

Branko S. Jursic* and Donna M. Neumann

Department of Chemistry, University of New Orleans, New Orleans, Louisiana 70148

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NMR reaction following experiments were used to find optimal conditions for the barbituric acid double addition to aromatic and heteroaromatic carboxaldehydes. It was established that aromatic aldehydes with electron-donating substituents such as hydroxy, methoxy, and dimethylamino produce only the single addition barbituric acid adduct (barbituric acid benzylidenes). If these electron-donating substituents are transformed into electron-withdrawing substituents by virtue of protonation (NMe_2 to NHMe_2^+) then the double barbituric acid adduct becomes the sole product of the reaction. This is also true regardless of the reaction media if strong electron-withdrawing substituents (such as a nitro group) are present. Considering that the reactive species for nitrogen containing aromatic heterocycles are actually the conjugated acids (electron deficient molecule) only the double barbituric acid adducts are isolated. All synthetic procedures presented are applicable to multi-gram scale preparations of double barbituric acid adducts.

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Introduction.

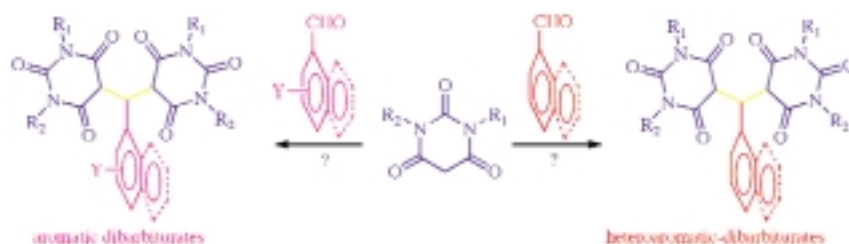
There are some molecular systems that are capable of modulating human immune responses, thus effectively opening an avenue for new and innovative treatments that combat terrible diseases such as AIDS and cancer [1]. Until recently barbituric acid derivatives were mostly used as sedative and anesthetic drugs [2]. However, more non-traditional uses for barbiturates may become predominant in medicinal chemistry due to the fact that recent results suggest that some aromatic-dibarbiturates may possess anticancer activity by modulating human immune responses [3]. A major problem associated with these compounds is the evaluation of the biological properties of aromatic-dibarbiturates, namely because there are not many derivatives available for testing, and those that are available do not have sufficient solubility in aqueous media. One can postulate that both of these problems can be eliminated if the aromatic moieties of the dibarbiturates are substituted with either a pyridine or quinoline moiety. These aromatic heterocycles are more water soluble than the corresponding benzene or naphthalene derivatives. Unfortunately, procedures for the preparation of aromatic and heterocyclic dibarbiturates are not available. From the point of synthetic simplicity and availability, ideal starting materials for the preparation of these compounds should

be aromatic and heteroaromatic aldehydes and nitrogen substituted barbituric acids (Scheme 1).

In general, barbituric acids condense with aromatic aldehydes to form Knoevenagel condensation products [4]. The outcomes of these condensations are not always the simple arylidenobarbiturate, but also some very interesting condensation products can be formed. The nature of these condensation products is determined by the nature of the applied arylcarboxaldehyde. For instance, when 1,3-dimethylbarbituric acid is condensed with 2-pyridinecarboxaldehyde, regardless of the reaction solvent used (DMSO, methanol, acetic acid, *etc.*) the final product is the unique dipyridine-dibarbituric acid ylide **2** (Scheme 2) [5]. When barbituric acid is used instead of 1,3-dimethylbarbituric acid the reaction outcome is different. Thus, in trifluoroacetic acid the condensation product between 2-pyridinecarboxaldehyde and barbituric acid is 2-pyridinemethylenedibarbiturate **1** rather than the corresponding dipyridine-dibarbituric acid ylide **2** (Scheme 2). This is not true for all reaction conditions. Even with barbituric acid as a starting material ($\text{R}=\text{H}$) the reaction conditions can be optimized in such way that ylide **2** ($\text{R}=\text{H}$) becomes the major product of the condensation [6]. This finding suggests that through careful exploration of the reaction conditions, a variety of aromatic-dibarbiturates

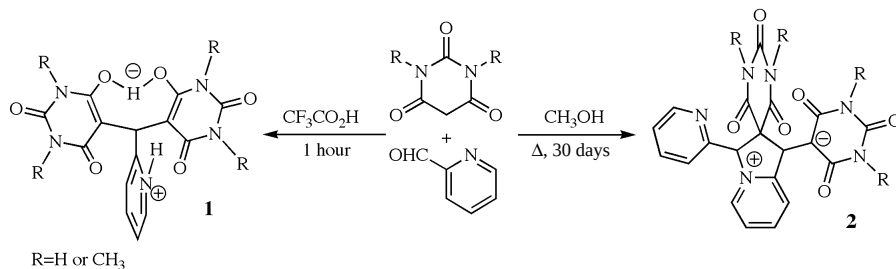
Scheme 1

Possible precursors for one-pot preparation of aromatic and heteroaromatic-dibarbiturates.



Scheme 2

Two different products of barbituric acid ($R=H$) and 1,3-dimethylbarbituric acid ($R=CH_3$) condensation with 2-pyridinecarbaldehyde.



can be prepared from the same starting materials. Here we would like to present a systematic study of aromatic and heteroaromatic aldehydes in condensation with barbituric acids with the target being to prepare both aromatic and heteroaromatic-dibarbiturates.

Results and Discussion.

The fact that the major product of the Knoevenagel condensation between aromatic aldehydes and barbituric acid is the 5-arylidenebarbituric acid is perfectly demonstrated in our NMR following experiment for the condensation between 1-naphthaldehyde and barbituric acid (Figure 1). Regardless of the nature of the reaction media (neutral, acidic, or basic) only one product of the reaction is detected and isolated, 5-naphthalen-1-ylmethylenebarbituric acid. This reaction can be completed in many different solvents (methanol, dioxane, tetrahydrofuran, and dimethyl sulfoxide to name some of them) in a period of 20-40 hours at room temperature. In acidic solvents such as trifluoroacetic acid, the reaction is practically over in two hours at room temperature. We were not able to obtain the double barbituric acid addition product with 1-naphthaldehyde even when the reaction was conducted using a ten-fold molar excess of barbituric acid and at higher temperatures (~ 70 - 120 °C) overnight. The same reaction outcome was obtained when the reaction was carried out with benzaldehyde instead of naphthaldehyde.

Now we will demonstrate the influence of both the solvent and the nature of the substituents attached to benzaldehyde on the outcome of the condensation reaction. In our previous studies we demonstrated that a benzaldehyde with electron donating substituents, such as the dimethylamino group, form the Knoevenagel condensation product easily [4]. This reaction is practically completed after several minutes in refluxing methanol. The same product is detected if the condensation reaction is performed in dimethyl sulfoxide as a reaction media (dimethyl sulfoxide is selected as the reaction media for NMR following reactions because the reaction mixture is a solution, while with methanol as a reaction media the condensation product **4** precipitates from the reaction mixture). Even in dimethyl sulfoxide the Knoevenagel condensation reaction is completed after fourteen hours at room temperature (Figure 2). In this NMR following reaction, we were not able to detect traces of the double barbituric acid addition product **5**. One can argue that this is due to the fact that the addition of the second barbituric acid to the condensation product **4** is a slow process. The second addition of barbituric acid in many ways resembles the Michael-type of nucleophilic addition to α,β -unsaturated carbonyl compounds [7]. In order to perform this reaction a strong nucleophile should be used. The second addition of barbituric acid can only be accomplished with the enol form of barbituric acid. Therefore, strong acidic media are required for this reaction.

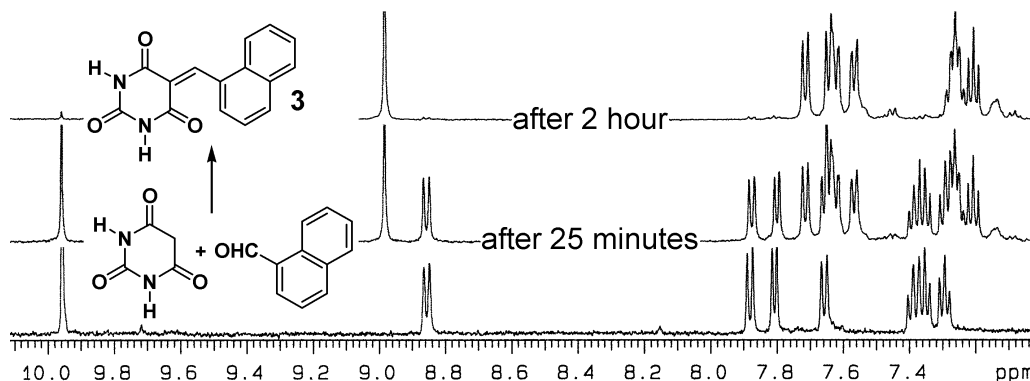


Figure 1. ^1H -NMR (500 MHz) reaction following for 1-naphthaldehyde (1 mM) condensation with barbituric acid (5 mM) in CF_3COOH .

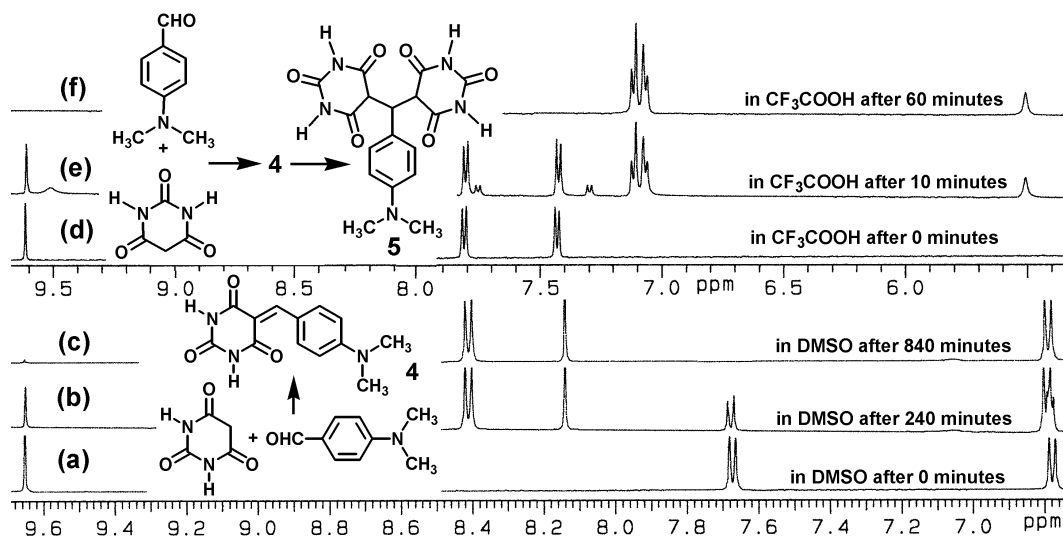


Figure 2. The NMR (500 MHz) reaction following of 4-dimethylaminobenzaldehyde condensation with barbituric acid in DMSO (a, b, and c) and CF_3COOH (d, e, and f).

Through our NMR following experiments in many acidic media ($\text{D}_2\text{O-HCl}$, $\text{CH}_3\text{CO}_2\text{H}$, H_2SO_4 , $\text{CF}_3\text{CO}_2\text{H}$, $\text{CF}_3\text{SO}_3\text{H}$, and H_2SO_4) the best results for the formation of the double addition products are obtained with trifluoroacetic acid. The reaction is practically over in one hour. Formation of the Knoevenagel condensation product **4** was observed (Figure 2e). This intermediate is a very good α,β -unsaturated carbonyl compound that facilitates the second barbituric acid addition in trifluoroacetic acid, which results in the dibarbituric acid adduct **5** (Figure 2e and 2f). In this way we were able to fully convert 4-dimethylaminobenzaldehyde into the double barbituric acid adduct **5**. At this

The $^1\text{H-NMR}$ barbituric acid condensation with both 4-methoxy and 4-hydroxybenzaldehyde (Figure 3) in trifluoroacetic acid fully confirm this assumption. Aromatic aldehydes with strong electron-donating groups such as hydroxy and methoxy react selectively with barbituric acid derivatives to produce only the Knoevenagel condensation product in quantitative yield regardless of the applied reaction media (methanol, $\text{H}_2\text{O-HCl}$, H_2SO_4 , $\text{CH}_3\text{CO}_2\text{H}$, $\text{CF}_3\text{CO}_2\text{H}$) [8]. That is clearly demonstrated on the NMR reaction following for the 4-hydroxybenzaldehyde condensation with barbituric acid in trifluoroacetic acid. Only the condensation product **6** was detected in the NMR solution (Figure 3).

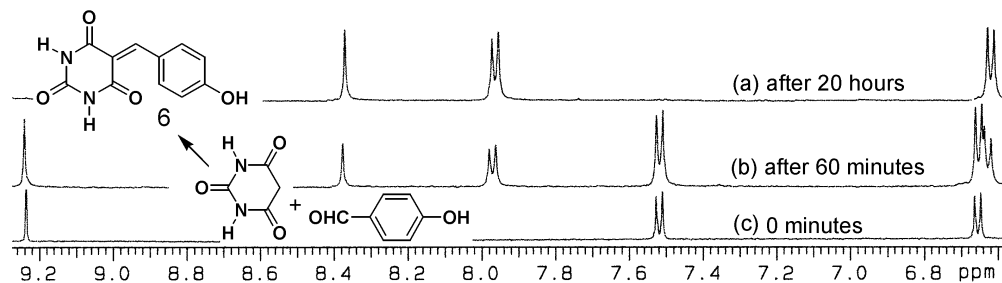


Figure 3. $^1\text{H-NMR}$ reaction following of 4-hydroxybenzaldehyde condensation with barbituric acid in $\text{CF}_3\text{CO}_2\text{H}$.

point one can argue that for the double barbituric acid addition to aromatic aldehydes, a strong electron-withdrawing group attached to the aldehyde's aromatic ring is required. In DMSO-d_6 as a reaction media the electron-donating $(\text{CH}_3)_2\text{N}$ group attached to the aromatic ring was not protonated, therefore only the Knoevenagel condensation product **4** was detected and isolated. In trifluoroacetic acid media ($\text{pK}_a=0.0$) the dimethylamino group is protonated, $(\text{CH}_3)_2\text{HN}^+$, and therefore electron-withdrawing [8].

If it is true that strong electron-withdrawing substituents on the aromatic ring facilitate the second barbituric acid addition to benzaldehyde, then the preparation of aromatic-dibarbiturates from nitrobenzaldehyde should occur in protic as well as aprotic solvents. This is perfectly demonstrated with the NMR reaction following experiments for the barbituric acid addition to benzaldehyde in both dimethyl sulfoxide and trifluoroacetic acid as solvents (Figure 4). The same double addition product **7**

was obtained regardless of the nature of the solvent, the difference being only the time required for the reaction completion. For instance, the reaction is completed in 40 minutes in trifluoroacetic acid media and in 24 hours in dimethyl sulfoxide media, both at room temperature.

A similar parallel can be drawn between the reactivity of nitronaphthaldehydes and quinolinecarboxaldehydes. If this assumption is true then the addition of barbituric acid to quinolinecarboxaldehyde in any solvent should afford the double addition product and the required reaction time

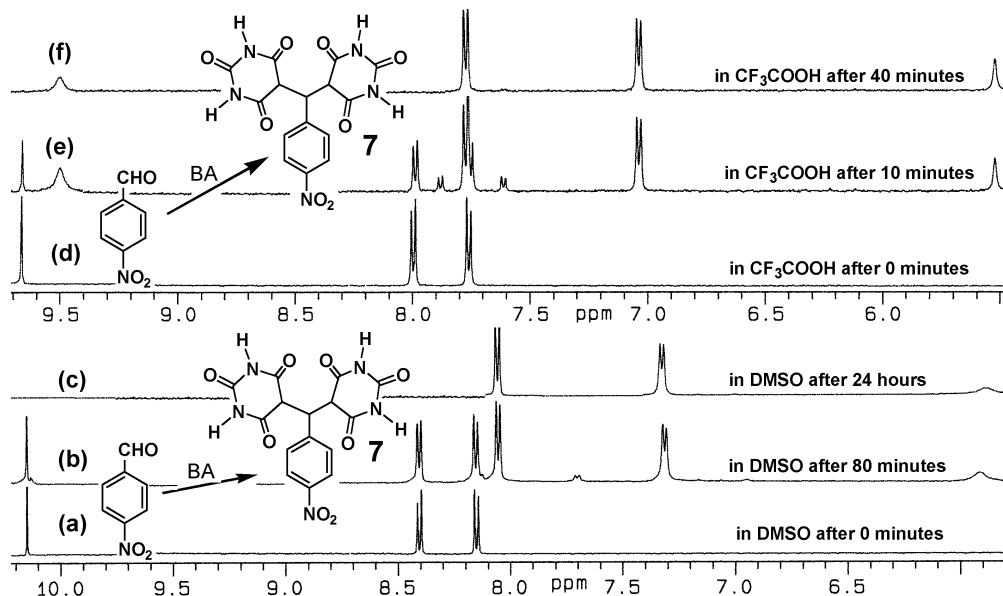


Figure 4. ^1H -NMR reaction following in DMSO-d_6 and CF_3COOH with electron-deficient aromatic aldehydes.

In many reactivity aspects nitrogen heterocycles are similar to the corresponding nitroaromatics [9]. Heterocyclic compounds similar to substituted benzenes have preferences for nucleophilic and electrophilic reactions. For pyridine [9] it is not the free base that is involved in the electrophilic reaction but it is its conjugate acid. This is also true if a neutral nucleophile such as barbituric acid, malonic ester, phenylacetonitrile, *etc.* is added to the heterocyclic carboxaldehyde *N*-oxide.

should be relatively short. This is perfectly demonstrated in the NMR reaction following for the barbituric acid addition to 4-quinolinecarboxaldehyde (Figure 5). The reaction is practically completed after one hour at room temperature. It appears that the second addition of barbituric acid to the Knoevenagel intermediate is a faster reaction than the first addition of barbituric acid to 4-quinolinecarboxaldehyde, because not even a trace of the condensation intermediate was detected in our NMR experiment.

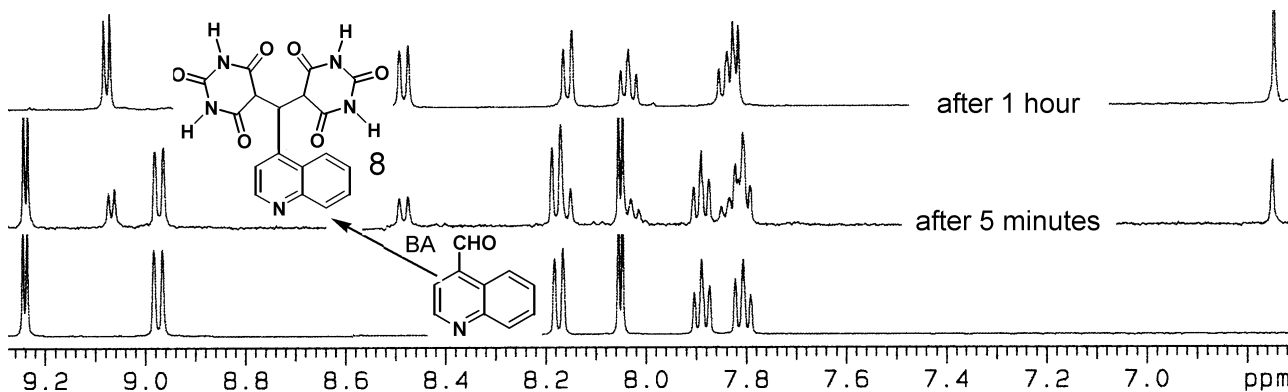


Figure 5. The ^1H -NMR (DMSO-d_6 , 500 MHz) reaction following for 4-quinolinecarboxaldehyde condensation with barbituric acid.

Scheme 3

Reactive intermediates that were detected in our NMR following experiments of the barbituric acid addition to 2,2'-dipyridine-4,4'-dicarboxaldehyde.

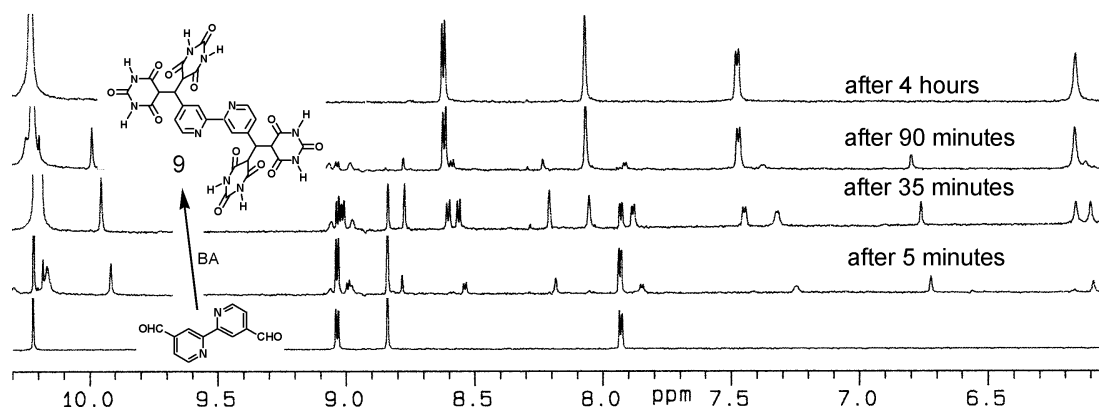
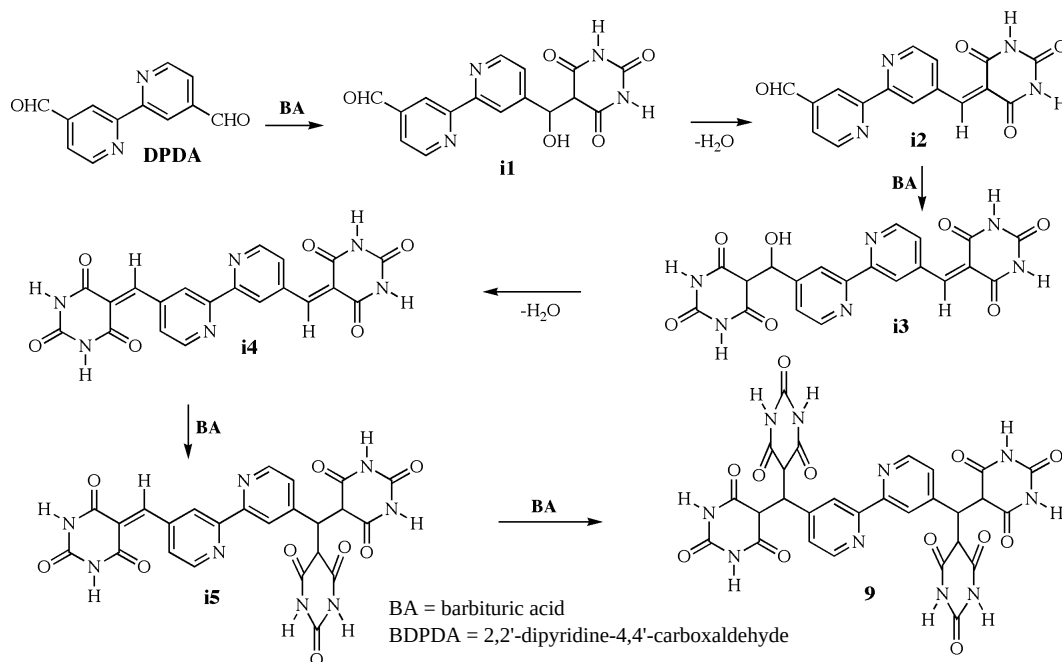


Figure 6. ¹H-NMR (500 MHz) following of barbituric acid (10 mM) condensation with 2,2'-bipyridine-4,4'-carboxaldehyde (2.5 mM) in TFA-DMSO (3:1) at room temperature.

It is now logical to assume that larger barbituric acid adducts can be formed if two or more heterocyclic carboxaldehydes are covalently bound together. There is considerable interest to prepare these compounds as immunomodulating agents, as well as to determine whether doubles of the structural moieties necessary for molecular activity would have additive effects on the biological activity. Synthetically, this is not always a simple task. Increasing the size and the number of the heterocycles makes the new target molecule hard to handle in regards to

the formation of various reaction intermediates, their solubility in the course of the reaction, as well as the solubility of the final compound. This is perfectly

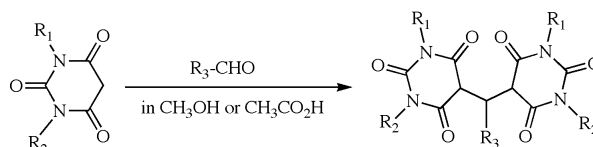


Table 1

Isolated Yields of Barbituric Acid Condensation with Aromatic Aldehydes

		$^1\text{H-NMR(DMSO-d}_6\text{)} \delta$	$^{13}\text{C-NMR (DMSO-d}_6\text{)} \delta$
11	R ¹ =H R ² =CH ₃ R ³ =2-pyridine Method=A Yield=80%	10.68 (2H, s, NH), 8.58 (1H, d, <i>J</i> =6 Hz, Pyridine 6-H), 8.41 (1H, t, <i>J</i> =8 Hz, pyridine 5-H), 7.84 (1H, t, <i>J</i> =6 Hz, pyridine 4-H), 7.80 (1H, d, <i>J</i> =7.8 Hz, pyridine 3-H), 6.31 (1H, s, CH), and 3.09 ppm (6H, s, CH ₃).	160.9, 159.1, 156.4 (carbonyl carbons), 147.4, 142.4, 137.6, 122.2, 120.5 (aromatic carbons), 83.0, 30.5 and 23.472 ppm (aliphatic carbons).
12	R ¹ =H R ² =C ₆ H ₅ R ³ =2-pyridine Method=A Yield=78%	10.84 (2H, s, NH), 8.64 (2H, d, <i>J</i> =6.9 Hz, pyridine 6-H), 8.44 (1H, t, <i>J</i> =6.9 Hz, pyridine 4-H), 7.98 (1H, d, <i>J</i> =6.9 Hz, pyridine 3-H), 7.83 (1H, t, <i>J</i> =6.9 Hz, pyridine 4-H), 7.40 (4H, t, <i>J</i> =6.9 Hz, phenyl <i>m</i> -H), 7.32 (2H, t, <i>J</i> =6.9 Hz, phenyl <i>p</i> -H), 7.20 (4H, d, <i>J</i> =6.9 Hz, phenyl <i>o</i> -H), 6.23 (1H, benzyl).	163.0, 159.9, 156.2 (three different carbonyls), 147.9, 147.2, 142.4, 137.6, 133.0, 125.7, 124.8, 123.9, 122.4 (nine aromatic carbons), 82.30, 30.84 ppm (two aliphatic carbons).
13	R ¹ =H R ² =H R ³ =3-pyridine Method=C Yield=97%	10.21 (4H, s, NH), 8.64 (1H, d, <i>J</i> =5.7 Hz, pyridine 6-H), 8.43 (1H, s, pyridine 2-H), 8.20 (1H, d, <i>J</i> =5.7 Hz, pyridine 4-H), 7.89 (1H, d-d, <i>J</i> ₁ =5.7 Hz, <i>J</i> ₂ =5.7 Hz, pyridine 5-H), and 6.13 (1H, s, pyridine H).	160.9, 147.0 (two different carbonyls), 141.9, 140.8, 136.4, 135.2, 122.7 (five pyridine carbons), 85.5 and 25.9 ppm (two aliphatic carbons).
14	R ¹ =CH ₃ R ² =CH ₃ R ³ =3-pyridine Method=A Yield=92%	8.64 (1H, d, <i>J</i> =6 Hz, pyridine 6-H), 8.56 (1H, s, pyridine 2-H), 8.29 (1H, d, <i>J</i> =6 Hz, pyridine 4-H), 7.88 (1H, d, <i>J</i> ₁ =7.8 Hz, <i>J</i> ₂ =8.1 Hz, pyridine 5-H), 6.337 (1H, s, benzyl H), and 3.13 ppm (12H, s, CH ₃).	159.0, 147.8 (carbonyl carbons), 141.4, 141.1, 136.6, 135.0, 122.7 (aromatic carbons), 84.6, 29.0 and 24.4 ppm (aliphatic carbons).
15	R ¹ =H R ² =CH ₃ R ³ =3-pyridine Method=A Yield=97%	10.55 (2H, s, NH), 8.65 (1H, d, <i>J</i> =5.7 Hz, pyridine 6-H), 8.49 (1H, s, pyridine 2-H), 8.24 (1H, d, <i>J</i> =7.8 Hz, pyridine 4-H), 7.90 (1H, d-d, <i>J</i> ₁ =8.4 Hz, <i>J</i> ₂ =8.4 Hz, pyridine 5-H), 6.25 (1H, s, benzyl), and 3.08 (6H, s, CH ₃).	160.8, 158.7, 147.3 (carbonyls carbons), 141.7, 141.1, 136.3, 135.0, 122.8 (aromatic carbons), 85.5, 25.7, 23.4 ppm (aliphatic carbon).
16	R ¹ =H R ² =C ₄ H ₉ R ³ =3-pyridine Method=B Yield=81%	10.48 (2H, s, NH), 8.46 (1H, d, <i>J</i> =4.2 Hz, pyridine 6-H), 8.33 (1H, s, pyridine 2-H), 7.79 (1H, d, <i>J</i> =7.5 Hz), 7.56 (1H, t, <i>J</i> =5.1 Hz), 6.164 (1H, s, CH), 3.70 (4H, <i>J</i> =6.6 Hz, NCH ₂), 1.46 (4H, m, NCH ₂ CH ₂), 1.24 (4H, m, CH ₂ CH ₃), and 0.86 ppm (6H, t, <i>J</i> =6.6 Hz, CH ₃).	160.9, 158.9, 147.2 (carbonyl carbons), 140.5, 139.7, 138.5, 135.8, 120.9 (aromatic carbons), 86.0, 27.3, 26.5, 16.1, and 10.1 ppm (aliphatic carbons).
17	R ¹ =H R ² =C ₅ H ₆ R ³ =3-pyridine Method=A Yield=93%	10.74 (2H, s, NH), 8.66 (1H, d, <i>J</i> =6.3 Hz, pyridine 6-H), 8.63 (1H, s, pyridine 2-H), 8.40 (1H, d, <i>J</i> =8.7 Hz, pyridine 4-H), 7.93 (1H, d-d, <i>J</i> ₁ =7.8 Hz, <i>J</i> ₂ =7.2 Hz, pyridine 5-H), 7.392 (4H, t, <i>J</i> =0.023, phenyl <i>m</i> -H); 7.319 (2H, t, <i>J</i> =6.9 Hz, phenyl <i>p</i> -H), 7.19 (4H, d, <i>J</i> =6.9 Hz, <i>o</i> -H), and 6.23 (1H, s, CH).	160.8, 159.4, 147.1 (carbonyl carbons), 141.6, 141.3, 136.5, 135.1, 133.2, 125.8, 124.8, 123.8, 121.8 (aromatic carbons), 85.1, and 27.7 ppm (aliphatic carbons).
18	R ¹ =H R ² =H R ³ =4-pyridine Method=C Yield=97%	10.24 (4H, s, NH), 8.63 (2H, d, <i>J</i> =6.4 Hz, pyridine 2-H), 7.63 (2H, d, <i>J</i> =6.9 Hz, pyridine 3-H), and 6.18 ppm (1H, s, CH).	163.5, 162.3 (carbonyl carbons), 145.5, 121.5, 113.3 (aromatic carbons), 87.3, and 33.5 ppm (aliphatic carbons).
19	R ¹ =H R ² =CH ₃ R ³ =4-pyridine Method=A Yield=98%	10.60 (2H, s, NH), 8.64 (2H, d, <i>J</i> =6.6 Hz, pyridine 2-H), 7.69 (2H, d, <i>J</i> =5.7 Hz, pyridine 3-H), 6.32 (1H, s, CH), and 3.09 ppm (6H, s, CH ₃).	164.0, 160.9, 158.8 (carbonyl carbons), 147.3, 137.0, 121.6 (aromatic carbons), 85.6, 30.9, 23.5 ppm (aliphatic carbon).
20	R ¹ =H R ² =C ₄ H ₉ R ³ =4-pyridine Method=B Yield=92%	10.54 (2H, s, NH), 8.64 (2H, d, <i>J</i> =6.9 Hz, pyridine 4-H), 7.63 (2H, d, <i>J</i> =6.3 Hz, pyridine 3-H), 6.32 (1H, s), 3.70 (4H, t, <i>J</i> =6.6 Hz), 1.46 (4H, m), 1.28 (4H, m), and 0.87 ppm (6H, t, <i>J</i> =6.6 Hz, CH ₃).	164.2, 160.7, 158.9 (carbonyl carbons), 147.1, 137.1, 121.5 (aromatic carbons), 85.5, 30.8, 26.5, 16.1, 10.1 ppm (aliphatic carbons).
21	R ¹ =H R ² =C ₆ H ₅ R ³ =4-pyridine Method=A Yield=92%	10.74 (2H, s, NH), 8.67 (2H, d, <i>J</i> =6.9 Hz, pyridine 2-H), 7.84 (2H, d, <i>J</i> =6.9 Hz, pyridine 3-H), 7.40 (4H, t, <i>J</i> =6.9 Hz, phenyl <i>m</i> -H), 7.32 (2H, t, <i>J</i> =6.9 Hz, phenyl <i>p</i> -H), 7.19 (4H, d, <i>J</i> =6.9 Hz, <i>o</i> -H), 6.27 ppm (1H, s, CH).	163.7, 160.7, 159.4 (carbonyl carbon), 147.0, 137.1, 133.2, 125.9, 124.8, 123.8, 121.7 (aromatic carbon), 85.5, 30.8 ppm.
22	R ¹ =CH ₃ R ² =CH ₃ R ³ =3-quinoline Method=A Yield=86%	9.023 (1H, s, quinoline 2-H), 8.80 (1H, s, q-2-H), 8.30 (2H, d, <i>J</i> =8.1 Hz, q-8-H), 8.19 (1H, d, <i>J</i> =6.0 Hz, q-5-H), 8.02 (1H, t, <i>J</i> =8.1 Hz, q-7-H), 7.86 (1H, t, <i>J</i> =7.2 Hz, q-6-H), 6.43 (1H, s, CH), and 3.15 ppm (12H, s, CH ₃).	159.1, 147.9, 142.4, 138.7, 135.7, 132.8, 129.3, 125.6, 125.2, 124.7, 123.9, 117.3 (two carbonyl and nine aromatic carbons), 84.5, 29.4, and 24.5 ppm (aliphatic carbon).

Table 1 (continued)

		$^1\text{H-NMR}(\text{DMSO-}d_6) \delta$	$^{13}\text{C-NMR}(\text{DMSO-}d_6) \delta$
23	R ¹ =H R ² =C ₆ H ₅ R ³ =3-quinoline Method=A Yield=93%	10.78 (2H, s, NH), 9.05 (1H, s, q-2-H), 8.93 (1H, s, q-4-H), 8.36 (1H, d, <i>J</i> =6.3 Hz, q-8-H), 8.20 (1H, d, <i>J</i> =6.3 Hz, q-5-H), 8.00 (1H, t, <i>J</i> =5.4 Hz, q-7-H), 7.88 (1H, t, <i>J</i> =5.7 Hz, q-6-H), 7.39 (4H, t, <i>J</i> =5.7 Hz, phenyl <i>m</i> -H), 7.31 (2H, t, <i>J</i> =5.7 Hz, phenyl <i>p</i> -H), 7.24 (4H, d, <i>J</i> =5.7 Hz, phenyl <i>o</i> -H), and 6.34 ppm (1H, s, CH).	161.0, 160.9, 159.6 (carbonyl carbons), 147.2, 142.1, 139.1, 135.8, 133.2, 132.6, 129.6, 125.9, 125.3, 124.8, 124.7, 123.9 117.2 (aromatic carbons), 84.8, and 28.3 ppm (aliphatic carbons).
24	R ¹ =CH ₃ R ² =CH ₃ R ³ =4-quinoline Method=A Yield=84%	9.07, d, <i>J</i> =5.7 Hz, q-2-H), 8.39 (1H, d, <i>J</i> =8.7 Hz, q-8-H), 8.16 (1H, d, <i>J</i> =7.8 Hz, q-5-H), 8.03 (1H, t, <i>J</i> =6.3 Hz, q-C-7), 7.92 (1H, d, <i>J</i> =5.7 Hz, q-3-H), 7.84 (1H, t, <i>J</i> =7.8 Hz, q-6-H), 6.97 (1H, s, CH), 3.69 (1H, s, CH), and 3.13 ppm (12H, s, CH ₃).	160.5, 159.2 (carbonyl carbons), 147.6, 139.9, 133.8, 130.0, 125.6, 123.6, 121.7, 117.9 (aromatic carbons), 85.9, 30.3, and 24.5 ppm (aliphatic carbons).
25	R ¹ =H R ² =CH ₃ R ³ =4-quinoline Method=A Yield=78%	10.63 (2H, s, NH), 9.06 (1H, d, <i>J</i> =5.4 Hz, q-2-H), 8.42 (1H, d, <i>J</i> =6.0 Hz, q-8-H), 8.14 (1H, d, <i>J</i> =8.7 Hz, q-5-H), 8.00 (1H, t, <i>J</i> =8.1 Hz, q-7-H), 7.83 (1H, d, <i>J</i> =5.7 Hz, q-3-H), 7.83 (1H, t, <i>J</i> =8.7 Hz, q-6-H), 6.87 (1H, s, CH), and 3.061 ppm (6H, s, CH ₃).	160.7, 160.2, 159.2 (carbonyl carbons), 147.141, 140.171, 134.257, 129.778, 125.343, 123.616, 121.788, 118.263, 117.7 (aromatic carbons), 86.5, 29.1, and 23.5 ppm (aliphatic carbon).
26	R ¹ =H R ² =C ₆ H ₅ R ³ =4-quinoline Method=A Yield=95%	10.83 (2H, s, NH), 9.12 (1H, d, <i>J</i> =5.7 Hz, q-2-H), 8.49 (1H, d, <i>J</i> =8.7 Hz, q-8-H), 8.17 (1H, d, <i>J</i> =8.1 Hz, q-5-H), 8.05 (1H, t, <i>J</i> =7.2 Hz, q-7-H), 7.98 (1H, d, <i>J</i> =5.7 Hz, q-3-H), 7.90 (1H, t, <i>J</i> =8.4 Hz, q-6-H), 7.39 (4H, t, <i>J</i> =7.5 Hz, phenyl <i>m</i> -H), 7.32 (2H, t, <i>J</i> =6.0 Hz, phenyl <i>p</i> -H), 7.14 (4H, d, <i>J</i> =7.5 Hz, phenyl <i>o</i> -H), and 6.87 ppm (1H, s, CH).	160.8, 160.5, 159.9 (carbonyl carbons), 146.9, 140.0, 133.9, 133.0, 130.2, 125.7, 125.6, 124.9, 123.9, 123.7, 121.8, 118.0, 117.8 (aromatic carbons), 86.2, and 29.2 ppm.

demonstrated on the example for the tetra barbituric acid addition to the dipyridinedicarboxaldehyde (Figure 6). Although the reaction occurs in any given solvent that can dissolve both barbituric acid and dipyridinedicarboxaldehyde, the solubility of various reaction intermediates as well as tetra-adduct **9** limits us to dimethyl sulfoxide as a solvent and the reaction concentration must not be higher than 0.1 mM. In the course of the NMR reaction, signals for every intermediate of the barbituric acid adducts can be detected (the first Knoevenagel adduct, the second Knoevenagel adduct, the first Michael-type of adduct and the second Michael-type of adduct (compound **9**, Scheme 3). There are many more intermediates involved in the barbituric acid tetra-addition to dipyridinedialdehyde **DPDA**. With close evaluation of the NMR spectra five minutes after the reagents are mixed (Figure 6) two new aldehyde hydrogen signals around 9.9 ppm and a signal for α -CHOH at 6.7 ppm (besides the signals for the starting aldehyde **DPDA**) indicate the formation of **i1**. Signals at 10.15 ppm and 8.2 ppm are assigned to the aldehyde and the vinyl hydrogen of intermediate **i2**, respectively. A small singlet at 8.25 ppm belongs to intermediate **i4**, and the singlet at 6.08 ppm belongs to the α -CH(Ba)₂ of intermediate **i5**, while the singlet at 6.15 ppm belongs to the same hydrogen (α -CH(Ba)₂) of the tetra-adduct **9** (Scheme 3 and Figure 6). This analysis is performed with the assumption that the barbituric acid addition to the C=O is faster than the addition to the C=C double bond, and that elimination of water is faster from intermediates **i1** and **i3** than both the barbituric acid additions. Further spectroscopic study of the mechanism of the tetra-addition of barbituric acid is currently underway [10].

Finally, we carefully explored the double addition reaction through NMR experiments in various organic solvents, as well as various acid-base conditions, and simple and very efficient reaction conditions were developed for the preparation of these valuable compounds. Isolated yields are almost quantitative and in many cases isolation and purification of the product simply involve filtration and washing the precipitate with solvent.

In conclusion, it can be stated that through careful NMR experiments with aromatic and heteroaromatic carboxaldehydes in both protic and aprotic solvents, optimal reaction conditions for the preparation of double barbituric acid addition adducts to aromatic aldehydes were developed. The preparation procedures are applicable to multi-gram as well as multi kilogram scales. Considering the simplicity of the preparation and isolation of these compounds, the presented procedures are directly applicable to the industrial scale preparation. All reactive intermediates involved in the condensation reactions were also spectroscopically identified.

EXPERIMENTAL

All NMR reaction following experiments were performed on 500 MHz UNITY500 Varian NMR instrument with DMSO-*d*₆ (2.50 ppm, for hydrogen and 39.51 ppm for carbon) as an internal reference. All reaction solutions for NMR monitoring reactions were 1 mM for aromatic aldehydes and 5 mM for barbituric acid, except for the study of barbituric acid tetra-addition to 2,2'-dipyridine-4,4'-dicarboxaldehyde for which the concentration was 0.1 mM. All DMSO-*d*₆ samples were clear solutions. The CF₃COOH

samples contained a few drops of DMSO- d_6 as an internal reference and part of barbituric acid was not in the solution. Electrospray mass spectral analysis was performed on a Micromass Quattro 2 Triple Quadrupole Massspectrometer. Melting points were determined on Electrothermal 9100 melting point apparatus and are not corrected. Preparation procedures for compounds **1** and **2** have been reported previously. There are literature reports for the preparation of compounds **3**, **4**, and **6** but our procedures are superior, and the isolated yields are higher and for some of them there are no spectroscopic characterizations reported in the literature. Therefore, for these compounds our preparation procedures and our spectroscopic characterization data are reported.

Preparation of 5-Naphthalen-1-ylmethylenepyrimidine-2,4,6-trione (**3**).

Acetic acid (400 mL) solution of 1-naphthalenecarboxaldehyde (3.12 g; 0.02 mol) was added at once into a stirring hydrochloric acid (100 mL) solution of barbituric acid (2.56 g; 0.02 mol). The brown emulsion was heated at 80 °C for thirty minutes. After a few minutes a yellow precipitate was formed and the suspension became very hard to stir. The reaction suspension was cooled to room temperature, and product was separated by filtration, washed with water (3x20 mL), methanol (3x30mL) and dried at 110 °C for six hours to afford 5.13 g (96%) of product **3**. Product decomposition occurs at temperatures exceeding 270 °C. $^1\text{H-NMR}$ (DMSO- d_6 , 500 MHz): δ 11.51 (1H, s, NH), 11.22 (1H, s, NH), 8.29 (1H, s, vinyl H), 8.02 (1H, d, $J=8.0$ Hz), 7.99 (1H, m), 7.81 (1H, m), 7.84 (1H, d, $J=7.0$ Hz), and 7.57 ppm (3H, m). $^{13}\text{C-NMR}$ (DMSO- d_6 , 500 MHz instrument): δ 163.0, 161.0 (two carbonyl carbons), 152.4, 150.4 (two vinyl carbons), 132.7, 131.0, 130.7, 128.7, 128.4, 127.1, 126.3, 124.9, 124.3 and 121.9 ppm (ten aromatic carbons).

Anal. Calcd. for $\text{C}_{15}\text{H}_{10}\text{N}_2\text{O}_3$: C, 67.67; H, 3.79; N, 10.52. Found: C, 67.58; H, 3.85; N, 10.37.

Preparation of 5-(4-Dimethylaminobenzylidene)pyrimidine-2,4,6-trione (**4**).

Methanol solution (300 mL) of 4-dimethylaminobenzaldehyde (3 g; 0.02 mol), barbituric acid (2.56 g; 0.02 mol), and a few drops of sulfuric acid was refluxed in an open beaker with stirring. Resulting deep red suspension was concentrated to volume of about $\frac{1}{4}$ of its original volume by evaporation of methanol at atmospheric pressure, cooled in ice-water bath and the solid product was separated by filtration, washed with methanol (3x30 mL) and dried at 110 °C for five hours to afford pure product in 95% (4.95g) yield. Product decomposition occurs at temperatures exceeding 285 °C. $^1\text{H-NMR}$ (DMSO- d_6 , 500 MHz): δ 11.0 (2H, broad singlet, NH), 8.41 (2H, d, $J=9$ Hz, *o*-hydrogens), 8.14 (1H, s, vinyl hydrogen), 6.78 (2H, d, $J=9$ Hz, *m*-hydrogens), and 3.11 (6H, s, methyl hydrogens). $^{13}\text{C-NMR}$ (DMSO- d_6 , 500 MHz instrument): δ 164.7, 162.7, 155.5 (three carbonyl carbons), 154.1, 150.3 (two vinyl carbons), 139.0, 120.0, 111.1, 109.5 (four aromatic carbons), and 39.7 ppm (one aliphatic carbon).

Anal. Calcd for $\text{C}_{13}\text{H}_{13}\text{N}_3\text{O}_3$: C, 60.22; H, 5.05; N, 16.21. Found: C, 60.07; H, 5.13; N, 16.11.

Preparation of 5,5'-(4-Dimethylaminobenzylidene)dibarbituric Acid (**5**).

Into a clear trifluoroacetic acid solution (30 mL) of barbituric acid (0.270 mg; 0.0021 mol), 4-dimethylaminobenzaldehyde (0.149 g; 0.001 mol) was added. The clear reaction mixture was

left at room temperature and the solvent was slowly evaporated at room temperature almost to dryness (eight days). The white crystalline product that formed was separated by filtration and washed with trifluoroacetic acid. The yield of the product is 0.37 g (95%). This compound is very sensitive to elevated temperature and other solvents that are not strong acids, such as alcohol. It immediately decomposes to barbituric acid and the benzylidene product. It is stable in crystalline form and in strong acid at room temperature. The trifluoromethanesulfonic acid solution was stable for several months at 0 °C. The NMR spectra were recorded in $\text{CF}_3\text{SO}_3\text{H}$ with three drops of DMSO- d_6 as an internal standard and source of the deuterium lock signal. Product decomposition occurs at temperatures above 285 °C. $^1\text{H-NMR}$ ($\text{CF}_3\text{SO}_3\text{H}$ -DMSO- d_6 , 300 MHz): δ 7.57 (1H, broad singlet), 6.94 (2H, d, $J=8.7$ Hz), 6.87 (2H, d, $J=8.4$ Hz), 5.48 (1H, s), and 2.71 (6H, d, $J=5.1$ Hz); $^{13}\text{C-NMR}$ ($\text{CF}_3\text{SO}_3\text{H}$ -DMSO- d_6 , 300 MHz): δ 167.6, and 152.8 (two carbonyl carbons), 143.9, 138.0, 131.7, and 122.7 (four aromatic carbons), 95.5 (benzyl carbon), 49.8 (two dimethylamino carbons), and 34.2 ppm (barbituric acid C-5 carbon).

Preparation of 5-(4-Hydroxybenzylidene)pyrimidine-2,4,6-trione (**6**).

This compound was previously prepared by several groups. Concentrated hydrochloric (100 mL) solution of barbituric acid (1.28 g; 0.01 mol) and 4-hydroxybenzaldehyde (1.22 g; 0.01 mol) was stirred at room temperature for 20 hours. Both of the reagents are soluble in concentrated hydrochloric acid and the reaction mixture is a solution at the beginning of the reaction. The color of the reaction changes to yellow and a yellow precipitate starts to form after approximately fifteen minutes stirring at room temperature. After twenty hours stirring at room temperature the reaction suspension was filtered and yellow solid product, thus collected, was washed with cold water (3x10 mL), slurred in methanol (30 mL) again collected by filtration and dried at 110 °C for five hours. The yield of **6** is 2.15 g (93%). Product decomposition occurs at temperatures greater than 300 °C. $^1\text{H-NMR}$ (DMSO- d_6 , 500 MHz): δ 11.23 (1H, s, NH), 11.09 (1H, s, NH), 10.78 (1H, s, OH), 8.30 (2H, d, $J=9.0$ Hz, *o*-H), 8.20 (1H, s, vinyl H), and 6.86 ppm (2H, d, $J=9.0$ Hz, *m*-H). $^{13}\text{C-NMR}$ (DMSO- d_6 , 500 MHz instrument): δ 164.20, 163.11, 162.37 (three different carbonyl carbons), 155.7, 150.3 (two carbons of vinyl double bond), 138.4 123.9, 115.6, and 114.2 (four different aromatic carbons).

Preparation of 5,5'-(4-Nitrobenzylidene)dibarbituric Acid (**7a**).

Into a clear trifluoroacetic acid solution (30 mL) of barbituric acid (0.270 mg; 0.0021mol), *p*-nitrobenzaldehyde (151 mg; 1 mmol) was added. The clear reaction mixture was left at room temperature for solvent to slowly evaporate. A hard white precipitate was formed. Solid was separated by filtration, washed with cold trifluoroacetic acid (3x3 mL), with methanol (3x10 mL), and dried in vacuum at 60 °C for three hours to afford pure white product in 87% yield (340 mg). Compound decomposes in neutral solvents such as DMSO. In this solvent an equilibrium is established between dibarbiturate **7** and its decomposition products, free barbituric acid and 5-(4-nitrobenzylidene)pyrimidine-2,4,6-trione. The amount of 5-(4-nitrobenzylidene)pyrimidine-2,4,6-trione can be diminished if the concentration of barbituric acid is increased in the solution. On the other hand, the acetic acid solution is sufficiently stable that $^1\text{H-NMR}$ spectra can be recorded. Product

decomposes at temperatures above 200 °C. ¹H-NMR (CF₃SO₃H-DMSO-d₆, 300 MHz): δ 7.67 (2H, d, *J*=7.5 Hz, 3H-benzene hydrogens), 6.88 (2H, d, *J*=7.5 Hz, benzene 2H hydrogens), and 5.49 ppm (1H, benzyl hydrogen). ¹³C-NMR (CF₃SO₃H-DMSO-d₆, 300 MHz): δ 167.7 and 152.5 (two different barbituric acid carbonyls), 148.6, 144.8, 130.6, and 127.1 (four aromatic carbons), 127.0, 122.8, 118.6, 114.5 (quartet from solvent – CF₃SO₃H), 94.9 (benzyl carbon, and 34.8 ppm (barbituric C-5 carbon).

Preparation of 5,5'-(4-Nitrobenzylidene)di(1,3-dimethylbarbituric Acid) (**7b**).

A trifluoroacetic acid solution (30 mL) of 1,3-dimethylbarbituric acid (328 mg; 2.1 mmol) and 4-nitrobenzaldehyde (151 mg; 1 mmol) was left at room temperature for solvent to slowly evaporate for four days. In this period the volume of the solvent was reduced to approximately 10 mL and a hard white solid was formed. Solid was separated by filtration, washed with ice-cold trifluoroacetic acid (3x 2 mL), ice-cold methanol (3x3 mL) and dried in open air to afford 365 mg (82%) pure product. This compound has very low solubility in DMSO, and it is temperature sensitive. The NMR sample was prepared in ice-cold trifluoromethanesulfonic acid by keeping a suspension of 70 mg/0.7 mL of CF₃SO₃H at room temperature for approximately one hour. Two drops of DMSO-d₆ were added as both internal reference signal as well as solvent for the NMR signal lock. Product melting point is 179.2–181.1 °C. ¹H-NMR (CF₃SO₃H-DMSO-d₆, 300 MHz): δ 7.67 (2H, d, *J*=8.4 Hz, 3H aromatic hydrogens), 6.85 (2H, d, *J*=8.4 Hz, 2H aromatic hydrogens), 5.50 (1H, s, benzyl hydrogen), 3.05 ppm (12H, s, methyl hydrogens); ¹³C-NMR (CF₃SO₃H-DMSO-d₆, 300 MHz): δ 166.2, 153.8 (two different carbonyls), 148.8, 144.0, 130.5, 127.4 (four aromatic carbons), 127.0, 122.8, 118.6, and 144.4 (quartet from CF₃SO₃H), 96.2 (benzyl carbon), 37.3 (barbituric C-5 carbon), and 34.0 ppm (methyl carbons).

Anal. Calcd. for C₁₉H₁₉N₅O₈: C, 51.24; H, 4.30; N, 15.72. Found: C, 51.15; H, 4.43; N, 15.61.

Preparation of 5,5'-(4-Quinolidinylmethylene)dibarbituric Acid (**8**).

4-Quinolincarboxaldehyde (0.160 g; 0.001 mol) was added into refluxing methanol (400 mL) solution of barbituric acid (0.256 mg; 0.002 mol). Reaction mixture was refluxed for three hours and the volume was reduced to 1/5 by evaporation of methanol at atmospheric pressure. Solid product was separated by filtration, washed with ice-cold methanol (3x30 mL) and dried at 110 °C for three hours to give 0.36 g (91%) product **8**. Product decomposes at temperatures exceeding 280 °C. ¹H-NMR(DMSO-d₆, 300 MHz): δ 10.324 (4H, s, NH), 9.096 (1H, d, *J*=0.020, quinoline 2-H), 8.483 (1H, d, *J*=0.030, quinoline 8-H), 8.155 (1H, d, *J*=0.029, quinoline 5-H), 8.031 (1H, t, *J*=0.024, quinoline 7-H), 8.401(1H, t, *J*=0.021, quinoline 6-H), 7.830 (1H, d, *J*=0.019, quinoline 3-H), and 6.761 ppm (1H, s, benzyl H); ¹³C-NMR (DMSO-d₆, 300 MHz): δ 161.139 and 161.016 (two different carbonyl carbons), 146.879, 139.916, 133.806, 130.040, 125.415, 123.624, 121.919, 117.936, 117.622 (nine quinoline carbons), 86.450 (benzyl carbon), and 27.479 ppm (barbituric C-5).

Anal. Calcd. for C₂₂H₂₁N₅O₆: C, 58.53; H, 4.69; N, 15.51. Found: C, 58.35; H, 4.81; N, 15.42.

Preparation of 2,2'-Di[4,4'-di(2,4,6-trioxa-3,5-diazacyclohexyl)methyl]pyridine (**9**).

Into a clear trifluoroacetic acid solution (30 mL) of barbituric acid (0.320 g; 0.0025 mol) the trifluoroacetic acid solution (5 mL) of 2,2'-bipyridine-4,4'-carboxaldehyde (0.106 mg; 0.0005 mol) was kept at room temperature for three days. Formed white precipitate was separated by filtration, washed with trifluoroacetic acid (3x1 mL), methanol (3x5 mL) and dried in vacuum at 90 °C for one hour to afford 0.330 g (97%) of pure product. Product decomposition occurs at temperatures exceeding 290 °C. ¹H-NMR (DMSO-d₆, 300 MHz): δ 10.32 (8H, s, NH), 8.60 (2H, d, *J*=5.4 Hz, 6H of pyridine ring), 8.03 (2H, s, 3H of pyridine ring) 7.47 (2H, d, *J*=5.4 Hz, 5H of pyridine ring), and 6.06 (2H, s, benzyl hydrogen). ¹³C-NMR(DMSO-d₆, 300 MHz): δ 161.4 and 158.6 (two barbituric acid carbonyls), 147.3, 144.4, 142.4, 121.8, and 118.4 (five pyridine carbonyls), 84.5 and 29.1 ppm (two aliphatic carbons). MS-ES⁺ (CH₃COOH) *m/z* 115 (100%), 277 (50%), 387 (45%), 483 (83%), 505 (43%), and 689 (*M*+1, 70%).

Anal. Calcd. for C₂₈H₂₀N₁₀O₁₂: C, 48.84; H, 2.93; N, 20.34. Found: C, 48.74; H, 2.98; N, 20.22.

Preparation of 2,2'-Di[4,4'-di(2,4,6-trioxa-3,5-diaza-3,5-dimethylcyclohexyl)methyl]pyridine (**10**).

A trifluoroacetic acid (50 mL) solution of 2,2'-bipyridine-4,4'-carboxaldehyde (0.106 g; 0.0005 mmol) and 1,3-dimethylbarbituric acid (0.343 g; 0.0022 mol) was kept at room temperature for three days. Solvent was evaporated to dryness. Solid material was crystallized from large amount of methanol to produce pure product **10** in 92% (0.370 mg) yield. If necessary, further purification can be obtained by crystallization from a small amount of acetic acid. Product decomposition occurs at temperatures exceeding 167 °C. ¹H-NMR (DMSO-d₆, 300 MHz): δ 8.60 (2H, d, *J*=5.4 Hz, 6H of pyridine ring), 8.02 (2H, s, 3H of pyridine ring) 7.56 (2H, d, *J*=5.4 Hz, 5H of pyridine ring), 6.37 (2H, s, benzyl hydrogen), and 3.14 ppm (24H, s, methyl hydrogens). ¹³C-NMR(DMSO-d₆, 300 MHz): δ 159.2 and 159.0 (two different carbonyls of the barbituric acid moiety), 147.8, 143.5, 141.9, 122.0, 118.3 (five carbons of the pyridine moiety), 85.1 (benzyl carbon), 31.7 (C-5 of the barbituric acid moiety), and 24.5 ppm (methyl carbon). MS-ES⁺ (CH₃COOH) *m/z* 143 (35%), 277 (50%), 415 (44%), 539 (83%), 661 (33%), 677 (22%), 801 (*M*+1, 42%).

Anal. Calcd. for C₃₆H₃₆N₁₀O₁₂: C, 54.00; H, 4.53; N, 17.49. Found: C, 53.88; H, 4.61; N, 17.36.

General Procedures for Preparation of Heterocyclic-Dibarbiturates.

Procedure A. Preparation of 1-Methyl-5-[(1-methyl-2,4,6-trioxa-hexahydropyrimidin-5-yl)(pyridin-2-yl)methyl]pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**11**).

After 1-methylbarbituric acid (0.71 g; 0.005 mol) was dissolved in refluxing methanol (100 mL) 2-pyridinecarboxaldehyde (0.27 g; 0.005 mol) was added. After a few minutes a white precipitate starts to form. The resulting methanol suspension was refluxed for an additional twenty minutes and the reaction suspension was reduced to a volume of about 30 mL by evaporating methanol at atmospheric pressure. Suspension was cooled to room temperature. Solid product was separated by filtration, washed with methanol (3x20 mL), ether (3x50 mL) and dried at

110 °C for 30 minutes. The isolated yield of **11** is 80.0 % (0.75g). Product decomposition occurs at temperatures above 200 °C.

Procedure B. Preparation of 1-Butyl-5-[(1-butyl-2,4,6-trioxohexahydropyrimidin-5-yl)(pyridin-2-yl)methyl]pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**12**).

Acetic acid solution (300 mL) of 1-butylbarbituric acid (920 mg; 5 mmol) and 2-pyridinecarbaldehyde (255 mg; 2.5 mmol) was refluxed for four hours. Almost immediately, a dark solution was formed. Solvent was evaporated to gummy residue. This residue was dissolved in refluxing methanol (200 mL). The methanol solution was left at room temperature in a paraffin foil covered beaker with a small opening for solvent evaporation. After seven days at room temperature, the volume of the mixture was reduced to 50 mL and an orange precipitate was formed. From the ice-cooled suspension the solid was separated by filtration, washed with cold methanol (3x30 mL) and dried at 80 °C under reduced pressure for five hours. The yield of the product is 750 mg (66%) of product. Product decomposition occurs at 200 °C. (See Table 1 NMR data).

Procedure C. Preparation of 5-[(2,4,6-Trioxohexahydropyrimidin-5-yl)(pyridin-3-yl)methyl]pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**14**).

Into a hot (110 °C) acetic acid (200 mL) solution of barbituric acid (1.28 g; 10 mmol) 3-pyridinecarbaldehyde (0.55 g; 0.005 mol) was added. After a few minutes a pink precipitate starts to form. Resulting suspension was heated at 110 °C for 30 minutes and the formed precipitate was separated by filtration, washed with acetic acid (3x20 mL), acetone (3x20 mL) and dried at 80 °C under reduced pressure for several hours. Product decomposition occurs at temperatures above 250 °C. MS-ES⁺ (in acetic acid) 140 (38%), 209 (43%), 223 (100%), 251 (84%), 283 (26%), and 346 (M+1, 10%). (See Table 1 NMR data).

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REFERENCES AND NOTES

- [1a] T. F. Kresina, Editor "Immune-Modulating Agents" Dekker, New York, N. Y. (1998); [b] G. G. Gomez, R. B. Hutchison and C. A. Kruse, *Cancer Treat. Rev.*, **27**, 375 (2001); [c] F. Lori, *AIDS (London)*, **13**, 1433 (1999); [d] H. Baba, T. Kunimoto, K. Nitta, K. Sato, S. Hashimoto, M. Kohno, Y. Kita and H. Ogawa, *Int. J. Immunopharmacol.*, **8**, 569 (1986).
- [2a] I. Watanabe, T. Andoh, R. Furuya, T. Sasaki, Y. Kamiya and H. Itoh, *Anesthesia & Analgesia (Baltimore)*, **88**, 1406 (1999); [b] J. M. Gonzales, *J. Neurochem.*, **64**, 2559 (1995); [c] K. Hirota, M. Kudo, T. Kudo, M. Kitayama, T. Kushikata, D. G. Lambert and A. Matsuki, *Neuroscience Lett.*, **291**, 175 (2000); [d] P. R. Andrews, G. P. Jones and D. B. Poulton, *Eur. J. Pharmacol.*, **79**, 61 (1982); [e] G. B. Young, W. T. Blume, C. F. Bolton and K. G. Warren, *Can. J. Neurological Sciences*, **7**, 291 (1980).
- [3a] T. R. Bailey and D. C. Young, *International Patent* WO 13708 (2000); *Chem. Abstr.*, **132**, 203127 (2000); [b] R. I. Ashkinazi, *International Patent* WO 25699 (1999); *Chem. Abstr.*, **131**, 5267 (1999); [c] L. R. Morgan, B. S. Jursic, C. L. Hooper, D. M. Neumann, K. Thangaraj and B. LeBlanc, *Bioorg. Med. Chem. Lett.*, **12**, 3407 (2002).
- [4] For instance see B. S. Jursic, *J. Heterocyclic Chem.*, **38**, 655 (2001), and references therein.
- [5] B. S. Jursic, D. M. Neumann, Z. Moore and E. D. Stevens, *J. Org. Chem.*, **67**, 2372 (2002).
- [6] B. S. Jursic, *J. Heterocyclic Chem.*, **00**, 0000 (2003).
- [7] For reviews of Michael reactions see: [a] E. D. Bergmann, D. Ginsburg and R. Pappo, *Org. React.*, **10**, 179 (1959); [b] L. A. Yanovskaya, G. V. Kryshal and V. V. Kulganek, *Russ. Chem. Rev.*, **53**, 744 (1984).
- [8] The pK_a of protonated anilines 10-12 is considerably higher than the pK_a of trifluoroacetic acid. Therefore anilines should be protonated in trifluoroacetic acid. On the other hand the pK_a for protonated phenols and anisoles is between -6 to -8. In trifluoroacetic acid they are practically in Ar-OH and Ar-OCH₃ forms. For more information see: T. H. Lowry and K. S. Richardson "Mechanism and Theory in Organic Chemistry" Third Edition, Harper & Row, Publishers, New York, N.Y. 1987 and references therein.
- [9] For instance see: [a] A. R. Katritzky, "Handbook of Heterocyclic Chemistry" Pergamon Press, New York, N. Y. 1985; [b] D. L. Comins, and S. Connor, *Adv. Heterocycl. Chem.*, **44**, 199 (1988); [c] G. A. Olah, J. A. Olah and N. A. Overchuk, *J. Org. Chem.*, **30**, 3373 (1965).
- [10] Positive electro-spray studies in diluted acetic acid and diluted methanol are underway to fully characterize mechanism and intermediates in diaromaticdialdehydes with substituted barbituric acid. These experiments in conjunction with NMR spectroscopic studies will provide close insight into the nature of tetra-barbituric acid adducts of potential immuno-modulating agents.

[1a] T. F. Kresina, Editor "Immune-Modulating Agents" Dekker, New York, N. Y. (1998); [b] G. G. Gomez, R. B. Hutchison and C. A.