was stirred for another 15 min at −78 °C followed by the addition of 2-[(methoxycarbonyl)amino]-1-propanol (3.01 g, 22.6 mmol) in methylene chloride (30 mL). The mixture was stirred for 1 h at −78 °C, then triethylamine (7.26 g, 72.0 mmol) was added, and the mixture was allowed to warm to room temperature, filtered, and concentrated *in vacuo* at 30 °C to provide 2-[(methoxycarbonyl)amino]-1-propanal (2.40 g, 80%).

To a solution of 2-[(methoxycarbonyl)amino]-1-propanal in methanol (100 mL) was added aniline (2.05 g, 22.0 mmol) and the mixture adjusted to pH 5−6 with 10% ethanolic HCl. Sodium cyanoborohydride (1.57 g, 25 mmol) was added slowly, and the mixture was stirred at room temperature for 16 h, maintaining the pH at 5−6 with occasional addition of 10% ethanolic HCl. The mixture was acidified to pH 1 with 10% ethanolic HCl and concentrated *in vacuo* at 30 °C. The residue was dissolved in methylene chloride (100 mL) and washed with 10% K_2CO_3 (20 mL), the organic layer was dried over $MgSO_4$ and concentrated *in vacuo*, and the residue was purified by chromatography (silica gel, 10% methylene chloride/ether) to provide methyl *N*-[1-(phenylamino)prop-2-yl]carbamate (2.09 g, 45%).

To a mechanically stirred solution of the carbamate intermediate (4.54 g, 0.021 mol) in water (20 mL) chilled to −10

°C was added concentrated HCl (4.5 mL) followed by dropwise addition of sodium nitrite (1.66 g, 0.02 mol) in water (4 mL). Dimethoxyethane (15 mL) was added to facilitate the stirring. After 1 h at 0 °C the mixture was extracted with benzene and the extracts were dried ($MgSO_4$) and concentrated *in vacuo* to yield methyl *N*-[1-(phenylnitrosoamino)prop-2-yl]carbamate (5.05 g, 97%).

A suspension of zinc dust (5.30 g, 0.08 mol) in water (15 mL) was stirred and cooled to 15 °C while a solution of the *N*-nitroso intermediate (5.05 g, 0.021 mol) in acetic acid (12 mL) was added dropwise while a reaction temperature of 15−20 °C was maintained. The mixture was allowed to warm to room temperature and stirred for 1 h, after which water (100 mL) and methylene chloride (100 mL) were added and the pH was adjusted to 6 with dilute NaOH. The layers were decanted from the zinc residue, and the organic layer was separated, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide crude *N*-[2-[(methoxycarbonyl)amino]propyl-*N*-phenylhydrazine (4.28 g, 90%).

To a stirred solution of the hydrazine intermediate (4.28 g, 0.019 mol) in methylene chloride (25 mL) at −25 °C was added dropwise EtMgBr (2 M solution in THF, 12.5 mL, 0.025 mol), and then the mixture was heated at 45 °C for 48 h, treated with ice water, and adjusted to pH 3−4 with 6 N HCl. A portion of the precipitated product was isolated by filtration, while the remainder was isolated by drying and evaporation of the methylene chloride layer. The combined solids were crystallized from ethanol to provide **21** (1.15 g, 32%): mp 238−240 °C; ^{1}H NMR (300 MHz, DMSO-d_6) 1.00 (3 H, d, J = 6.0 Hz), 2.89 (1 H, dd, J = 15, 10.5 Hz), 3.25 (1 H, m), 4.03 (1 H, dd, J = 13.5, 4.5 Hz), 6.68 (1 H, s), 6.86 (1 H, t, J = 7.5 Hz), 7.03 (2 H, d, J = 7.5 Hz), 7.25 (2 H, t, J = 7.5 Hz), 8.42 (1 H, d, J = 1.5 Hz). Anal. ($C_{10}H_{13}N_3O$) C, H, N.

5,5-Dimethyl-1-phenyl-2*H*,4*H*-tetrahydro-1,2,4-triazin-3-one (22). Method C: 14% overall yield; mp 273 °C; ^{1}H NMR (300 MHz, DMSO-d_6) 0.95 (6 H, s), 3.58 (2 H, s), 6.72 (1 H, t, J = 7.5 Hz), 6.81 (1 H, br s), 7.01 (2 H, d, J = 7.5 Hz), 7.2 (2 H, t, J = 7.5 Hz), 8.39 (1 H, br s). Anal. Calcd for $C_{11}H_{15}N_3O$: C, 64.37; H, 7.37; N, 20.47. Found: C, 64.39; H, 7.34; N, 20.55.

5-Ethyl-1-phenyl-2*H*,4*H*-tetrahydro-1,2,4-triazin-3-one (23). Method C: 41% overall yield; mp 205 °C; ^{1}H NMR (300 MHz, DMSO-d_6) 0.82 (3 H, t, J = 7 Hz), 1.3−1.45 (2 H, m), 2.99 (1 H, dd, J = 12, 10 Hz), 3.03−3.12 (2 H, m), 4.04 (1 H, dd, J = 13, 3 Hz), 6.68 (1 H, br s), 6.85 (1 H, t, J = 7.5 Hz), 7.03 (2 H, d, J = 7.5 Hz), 7.25 (2 H, t, J = 7.5 Hz), 8.39 (1 H, br s). Anal. ($C_{11}H_{15}N_3O$) C, H, N.

5-Isopropyl-1-phenyl-2*H*,4*H*-tetrahydro-1,2,4-triazin-3-one (24). Method C: 18% overall yield; mp 181−182 °C; ^{1}H NMR (300 MHz, DMSO-d_6) 0.85 (6 H, d, J = 7.5 Hz), 1.64 (1 H, m), 2.96−3.12 (2 H, m), 4.00 (1 H, d, J = 7.5 Hz), 6.56 (1 H, br s), 6.86 (1 H, t, J = 7.5 Hz), 7.03 (2 H, d, J = 7.5 Hz), 7.26 (2 H, t, J = 7.5 Hz), 8.44 (1 H, d, J = 1.5 Hz). Anal. ($C_{12}H_{17}N_3O$) C, H, N.

5-*n*-Butyl-1-phenyl-2*H*,4*H*-tetrahydro-1,2,4-triazin-3-one (25). Method C: 35% overall yield; mp 153−155 °C; ^{1}H NMR (300 MHz, DMSO-d_6) 0.83 (3 H, t, J = 7.5 Hz), 1.10−1.50 (6 H, m), 2.99 (1 H, dd, J = 15, 10.5 Hz), 3.09−3.19 (1 H, m), 4.03 (1 H, dd, J = 13.5, 4.5 Hz), 6.62 (1 H, s), 6.86 (1 H, t, J = 7.5 Hz), 7.04 (2 H, d, J = 7.5 Hz), 7.26 (2 H, t, J = 7.5 Hz), 8.42 (1 H, d, J = 1.5 Hz). Anal. ($C_{13}H_{19}N_3O\cdot 0.125H_2O$) C, H, N.

5-Methyl-1-(3-methylphenyl)-2*H*,4*H*-tetrahydro-1,2,4-triazin-3-one (26). Method C: 14% overall yield; mp 228−229 °C; ^{1}H NMR (300 MHz, DMSO-d_6) 1.0 (3 H, d, J = 6 Hz), 2.26 (3 H, s), 2.86 (1 H, dd, J = 13, 10 Hz), 3.21−3.31 (1 H, m), 4.03 (1 H, dd, J = 13, 4.5 Hz), 6.57−6.62 (2 H, m), 6.8−6.87 (2 H, m), 7.13 (1 H, t, J = 7.5 Hz), 8.39 (1 H, br s). Anal. ($C_{11}H_{15}N_3O$) C, H, N.

1-(3-Fluorophenyl)-5-methyl-2*H*,4*H*-tetrahydro-1,2,4-triazin-3-one (27). Method B: 42% overall yield; mp 238−240 °C; ^{1}H NMR (300 MHZ, DMSO-d_6) 1.1 (3 H, d, J = 6 Hz), 2.91 (1 H, dd, J = 14 Hz, J = 10 Hz), 3.24−3.34 (2 H, m), 4.09 (1 H, dd, J = 14 Hz, J = 3 Hz), 6.14 (1 H, dt, J = 8 Hz, J = 2 Hz), 6.77 (1 H, br s), 6.8−6.89 (2 H, m), 7.23−7.32 (1 H, m), 8.52 (1 H, br s). Anal. ($C_{10}H_{12}FN_3O$) C, H, N, F.

5-Methyl-1-(3-chlorophenyl)-2*H*,4*H*-tetrahydro-1,2,4-triazin-3-one (28). Method C: 21% overall yield; mp 246−247 °C; ^{1}H NMR (300 MHz, DMSO-d_6) 1.02 (3 H, d, J = 7 Hz), 2.92 (1 H, dd, J = 13, 10 Hz), 3.22−3.33 (2 H, m), 4.08 (1 H, dd, J = 13, 4 Hz), 6.77 (1 H, br s), 6.88 (1 H, d, J = 7.5 Hz), 7.01 (1 H, dd, J = 7.5, 1.0 Hz), 7.27 (1 H, t, J = 7.5 Hz), 8.53 (1 H, d, J = 1 Hz). Anal. ($C_{11}H_{12}ClN_3O$) C, H, N.

1-(3-Bromophenyl)-5-methyl-2*H*,4*H*-tetrahydro-1,2,4-triazin-3-one (29). Method B: 36% overall yield; mp 230−232 °C; ^{1}H NMR (300 MHz, DMSO-d_6) 1.1 (3 H, d, J = 7 Hz), 2.91 (1 H, dd, J = 14, 10 Hz), 3.22−3.34 (2 H, m), 3.9 (1 H, dd, J = 14, 3 Hz), 6.79 (1 H, s), 7.02 (2 H, t, J = 9 Hz), 7.20 (2 H, t, J = 8 Hz), 8.02 (1 H, s). Anal. ($C_{10}H_{12}BrN_3O$) C, H, N.

5-Phenoxy-1-phenyl-2*H*,4*H*-tetrahydro-1,2,4-triazin-3-one (30). Method B: 34% overall yield; mp 161 °C; ^{1}H NMR (300 MHz, DMSO-d_6) 3.08 (2 H, m), 3.62 (2 H, t, J = 5.5 Hz), 6.45 (1 H, dd, J = 9, 2 Hz), 6.67 (1 H, br s), 6.74 (1 H, t, J = 2 Hz), 6.83 (1 H, dd, J = 9, 2 Hz), 6.98 (2 H, m), 7.12 (1 H, t, J = 7.5 Hz), 7.25 (1 H, t, J = 7.5 Hz), 7.38 (2 H, m), 8.45 (1 H, d, J = 3 Hz). Anal. ($C_{15}H_{15}N_3O_2$) C, H, N.

5-(4-Fluorophenoxy)-1-phenyl-2*H*,4*H*-tetrahydro-1,2,4-triazin-3-one (31). Method B: 37% overall yield; mp 199 °C; ^{1}H NMR (300 MHz, DMSO-d_6) 3.03 (2 H, m), 3.70 (2 H, t, J = 5.5 Hz), 6.38 (1 H, dd, J = 9, 2 Hz), 6.62 (1 H, br s), 6.68 (1 H, t, J = 2 Hz), 6.77 (1 H, dd, J = 9, 2 Hz), 7.01 (2 H, m), 7.15 (3 H, m), 8.41 (1 H, d, J = 3 Hz). Anal. ($C_{15}H_{14}FN_3O_2\cdot 0.25H_2O$) C, H, N.

Method D (Scheme 5). 5-(Hydroxymethyl)-1-phenyl-2*H*,4*H*-tetrahydro-1,2,4-triazin-3-one (32). To a solution of aniline (2.79 g, 0.03 mol) in dichloromethane (10 mL) cooled to 0 °C was added dropwise EtMgBr (2 M in THF, 15.0 mL, 0.03 mol). The mixture was stirred for 30 min, followed by portionwise addition of DL-serine methyl ester hydrochloride (1.56 g, 0.01 mol) over a 1 h period. The thick reaction mixture was diluted with additional dichloromethane (10 mL) and then heated at reflux for 3 days. The mixture was cooled to room temperature, saturated aqueous NH_4Cl (50 mL) was added, the mixture was extracted with dichloromethane (2 × 100 mL), dried ($MgSO_4$), and concentrated *in vacuo*, and the residue was triturated in pentane/ether (1:1) to give DL-serine phenylamide (0.47 g, 26%): mp 116−118 °C.

To a solution of DL-serine phenylamide (1.96 g, 0.01 mol) in THF (50 mL) was added dropwise a suspension of $LiAlH_4$ (0.84 g, 0.02 mol) in THF (35 mL) with stirring at room temperature. The mixture was stirred at reflux overnight, cooled, and quenched by dropwise addition of water (0.9 mL), followed by 15% NaOH solution (0.9 mL) and then more water (2.7 mL). The mixture was stirred for 3 h and filtered, and the filtrate was concentrated *in vacuo*. The residue which began to solidify within a short time was triturated in ether (10 mL) and the solid collected to give 2-amino-1-(phenylamino)-3-propanol (1.2 g, 67%): mp 89−92 °C.

2-Amino-1-(phenylamino)-3-propanol (1.20 g, 0.007 mol) and triethylamine (0.73 g, 7 mmol) in THF (50 mL) was stirred at −5 °C while a solution of methyl chloroformate (0.68 g, 7 mmol) in THF (15 mL) was added dropwise. The mixture was stirred at −5 °C for 2 h, allowed to warm to room temperature, filtered, and concentrated *in vacuo* to give methyl *N*-[1-(phenylamino)-3-hydroxyprop-2-yl]carbamate (1.73 g, 99%).

A mixture of methyl *N*-[1-(phenylamino)-3-hydroxyprop-2-yl]carbamate (1.73 g, 7.7 mmol), concentrated HCl (2.0 mL), water (10 mL), and dimethoxyethane (6 mL) was stirred at 0 °C and $NaNO_2$ (0.59 g, 8.5 mmol) in water (1.0 mL) was added dropwise. The mixture was stirred at 0 °C for 1 h, extracted with dichloromethane (100 mL), and concentrated *in vacuo* to give methyl *N*-[1-(nitrosophenylamino)-3-hydroxyprop-2-yl]-carbamate (1.78 g, 91%).

To a stirred suspension of zinc dust (1.80 g, 0.027 mol) in water (5.3 mL) cooled to 15 °C was added dropwise a solution of methyl *N*-[1-(nitrosophenylamino)-3-hydroxyprop-2-yl]carbamate (1.78 g, 0.007 mol) in acetic acid (4.5 mL). After the addition, the cooling bath was removed and the mixture was stirred at room temperature for 1 h. Dichloromethane (10 mL) was added, the mixture was adjusted to pH 6 with 15% NaOH, and the organic and aqueous layers were decanted from the zinc residue which was extracted with a fresh portion (10 mL)

of dichloromethane. The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to yield *N*-[2-[(methoxycarbonyl)amino]-3-hydroxyprop-1-yl]-*N*-phenylhydrazine (1.53 g, 92%).

To a solution of the hydrazine intermediate (1.53 g, 0.006 mol) in dichloromethane (10 mL), chilled to −30 °C, was added dropwise EtMgBr (2 M in THF, 12.0 mL, 0.024 mol), and the mixture was heated at 50 °C for 4 days, cooled, and treated with a solution of concentrated HCl (2.0 mL) in methanol (25 mL). The mixture was concentrated *in vacuo*, the residue was extracted with 10% methanol in dichloromethane (4 × 25 mL), dried ($MgSO_4$), and concentrated *in vacuo*, and the residue was purified by chromatography (silica gel, 1% methanol/dichloromethane) to give **32** (9 mg, 0.7%): mp 223−224 °C dec; ^{1}H NMR (300 MHz, DMSO-d_6) 3.08−3.30 (4 H, m), 4.01 (1 H, d, J = 10.5 Hz), 4.77 (1 H, t, J = 6.0 Hz), 6.46 (1 H, br s), 6.86 (1 H, t, J = 7.5 Hz), 7.02 (2 H, d, J = 7.5 Hz), 7.26 (2 H, t, J = 7.5 Hz), 8.47 (1 H, d, J = 1.5 Hz). Anal. ($C_{10}H_{13}N_3O_2$) C, H, N.

5-[(Methoxyethoxy)methyl]-1-phenyl-2*H*,4*H*-tetrahydro-1,2,4-triazin-3-one (33). Method B: 2% overall yield; mp 118−120 °C; ^{1}H NMR (300 MHz, DMSO-d_6) 3.35 (3 H, s), 3.44−3.96 (9 H, m), 5.42 (1 H, m), 6.85 (2 H, d, J = 7.5 Hz), 6.92 (1 H, t, J = 7.5 Hz), 7.28 (2 H, t, J = 7.5 Hz), 8.50 (1 H, s). Anal. ($C_{13}H_{19}N_3O_3$) C, H, N.

1-Pyrid-2-yl-2*H*,4*H*-tetrahydro-1,2,4-triazin-3-one (34). Method B: 35% overall yield; mp 174−176 °C; ^{1}H NMR (300 MHz, DMSO-d_6) 3.06−3.13 (2 H, m), 3.87 (2 H, t, J = 6 Hz), 6.77 (1 H, br s), 6.80−6.85 (1 H, m), 7.03 (1 H, d, J = 7.5 Hz), 7.64−7.7 (1 H, m), 8.15−8.2 (1 H, m), 8.63 (1 H, br s). Anal. ($C_8H_{10}N_4O\cdot0.125H_2O$) C, H, N.

1-Pyrid-3-yl-2*H*,4*H*-tetrahydro-1,2,4-triazin-3-one (35). Method B: 5% overall yield; ^{1}H NMR (300 MHz, DMSO-d_6) 3.08 (2 H, m), 3.69 (2 H, t, J = 5.5 Hz), 6.75 (1 H, br s), 7.29 (1 H, m), 7.41 (1 H, m), 8.08 (1 H, dd, J = 6, 1.5 Hz), 8.38 (1 H, d, J = 3 Hz), 8.55 (1 H, br s). Anal. ($C_8H_{10}N_4O$) C, H, N.

1-Pyrid-4-yl-2*H*,4*H*-tetrahydro-1,2,4-triazin-3-one (36). Method B: 21% overall yield; mp 179−181 °C; ^{1}H NMR (300 MHz, DMSO-d_6) 3.07 (2 H, q, J = 6 Hz), 3.22−3.29 (2 H, m), 5.72 (1 H, t, J = 7 Hz), 7.27 (1 H, br s), 7.72 (2 H, d, J = 6 Hz), 8.31 (2 H, d, J = 6 Hz). Anal. ($C_8H_{10}N_4O$) C, H, N.

1-(6-Methylpyrid-2-yl)-2*H*,4*H*-tetrahydro-1,2,4-triazin-3-one (37). Method B: 36% overall yield; mp 191−193 °C; ^{1}H NMR (300 MHz, DMSO-d_6) 2.35 (1 H, s), 3.04−3.11 (2 H, m), 3.87 (2 H, t, J = 5 Hz), 6.68 (1 H, d, J = 7 Hz), 6.73 (1 H, bs), 6.8 (1 H, d, J = 8 Hz), 7.55 (1 H, t, J = 8 Hz) 8.58 (1 H, s); MS *m/e* 193 $(M + H)^+$. Anal. Calcd for $C_9H_{12}N_4O$: C, 56.23; H, 6.29; N, 29.14. Found: C, 55.80; H, 5.97; N, 29.05.

5-Methyl-1-(6-methylpyrid-2-yl)-2*H*,4*H*-tetrahydro-1,2,4-triazin-3-one (38). Method B: 12% overall yield; mp 253−254 °C; ^{1}H NMR (300 MHz, DMSO-d_6) 1.02 (3 H, d, J = 7 Hz), 2.33 (3 H, s), 2.9 (1 H, dd, J = 14, 10 Hz), 3.29−3.34 (1 H, m), 4.53 (1 H, dd, J = 14, 4 Hz), 6.65 (1 H, d, J = 7 Hz), 6.76 (1 H, br s), 6.78 (1 H, d, J = 7 Hz), 7.53 (1 H, t, J = 8 Hz), 8.56 (1 H, br s). Anal. ($C_{10}H_{14}N_4O$) C, H, N.

1-(6-Fluoro-2-pyridyl)-2*H*,4*H*-tetrahydro-1,2,4-triazin-3-one (39). Method B: 32% overall yield; mp 181−183 °C; ^{1}H NMR (300 MHz, DMSO-d_6) 3.07−3.15 (2 H, m), 3.82 (2 H, t, J = 6 Hz), 6.51 (1 H, dd, J = 9, 1.5 Hz), 6.85−6.90 (2 H, br m), 7.83 (1 H, q), 8.73 (1 H, br s); MS *m/e* 197 $(M + H)^+$. Anal. ($C_8H_9FN_4O\cdot0.25H_2O$) C, H, N.

1-(6-Fluoropyrid-2-yl)-5-methyl-2*H*,4*H*-tetrahydro-1,2,4-triazin-3-one (40). Method B: 15% overall yield; mp 240 °C dec; ^{1}H NMR (300 MHz, DMSO-d_6) 1.03 (3 H, d, J = 7 Hz), 3.0 (1 H, dd, J = 14, 9 Hz), 3.31−3.41 (1 H, m), 4.33 (1 H, dd, J = 14, 4 Hz), 6.47 (1 H, dd, J = 8, 3 Hz), 6.85 (1 H, dd, J = 8, 3 Hz), 6.81 (1 H, q), 8.71 (1 H, br s). Anal. ($C_9H_{11}FN_4O$) C, H, N.

1-(6-Chloropyrid-2-yl)-2*H*,4*H*-tetrahydro-1,2,4-triazin-3-one (41). Method B: 29% overall yield; mp 194−196 °C; ^{1}H NMR (300 MHz, DMSO-d_6) 3.08−3.16 (2 H, m), 3.84 (2 H, t, J = 5 Hz), 6.85 (1 H, d, J = 7 Hz), 6.89 (1 H, br s), 6.95 (1 H, d, J = 7 Hz), 7.70 (1 H, t, J = 8 Hz), 8.71 (1 H, s). Anal. ($C_8H_9ClN_4O$) C, H, N.

1-(6-Chloropyrid-2-yl)-5-methyl-2*H*,4*H*-tetrahydro-1,2,4-triazin-3-one (42). Method B: 12% overall yield; mp 255 °C dec; ^{1}H NMR (300 MHz, DMSO-d_6) 1.03 (3 H, d, J = 6 Hz), 3.02 (1 H, dd, J = 14, 9 Hz), 3.31−3.42 (1 H, m), 4.37 (1 H, dd, J = 14, 4 Hz), 6.85 (1 H, d, J = 7 Hz), 6.93 (1 H, d, J = 7 Hz), 6.95 (1 H, br s), 6.69 (1 H, t, J = 8 Hz), 8.69 (1 H, br s). Anal. ($C_9H_{11}ClN_4O\cdot0.125H_2O$) C, H, N.

1-(6-Bromopyrid-2-yl)-2*H*,4*H*-tetrahydro-1,2,4-triazin-3-one (43). Method B: 13% overall yield; mp 237−239.5 °C; ^{1}H NMR (300 MHz, DMSO-d_6) 3.10 (2 H, m), 3.86 (2 H, t, J = 5.25 Hz), 6.84 (1 H, br S), 6.99 (1 H, d, J = 9.0 Hz), 7.86 (1 H, dd, J = 3.0, 9.0 Hz), 8.26 (1 H, d, J = 3.0 Hz), 8.67 (1 H, d, J = 1.5 Hz); MS *m/e* 257 $(M + H)^+$. Anal. ($C_8H_9BrN_4O$) C, H, N.

1-(6-Bromopyrid-2-yl)-5-methyl-2*H*,4*H*-tetrahydro-1,2,4-triazin-3-one (44). Method B: 12% overall yield; mp 252−253 °C; ^{1}H NMR (300 MHz, DMSO-d_6) 1.04 (3 H, d, J = 6 Hz), 3.03 (1 H, dd, J = 14, 9 Hz), 3.31−3.43 (1 H, m), 4.35 (1 H, dd, J = 14, 4 Hz), 6.94−7.0 (3 H, m), 7.58 (1 H, t, J = 8 Hz), 8.69 (1 H, br s). Anal. ($C_9H_{11}BrN_4O\cdot0.25H_2O$) C, H, N.

1-(6-Methoxypyrid-2-yl)-2*H*,4*H*-tetrahydro-1,2,4-triazin-3-one (45). Method B: 18% overall yield; mp 235−236 °C; ^{1}H NMR (300 MHz, DMSO-d_6) 3.07−3.13 (2 H, m), 3.79 (3 H, s), 3.86 (2 H, t, J = 5 Hz), 6.22 (1 H, d, J = 7 Hz), 6.53 (1 H, d, J = 7 Hz), 6.74 (1 H, br s), 7.57 (1 H, t, J = 8 Hz), 8.61 (s). Anal. ($C_9H_{12}N_4O_2\cdot0.5H_2O$) C, H, N.

5-Methyl-1-(6-methoxypyrid-2-yl)-2*H*,4*H*-tetrahydro-1,2,4-triazin-3-one (46). Method B: 9% overall yield; mp 196−197 °C; ^{1}H NMR (300 MHz, DMSO-d_6) 1.02 (3 H, d, J = 6 Hz), 3.01 (1 H, dd, J = 14, 9 Hz), 3.27−3.41 (4 H, m, s), 4.43 (1 H, dd, J = 14, 3 Hz), 6.2 (1 H, d, J = 7 Hz), 6.51 (1 h, d, J = 7 Hz), 6.82 (1 H, br s), 7.55 (1 H, t, J = 8 Hz), 8.61 (1 H, br s). Anal. ($C_{10}H_{14}N_4O_2\cdot0.25H_2O$) C, H, N.

1-(7-Chloroquinol-4-yl)-2*H*,4*H*-tetrahydro-1,2,4-triazin-3-one (47). Method B: 26% overall yield; mp >250 °C; ^{1}H NMR (300 MHz, DMSO-d_6) 3.41 (2 H, t, J = 7.5 Hz), 3.51 (2 H, m), 6.75 (1 H, d, J = 6 Hz), 7.01 (1 H, br s), 7.51 (1 H, dd, J = 9, 3 Hz), 7.84 (1 H, d, J = 1.5 Hz), 8.15 (1 H, d, J = 9 Hz), 8.45 (1 H, d, J = 9 Hz), 9.31 (1 H, br s). Anal. ($C_{12}H_{11}ClN_4O\cdot0.5H_2O$) C, H, N.

1-Quinol-3-yl-2*H*,4*H*-tetrahydro-1,2,4-triazin-3-one (48). Method B: 12% overall yield; mp 184−186 °C; ^{1}H NMR (300 MHz, DMSO-d_6) 3.1−3.17 (2 H, m), 3.83 (2 H, t, J = 5 Hz), 6.82 (1 H, br s), 7.5−7.6 (2 H, m), 7.73 (1 H, d, J = 3.0 Hz), 7.84−7.87 (1 H, m), 7.91−7.96 (1 H, m), 8.67 (1 H, d, J = 1.5 Hz), 9.87 (1 H, d, J = 3 Hz). Anal. ($C_{12}H_{12}N_4O$) C, H, N.

1-Benzothiazol-2-yl-2*H*,4*H*-tetrahydro-1,2,4-triazin-3-one (49). Method B: 13% overall yield; mp 249−252 °C; ^{1}H NMR (300 MHz, DMSO-d_6) 3.31−3.36 (2 H, m), 3.53−3.6 (2 H, t, J = 7 Hz), 7.09 (1 H, dt, J = 7.5, 1 Hz), 7.15 (1 H, br s), 7.27 (1 H, dt, J = 7.5, 1 Hz), 7.45 (1 H, d, J = 7.5 Hz), 7.75 (1 H, d, J = 7.5 Hz), 9.75 (1 H, br s). Anal. ($C_{10}H_{10}N_4OS$) C, H, N.

1-Benzoxazol-2-yl-2*H*,4*H*-tetrahydro-1,2,4-triazin-3-one (50). Method B: 8% overall yield; mp 240−241 °C; ^{1}H NMR (300 MHz, DMSO-d_6) 3.28−3.34 (2 H, m), 3.83 (2 H, t, J = 5 Hz), 7.08 (1 H, br s), 7.16 (1 H, dt, J = 7.5, 1.5 Hz), 7.25 (1 H, dt, J = 7.5, 1.5 Hz), 7.45 (1 H, d, J = 7.5 Hz), 7.55 (1 H, d, J = 7.5 Hz), 9.05 (1 H, br s). Anal. ($C_{10}H_{10}N_4O\cdot0.25H_2O$) C, H, N.

1-(3-Pyrid-2-ylphenyl)-2*H*,4*H*-tetrahydro-1,2,4-triazin-3-one (51). Method E: 17% overall yield; mp 261 °C dec; ^{1}H NMR (300 MHz, DMSO-d_6) 3.08 (2 H, m), 3.71 (2 H, t, J = 5.25), 6.67 (1 H, d, J = 1.5 Hz), 7.12 (1 H, dd, J = 1.5, 7.5 Hz), 7.32−7.42 (2 H, m), 7.56 (1 H, d, J = 7.5 Hz), 7.79 (1 H, t, J = 1.5 Hz), 7.83−7.96 (2 H, m), 8.51 (1 H, d, J = 1.5 Hz), 8.66 (1 H, d, J = 4.5 Hz). Anal. ($C_{14}H_{14}N_4O$) C, H, N.

1-(3-Pyrid-4-ylphenyl)-2*H*,4*H*-tetrahydro-1,2,4-triazin-3-one (52). Method E: 13%; mp 250 °C dec; ^{1}H NMR (300 MHz, DMSO-d_6) 3.04 (2 H, m), 3.75 (2 H, t, J = 5.25 Hz), 6.69 (1 H, d, J = 1.5 Hz), 7.16 (1 H, dd, J = 1.5, 7.5 Hz), 7.29 (1 H, d, J = 7.5 Hz), 7.38−7.47 (2 H, m), 7.67 (2 H, d, J = 6.0 Hz), 8.54 (1 H, s), 8.64 (2 H, d, J = 6.0 Hz). Anal. ($C_{14}H_{14}N_4O\cdot0.5H_2O$) C, H, N.

1-(3-Thien-2-ylphenyl)-2*H*,4*H*-tetrahydro-1,2,4-triazin-3-one (53). Method E: 15% overall yield; mp 212−215 °C; ^{1}H NMR (300 MHz, DMSO-d_6) 3.08 (2 H, dt, J = 2, 5 Hz), 3.70 (2 H, t, J = 5 Hz), 6.68 (1 H, d, J = 2 Hz), 6.99 (1 H, dd,

J = 2, 7 Hz), 7.15 (2 H, m), 7.30 (2 H, m), 7.47 (1 H, dd, J = 1, 3 Hz), 7.54 (1 H, dd, J = 1, 4 Hz), 8.50 (1 H, d, J = 2 Hz). Anal. ($C_{13}H_{13}N_3OS$) C, H, N.

Method E (Scheme 6). 5-Methyl-1-(3-thien-2-ylphenyl)-2*H*,4*H*-tetrahydro-1,2,4-triazin-3-one (54). To a stirred solution of thiophene (4.88 g, 58 mmol) in ether (60 mL) at 0 °C was added dropwise *n*-butyllithium (2.5 M in hexanes, 23.0 mL, 58 mmol). After 3 h of stirring at 0 °C, the mixture was cooled to −78 °C and a solution of trimethyltin chloride (11.5 g, 58 mmol) in ether (60 mL) was added dropwise. The mixture was allowed to warm to room temperature, filtered, and concentrated *in vacuo*. The residue was distilled at reduced pressure to give 2-(trimethylstannyl)thiophene (9.61 g, 67%), bp 79−81 °C at 12 mmHg.

A mixture of 2-(trimethylstannyl)thiophene (1.92 g, 7.8 mmol), 3-bromophenyl-2*H*,4*H*-tetrahydro-1,2,4-triazin-3-one (**29**, 1.05 g, 3.9 mmol), and tetrakis(triphenylphosphine)-palladium(0) (0.23 g, 0.2 mmol) in toluene (15 mL) was stirred under nitrogen at reflux 4 h, cooled to room temperature, and poured into saturated aqueous NH_4Cl (50 mL). The mixture was extracted with 15−20% methanol/dichloromethane (2 × 85 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude produce was purified by chromatography (silica gel, 2−3% methanol/dichloromethane) followed by two crystallizations from ethanol to provide **54** (0.27 g, 26%): mp 198.5−200.5 °C; ^{1}H NMR (300 MHz, DMSO-d_6) 1.02 (3 H, d, J = 6.0 Hz), 2.93 (1 H, dd, J = 10.5, 13.5 Hz), 3.32 (1 H, m), 4.13 (1 H, dd, J = 4.5, 13.5 Hz), 6.73 (1 H, s), 6.99 (1 H, dd, J = 2.5, 7.5 Hz), 7.14 (2 H, m), 7.29 (2 H, m), 7.47 (1 H, m), 7.54 (1 H, m), 8.51 (1 H, d, J = 1.5 Hz). Anal. ($C_{14}H_{15}N_3OS$) C, H, N.

1-(3-Thien-2-ylphenyl)-2*H*,4*H*-tetrahydro-1,2,4-triazin-3-one (55). Method E: 32% overall yield; mp 227 °C dec; ^{1}H NMR (300 MHz, DMSO-d_6) 3.08 (2 H, m), 3.72 (2 H, t, J = 5.25 Hz), 6.66 (1 H, d, J = 1.5 Hz), 6.97 (1 H, m), 7.16−7.39 (3 H, m), 7.52 (1 H, dd, J = 1.5, 6.0 Hz), 7.64 (1 H, dd, J = 3.0, 4.5 Hz), 7.81 (1 H, dd, J = 1.5, 3.0 Hz), 8.47 (1 H, d, J = 1.5 Hz). Anal. ($C_{13}H_{13}N_3OS$) C, H, N.

5-Methyl-1-(3-fur-2-ylphenyl)-2*H*,4*H*-tetrahydro-1,2,4-triazin-3-one (56). Method E: 64% overall yield; mp 212−214 °C; ^{1}H NMR (300 MHz, DMSO-d_6) 1.02 (3 H, d, J = 6.0 Hz), 2.93 (1 H, dd, J = 10.5, 13.5 Hz), 3.30 (1 H, m), 4.11 (1 H, dd, J = 4.5, 13.5 Hz), 6.59 (1 H, m), 6.72 (1 H, s), 6.91 (1 H, d, J = 3.0 Hz), 6.97 (1 H, dd, J = 1.5, 7.5 Hz), 7.17−7.39 (3 H, m), 7.74 (1 H, d, J = 1.5 Hz), 8.48 (1 H, d, J = 1.5 Hz). Anal. ($C_{14}H_{15}N_3O_2$) C, H, N.

1-(3-Thiazol-2-ylphenyl)-2*H*,4*H*-tetrahydro-1,2,4-triazin-3-one (57). Method E: 15% overall yield; mp 239 °C dec; ^{1}H NMR (300 MHz, DMSO-d_6) 3.09 (2 H, m), 3.72 (2 H, t, J = 5.25 Hz), 6.72 (1 H, s), 7.17 (1 H, d, J = 7.5 Hz), 7.34−7.48 (2 H, m), 7.66 (1 H, s), 7.78 (1 H, d, J = 3.0 Hz), 7.92 (1 H, d, J = 3.0 Hz), 8.56 (1 H, d, J = 1.5 Hz). Anal. ($C_{12}H_{12}N_4OS$) C, H, N.

1-(6-Thien-2-ylpyrid-2-yl)-2*H*,4*H*-tetrahydro-1,2,4-triazin-3-one (58). Method E: 35% overall yield; mp 253 °C dec; ^{1}H NMR (300 MHz, DMSO-d_6) 3.15 (2 H, m), 3.95 (2 H, t, J = 5.25 Hz), 6.80 (1 H, d, J = 1.5 Hz), 6.90 (1 H, d, J = 7.5 Hz), 7.14 (1 H, dd, J = 3.0, 4.5 Hz), 7.33 (1 H, d, J = 7.5 Hz), 7.59 (1 H, dd, J = 1.5, 4.5 Hz), 7.67−7.78 (2 H, m), 8.67 (1 H, d, J = 1.5 Hz). Anal. ($C_{12}H_{12}N_4OS$) C, H, N.

1-(6-Pyrid-2-ylpyrid-2-yl)-2*H*,4*H*-tetrahydro-1,2,4-triazin-3-one (59). Method E: 47% overall yield; mp 243 °C dec; ^{1}H NMR (300 MHz, DMSO-d_6) 3.18 (2 H, m), 4.05 (2 H, t, J = 5.25 Hz), 6.80 (1 H, d, J = 1.5 Hz), 7.09 (1 H, dd, J = 1.5, 7.5 Hz), 7.38−7.46 (1 H, m), 7.77−7.88 (2 H, m), 7.92 (1 H, dt, J = 1.5, 7.5 Hz), 8.33 (1 H, d, J = 7.5 Hz), 8.62−8.68 (1 H, m), 8.70 (1 H, d, J = 1.5 Hz). Anal. ($C_{13}H_{13}N_5O$) C, H, N.

4-Methyl-1-phenyl-2*H*,4*H*-tetrahydro-1,2,4-triazin-3-one (60). Method F: 30% overall yield; mp 174−178 °C; ^{1}H NMR (300 MHz, DMSO-d_6) 2.73 (3 H, s), 3.11 (2 H, t, J = 6.0 Hz), 3.74 (2 H, t, J = 6.0 Hz), 6.87 (1 H, t, J = 7.5 Hz), 7.02 (2 H, d, J = 7.5 Hz), 7.26 (2 H, t, J = 7.5 Hz), 8.49 (1 H, s). Anal. ($C_{10}H_{13}N_3O$) C, H, N.

4-Ethyl-1-phenyl-2*H*,4*H*-tetrahydro-1,2,4-triazin-3-one (61). Method F: 22% overall yield; mp 152.5−154.5 °C; ^{1}H NMR (300 MHz, DMSO-d_6) 0.94 (3 H, t, J = 7.5 Hz), 3.11 (2 H, t, J = 6.0 Hz), 3.18 (2 H, q, J = 7.5 Hz), 3.73 (2 H, t, J = 6.0 Hz), 6.87 (1 H, t, J = 7.5 Hz), 7.03 (2 H, d, J = 7.5 Hz), 7.26 (2 H, t, J = 7.5 Hz), 8.43 (1 H, s). Anal. ($C_{11}H_{15}N_3O$) C, H, N.

Method F (Scheme 7). 4-(Phenymethyl)-1-phenyl-2*H*,4*H*-tetrahydro-1,2,4-triazin-3-one (62). To a stirred mixture of *N*-phenylethylenediamine (24.4 g, 0.179 mol) and triethylamine (18.1 g, 0.179 mol) in dichloromethane (100 mL) cooled to 0 °C was added dropwise a solution of benzoyl chloride (25.2 g, 0.179 mol) in dichloromethane (50 mL) while the reaction temperature was maintained below 10 °C. The mixture was then stirred at room temperature overnight and washed with 5% NH_4Cl (2 × 75 mL), and the organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to yield benzoic acid 2-(phenylamino)ethylamide (37.8 g, 87%).

To a stirred suspension of $LiAlH_4$ (3.80 g, 0.10 mol) in THF (100 mL) was added dropwise a solution of the benzoic acid amide intermediate (12.02 g, 0.05 mol) in THF (50 mL). The mixture was stirred at reflux overnight, cooled in an ice bath, followed by dropwise addition of water (3.8 mL), followed by 15% NaOH (3.8 mL), and then water (11.3 mL), stirred at room temperature for 1.5 h, filtered, and concentrated *in vacuo* to provide 2-(phenylamino)-1-[(phenymethyl)amino]ethane (11.29, 99%).

To a stirred solution of 2-(phenylamino)-1-[(phenylmethyl)-amino]ethane (11.29 g, 0.049 mol) and triethylamine (5.00 g, 0.049 mol) in dichloromethane (100 mL) cooled to 0 °C was added dropwise a solution of methyl chloroformate (4.68 g, 0.049 mol). The mixture was then stirred at room temperature overnight and washed with 5% NH_4Cl (2 × 75 mL), and the organic layer was dried ($MgSO_4$) and concentrated *in vacuo* to yield methyl *N*-[2-(phenylamino)ethyl]-*N*-(phenylmethyl)-carbamate (13.8 g, 99%).

To a stirred solution of methyl *N*-[2-(phenylamino)ethyl]-*N*-(phenylmethyl)carbamate (13.8 g, 0.048 mol) in dimethoxyethane (20 mL) at 5 °C was added concentrated HCl (9.1 mL) in water (45 mL) followed by dropwise addition of a solution of $NaNO_2$ (3.33 g, 0.048 mol) in water (6 mL). The product which separated as a heavy oil was extracted into dichloromethane, dried over $MgSO_4$, and concentrated *in vacuo* to give methyl *N*-[2-(nitrosophenylamino)ethyl]-*N*-(phenylmethyl)carbamate (15 g, 99%).

A solution of the *N*-nitroso intermediate (17.0 g, 0.054 mol) in glacial acetic acid (30 mL) was introduced dropwise into a mechanically stirred suspension of zinc dust (14.2 g) in water (35 mL), which was cooled in ice during the addition to maintain the reaction temperature between 15−20 °C. The cooling bath was removed and the stirring continued for another hour, during which time the reaction temperature was maintained below 40 °C. The reaction mixture was treated with dichloromethane (200 mL) and water (100 mL) and filtered through a Celite pad to remove the solid zinc residue. The filtrate was treated with 6 N NaOH to pH 6, and the layers were separated, the organic extract was dried over $MgSO_4$ and concentrated *in vacuo* to give *N*-[2-[*N* ′-(phenylmethyl)-*N* ′-(methoxycarbonyl)amino]ethyl]-*N*-phenylhydrazine (16.0 g, 99%).

To a stirred solution of the hydrazine intermediate (15.0 g, 0.05 mol) in dichloromethane (50 mL) at −30 °C was added dropwise EtMgBr (2 M in THF, 31.0 mL, 0.062 mol) under nitrogen. The mixture was gently warmed at 45 °C for 3 days, cooled, and treated with ice and 3 N HCl to pH 4−5, and the layers were separated. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo* and the residue triturated in ether. The crude product was crystallized from benzene to give **62** (3.79 g, 28%): mp 164−166 °C; ^{1}H NMR (300 MHz, DMSO-d_6) 3.02 (2 H, t, J = 6.0 Hz), 3.75 (2 H, t, J = 6.0 Hz), 4.42 (2 H, s), 6.89 (1 H, t, J = 7.5 Hz), 7.02−7.15 (4 H, m), 7.17−7.34 (5 H, m), 8.71 (1 H, s). Anal. ($C_{16}H_{17}N_3O$) C, H, N.

Method G (Scheme 8). 4-Hydroxy-5-methyl-1-phenyl-2*H*,4*H*-tetrahydro-1,2,4-triazin-3-one (63) To a stirred ice cold solution of phenylhydrazine (27.0 g, 0.25 mol) in methylene chloride (350 mL) was added pyridine (19.7 g, 0.25 mol), and the mixture was stirred for 15 min, after which methyl chloroformate (24.5 g, 0.26 mol) in methylene chloride (150 mL) was added dropwise over 0.5 h while the reaction temperature was maintained below 15 °C. The mixture was

stirred for 1 h at room temperature, water (200 mL) was added, the organic layer was separated, washed with 1 N HCl and brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude product was slurried in pentane (150 mL) and filtered to provide 1-(methoxycarbonyl)-2-phenylhydrazine (37.6 g, 90%), mp 110−111 °C.

To a stirred solution of 1-(methoxycarbonyl)-2-phenylhydrazine (25 g, 0.15 mol) and Na_2CO_3 (47.7 g, 0.45 mol) in dichloromethane (350 mL) was added chloroacetone oxime (21.9 g, 0.2 mol), and the mixture was heated at reflux for 18 h. The mixture was cooled to room temperature, filtered, concentrated *in vacuo*, and chromatographed (silica gel, 3% methanol/dichloromethane) to provide 1-(methoxycarbonyl)-2-(phenylhydrazino)acetone oxime (31.25 g, 88%).

To a stirred solution of 1-(methoxycarbonyl)-2-(phenylhydrazino)acetone oxime (31.0 g, 0.13 mol) in ethanol (300 mL) was added dropwise borane/pyridine (37.5 g, 0.4 mol), and the mixture was stirred for 1 h at room temperature and then cooled in an ice bath as 6 N ethanolic HCl (180 mL) was added dropwise. The ethanol was removed *in vacuo*, water (200 mL) was added, and the mixture was extracted with ether (2 × 150 mL). The aqueous layer was brought to pH 11 by addition of 6 N NaOH, extracted with dichloromethane (3 × 150 mL), washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Recrystallization from benzene/ether gave [1-[1-(methoxycarbonyl)-2-phenylhydrazino]-2-propyl]hydroxylamine (16.4 g, 50%).

To a solution of [1-[1-(methoxycarbonyl)-2-phenylhydrazino]-2-propyl]hydroxylamine (0.5 g, 2 mmol) in THF (15 mL) was added potassium *tert*-butoxide (0.24 g, 2 mmol), the mixture was stirred at room temperature for 18 h, ice cold water was added followed by 6 N HCl to pH 5, and the mixture was extracted with dichloromethane (2 × 50 mL), dried ($MgSO_4$), filtered, concentrated *in vacuo*, and recrystallized from ether/pentane to provide **63** (0.22 g, 54%): mp 174−176 °C; ^{1}H NMR (300 MHz, DMSO-d_6) 1.06 (3 H, d, J = 6 Hz), 3.41 (1 H, dd, J = 15, 3 Hz), 3.55 (1 H, m), 4.08 (1 H, dd, J = 15, 3 Hz), 6.86 (1 H, t, J = 7 Hz), 7.05 (2 H, d, J = 7.0 Hz), 7.26 (2 H, t, J = 7 Hz), 8.61 (1 H, s), 9.01 (1 H, s). Anal. ($C_{10}H_{13}N_3O_2$) C, H, N.

4-Hydroxy-5-methyl-1-(3-chlorophenyl)-2*H*,4*H*-tetrahydro-1,2,4-triazin-3-one (64). Method G: 26% yield; mp 180−182 °C; ^{1}H NMR (300 MHz, DMSO-d_6) 1.08 (3 H, d, J = 7 Hz), 3.43 (1 H, m), 3.60 (1 H, m), 4.11 (1 H, dd, J = 15, 4.5 Hz), 6.88 (1 H, dd, J = 9, 3 Hz), 7.06 (2 H, m), 7.27 (2 H, t, J = 9 Hz), 8.71 (1 H, s), 9.13 (1 H, s). Anal. Calcd for $C_{10}H_{12}ClN_3O_2$: C, 49.69; H, 5.01; N, 17.38. Found: C, 49.74; H, 5.13; N, 16.82.

4-Hydroxy-5-methyl-1-(3-methylphenyl)-2*H*,4*H*-tetrahydro-1,2,4-triazin-3-one (65). Method G: 17% yield; mp 177−179 °C; ^{1}H NMR (300 MHz, DMSO-d_6) 1.06 (3 H, d, J = 7 Hz), 2.27 (3 H, s), 3.46 (1 H, m), 3.55 (1 H, m), 4.06 (1 H, dd, J = 15, 4.5 Hz), 6.88 (1 H, d, J = 9 Hz), 6.85 (2 H, m), 7.13 (2 H, t, J = 9 Hz), 8.56 (1 H, s), 9.08 (1 H, s). Anal. ($C_{11}H_{15}N_3O_2 \cdot 0.125H_2O$) C, H, N.

4-Methoxy-5-methyl-1-phenyl-2*H*,4*H*-tetrahydro-1,2,4-triazin-3-one (66). To a solution of 4-hydroxy-5-methyl-1-phenyl-2*H*,4*H*-tetrahydro-1,2,4-triazin-3-one (**63**) (0.2 g, 1 mmol) in acetone (15 mL) was added K_2CO_3 (1.0 g, 7 mmol) and methyl iodide (0.21 g, 1.5 mmol), and the mixture was stirred for 18 h at room temperature, filtered, concentrated *in vacuo*, chromatographed (silica gel, 1:1 ether/dichloromethane), and recrystallized from ether to provide **72** (0.08 g, 36%): mp 138−140 °C; ^{1}H NMR (300 MHz, DMSO-d_6) 1.1 (3 H, d, J = 6 Hz), 3.45 (1 H, dd, J = 15, 4.5 Hz), 3.56 (3 H, s), 3.65 (1 H, m), 4.03 (1 H, dd, J = 15, 4.5 Hz), 6.88 (1 H, t, J = 7 Hz), 7.04 (2 H, d, J = 7.0 Hz), 7.28 (2 H, m), 8.82 (1 H, s). Anal. ($C_{11}H_{15}N_3O_2$) C, H, N.

4-Phenyl-3*H*-trihydro-1,3,4-oxadiazin-2-one (67). A solution of acetyl-2-phenylhydrazine (75.3 g, 0.5 mol), 2-bromoethanol (64.0 g, 0.55 mol), and diisopropylethylamine (68.0 g, 0.55 mol) in toluene (300 mL) was refluxed with stirring for 48 h. The mixture was allowed to cool to room temperature, and dichloromethane (500 mL) and water (250 mL) were added. The organic layer was washed with water (2 × 250 mL), dried ($MgSO_4$), filtered, concentrated *in vacuo*, and purified by chromatography (silica gel, 10% methanol in dichloromethane) to provide acetyl-2-(2-hydroxyethyl)-2-phenylhydrazine (30.4 g, 32%).

Acetyl-2-(2-hydroxyethyl)-2-phenylhydrazine (13.5 g, 0.07 mol) in 6 N HCl (50 mL) was refluxed under nitrogen for 2 h. The mixture was cooled in an ice bath, and 6 N KOH was added to pH 7. The mixture was extracted with ethyl acetate (5 × 100 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give 1-(2-hydroxyethyl)-1-phenylhydrazine (10.2 g, 95%).

To a solution of 1-(2-hydroxyethyl)-1-phenylhydrazine (10.2 g, 0.067 mol) in THF (50 mL) was added carbonyldiimidazole (10.9 g, 0.067 mol), and the mixture was stirred at room temperature for 3 h. Dichloromethane (100 mL) was added, and the organic layer was separated, washed with water (2 × 50 mL) and brine (50 mL), dried ($MgSO_4$), filtered, concentrated *in vacuo*, and purified by chromatography (silica gel, 7% methanol in dichloromethane) followed by recrystallization from ether to provide **67** (2.28 g, 20%): mp 99−100 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 3.74 (2 H, t, J = 10 Hz), 4.29 (2H t, J = 10 Hz), 7.08 (3 H, m), 7.23 (1 H, br), 7.33 (2 H, m). Anal. ($C_9H_{10}N_2O_2$) C, H, N.

1-Phenyl-2*H*,4*H*-tetrahydro-1,2,4-triazine-3-thione (68). To a suspension of 1-phenyl-2*H*,4*H*-triazin-3-one (4.0 g, 23 mmol) in toluene (150 mL) was added Lawesson's reagent (2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane 2,4-disulfide, 10.0 g). The mixture was heated at 80 °C for 15 h and then cooled, and a mixture of methanol/dichloromethane (1:1, 50 mL) and water (100 mL) was added. The organic layer was collected and concentrated to provide a residue which was purified by chromatography (silica gel, 5% methanol in dichloromethane) to provide **68** (1.8 g, 42%): mp 180 °C; ^{1}H NMR (300 MHz, DMSO-d_6) 2.95−3.02 (2 H, m), 3.63 (2 H, t, J = 5 Hz), 6.91−7.01 (3 H, m), 7.30 (2 H, t, J = 7.5 Hz), 8.39 (1 H, br s), 9.97 (1 H, br s). Anal. ($C_9H_{11}N_3S$) C, H, N.

Biological Methods. The biological methods for the inhibition assays *in vitro* and *in vivo* have been previously reported.[2] Percent inhibition was computed by comparing individual values in treatment groups to the mean value of the control group. Statistical significance was determined using one-way analysis of variance and Tukey's multiple comparison procedure. Linear regression was used to estimate IC_{50} and ED_{50} values.

Determination of Drug Plasma Concentrations. Compounds for oral administration were suspended in 0.2% HPMC with a Potter−Elvehjem homogenizer equipped with a Teflon-coated pestle and administered orally to cynomolgus monkeys. Blood samples were collected at various times following compound administration to dogs or cynomolgus monkeys. Blood samples were centrifuged, and the plasma was removed and stored frozen until assayed. Plasma samples were thawed, 2 volumes of methanol was added, and precipitated plasma proteins were removed by centrifugation. Supernatants were injected directly onto a C18 reversed phase column (Adsorbosphere HL 7 micron column) and chromatographed using a mobile phase composed of 55% acetonitrile containing 10 mM acetohydroxamic acid and 8 mM triethylamine acetate, pH 6.5, at a flow rate of 1 mL/min. Compound peaks were quantitated by UV absorbance at 260 nm using an external calibration curve. Data presented are means from two animals.

***Ex Vivo* Leukotriene B_4 Biosynthesis Assay.** Compounds were suspended in 0.2% HPMC with a Potter−Elvehjem homogenizer equipped with a Teflon-coated pestle and administered orally to dogs or cynomolgus monkeys. Heparinized blood samples were obtained before and at various times after compound administration. Aliquots of blood were incubated at 37 °C with 50 μM calcium ionophore, A23187. After 30 min, the blood was placed in an ice bath and centrifuged at 400*g* for 20 min, and the plasma samples were analyzed for LTB_4. The level of LTB_4 in aliquots of the extracts was analyzed by EIA.

Evaluation of Methemoglobinemia *in Vivo*. When oxidative denaturation of hemoglobin to methemoglobin occurs in circulating erythrocytes, intracellular precipitates known as Heinz bodies are formed that can be detected histologically. Blood taken from rats or dogs dosed with test compound or

vehicle and stained with New Methylene Blue was examined under the light microscope for Heinz bodies. The severity of drug-induced methemoglobinemia was assessed by determining the amount of red blood cells in each field that contained Heinz bodies.

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