Simple, Efficient, High Yield Syntheses of Substituted and Unsubstituted 5-Benzoylbarbituric Acids, and Their Corresponding Schiff Base Phenylhydrazones

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Preparation procedures for biologically important benzoylbarbiturates are presented. Several procedures are optimized to cover the preparations of a wide variety of substituted 5-benzoylbarbiturates. To further explore the biological importance of these compounds, multi- gram preparation procedures for nitrophenylhydrazones of benzoylbarbiturates and their corresponding salts with organic amines are discussed. It is demonstrated that these compounds can exist in several tautomeric forms and that the equilibrium in solution can be changed by temperature as well as by the pH of the solution. X-ray structural analysis performed on one of the nitrophenylhydrazones of benzoylbarbiturates fully agrees with the presented spectroscopic studies. AM1 semi-empirical studies show that the enol form is preferred in the gas phase of benzoylbarbiturates over the keto form, which was also confirmed by NMR spectroscopic studies with chloroform as the solvent. Furthermore, AM1 computed structural and electronic properties of the dinitrophenylhydrazone of 4-hydroxybenzoylbarbiturate compared favorably with the X-ray determined structure.

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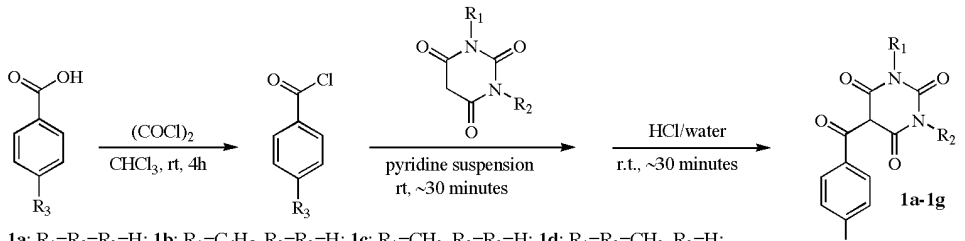
Introduction.

For the last one hundred years barbituric acids and their simple C5-substituted derivatives have had numerous applications in medicinal chemistry [1]. Traditionally barbituric acid derivatives have typically been used as hypnotic, sedative or anti-epileptic treatments [2], however, there have been recent reports that indicate that some aromatic substituted barbiturates, aromatic substituted barbituric acid phenylhydrazones, and other Schiff bases containing barbituric acid moieties may actually possess immuno-modulating properties [3]. To thoroughly explore the possibility of immune-modulation within aromatic substituted barbiturate Schiff bases, a large variety of both substituted and unsubstituted 5-benzoylbarbiturates were necessary precursors for the synthesis of the targeted Schiff bases. Here, we are presenting the simple and efficient synthetic procedures developed to synthesize these crucial intermediate precursors, as well as the optimal procedures for the sequential Schiff base reactions.

There are literature reports indicating that some substituted and unsubstituted 5-benzoyl barbiturates have been previously synthesized and are used as herbicides and insecticides [4]. However, the typical synthetic procedure for the preparation of these compounds involves several steps. In one of the preparation procedures, $Zn(CN)_2$ in acetonitrile was used as a catalyst for the acylation and benzoylation of barbituric acid with corresponding acid chlorides. Isolated yields are ~80%. Nevertheless, this synthetic approach is not applicable for the preparation of a wide variety of substituents attached to both aryl and barbituric moieties of 5-benzoylbarbituric acids. Therefore, there is a need for developing new synthetic methods for the preparation of these compounds.

One of our research targets is to develop simple and inexpensive synthetic procedures for heterocyclic compounds that are of interest for medical research. Substituted 5-benzoylbarbituric acid derivatives and the corresponding phenylhydrazones show promising results in some biomedical research. To be successful in finding suitable phenylhydrazone-barbiturate drug candidates in biomedical research, it is most important to initially have available a wide variety of substituted 5-benzoylbarbituric acids and phenylhydrazones. Here we would like to report our systematic study toward the preparation of these valuable compounds, finalized with their simple one, or at the most two step multi-gram preparation procedures.

Scheme 1



1a: R_1=R_2=R_3=H; **1b**: R_1=C_6H_5, R_2=R_3=H; **1c**: R_1=CH_3, R_2=R_3=H; **1d**: R_1=R_2=CH_3, R_3=H; **1e**: R_1=*n*-C_4H_9, R_2=R_3=H; **1f**: R_1=R_2=H, R_3=OCH_3 **1g**: R_1=R_2=CH_3, R_3=OCH_3

Syntheses of 5-benzoyl and 5-(methoxybenzoyl)barbiturates **1a**-**1g**.

Results and Discussion.

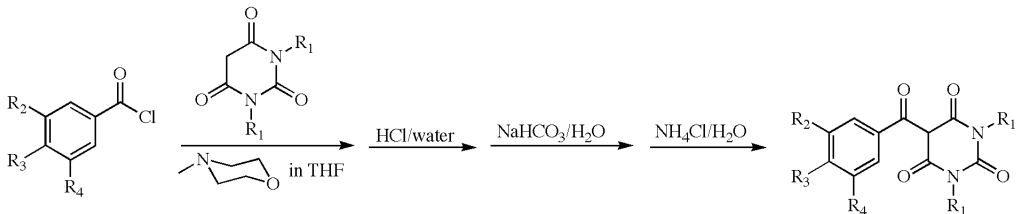
The simplest way to prepare benzoyl substituted barbituric acids is to condense *N*-substituted barbituric acids (R_1,R_2=H, alkyl, or aryl, Scheme 1) with the corresponding acid chloride. Many of these starting materials are commercially available, however if the desirable starting materials are not available they can be readily prepared [6]. Pyridine seems to be an ideal solvent for this reaction. It is not necessary to fully dissolve the reactants for the reaction to be completed; therefore a relatively small amount of pyridine is necessary. In many instances the reaction is completed after 30 minutes. Isolation involves pouring the pyridine reaction mixture into hydrochloric acid (conc. HCl:H_2O 3:1). The formed crystalline product is of sufficient purity (~98%) that further purification either by chromatography or by crystallization is not necessary.

These simple preparation procedures are not applicable for the preparation of 5-benzoylbarbiturates with strong electron-withdrawing groups, such as nitro groups. These compounds can also be prepared in pyridine as reaction media, but the isolation and separation from both pyridine and the resulting pyridinium chloride is very difficult. Therefore, another synthetic route using *N*-methyl morpholine as a base and dioxane or tetrahydrofuran as the reaction solvent was developed for the preparation of these compounds. In these cases, the desired product was isolated in higher than 90% yield (Scheme 2).

All of the 5-benzoylbarbiturates are relatively strong carbon acids due to the mobility of the hydrogen atom attached at the C-5 position of the barbituric acid ring. This acidity is responsible for the keto-enol equilibrium that is present in solution. The equilibrium is relatively slow and it is possible to follow the change in the equilibrium constant by ^{1}H-NMR. Depending on the method of purification and crystallization of the 5-benzoylbarbiturate, one can isolate either the keto only or enol only product. This was perfectly demonstrated on the example of 5-(3-nitrobenzoyl)-1,3-dimethylbarbituric acid (**1i**, Figure 1). The precipitated product formed by the condensation reaction between 3-nitrobenzoyl chloride and barbituric acid in THF and *N*-methylmorpholine as a base is exclusively in the keto form. If the product is purified by crystallization from large quantities of water, then the enol form is present in crystalline form. It is also obvious that the enol form is the thermally more stable species as demonstrated by NMR following thermal distribution of keto-enol forms in DMSO at 80 ºC (Figure 1).

There are couple of very interesting points that can be concluded from the NMR following of the keto-enol equilibrium presented in Figure 1. Presence of the enol form of **1i** is determined by the nature of the solvent as well as the temperature. In solvents that cannot form strong hydrogen bonding of deprotonated barbiturates, such as **1i**, the keto form is dominant or the only present tautomer. In solvents such as DMSO and water, which can form strong

Scheme 2



1h: R_1=R_2=R_3=H, R_4=NO_2; **1i**: R_1=CH_3, R_2=R_3=H; R_4=NO_2; **1j**: R_1=R_2=R_4=H, R_3=NO_2;
1k: R_1=CH_3, R_2=R_4=H, R_3=NO_2; **1l**: R_1=R_3=H, R_2=R_4=NO_2; **1m**: R_1=CH_3,R_3=H, R_2=R_4=NO_2 **1h-1m**

General route for preparation of 5-(nitrobenzoyl)barbiturates **1h**-**1m**.

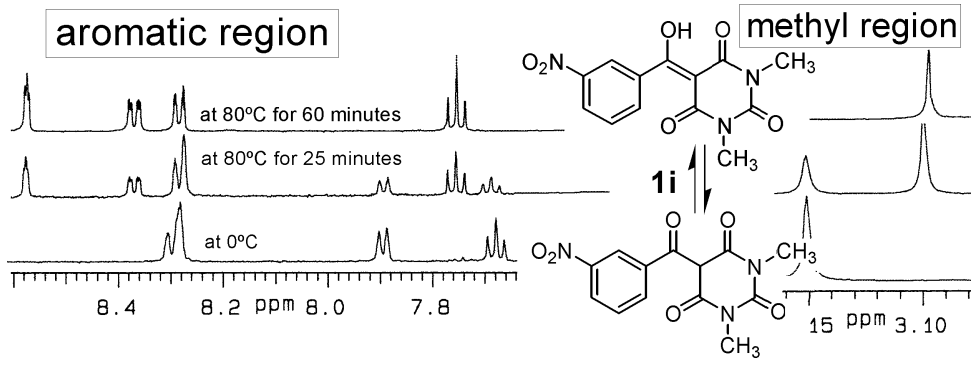


Figure 1. The NMR following of thermal induced transformation of the keto form of **1i** into the enol form in DMSO-d_6 at 80 ºC.

hydrogen bonding with the enol alcohol group, the enol tautomer is dominant. Our AM1 computational studies agree that the enol form is thermally more stable (by 0.8 kcal/mol). Structural properties for these two tautomers are considerably different. The carbonyl group of the *p*-nitrobenzoyl moiety of the keto form of **1a** is almost perpendicular to the barbituric ring (the O16-C10-C9-C14 dihedral is 79.4º) while in its enol form, it is almost coplanar with the barbituric acid ring (O16-C10-C9-C14 dihedral ring is 5.7º) (Figure 2). The structural orientation of the carbonyl group toward the *p*-nitrophenyl moiety is exactly opposite (almost coplanar in its keto-form) and perpendicular in its enol-form, Figure 2). There is also a very short distance between H27 and O15 of the enol-form (1.914 A), indicating strong hydrogen bonding in the gas phase. This might not be the case with such polar solvents as DMSO because the DMSO oxygen is a much better proton acceptor than the amide carbonyl of barbituric acid. This is also evident by the fact that it was not possible to observe the barbituric acid hydrogen in the NMR spectra of the DMSO-d_6 solution of **1a** due to the H-D exchange.

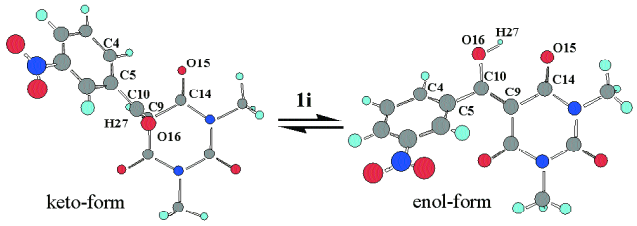


Figure 2. The AM1 semi-empirical computed structures of keto and enol forms of **1i**.

NMR spectroscopic studies of **1i** in chloroform should be much closer to our AM1 gas-phase computational studies. Therefore one can assume that the enol form with intramolecular hydrogen bonding should be present. Furthermore, the existence of C9-C10 double bond in the enol-form will make two of the methyl barbituric acid groups spectroscopically nonequivalent. In other words, the aromatic portion of the NMR spectra in chloroform at room temperature should be similar to the NMR in DMSO-d_6 at elevated temperature. The methyl range should be different because at 80 ºC in DMSO, due to low rotational barrier, the two methyl groups are equivalent and in chloroform at room temperature they are not (Figure 3). The strongest evidence for the enol-form of **1i** comes from the fact that at 17.8 ppm there is a broad singlet with an integral of 1H, corresponding to the enol hydrogen involved in internal hydrogen bonding interactions with one of the carbonyl oxygens of the barbituric acid moiety (Figure 3).

None of the discussed procedures applied for the preparation of methyl, methoxy, and nitrobenzoyl barbiturates but they can be used for the preparation of hydroxybenzoyl barbiturates. Additionally, our exhaustive literature searches provided no evidence that there is a method of preparation for these hydroxybenzoyl barbiturates. Naturally, the hydroxyl group attached to the benzoyl moiety must be protected during the course of the preparation of hydroxybenzoyl barbiturates. Since we already developed the preparation procedures for methoxybenzoyl barbiturates, we attempted to use these compounds as starting materials for the preparation of the corresponding hydroxybenzoyl barbiturates. Unfortunately, during the course of the methoxy group transformation into the unprotected hydroxyl group, the barbituric acid part of the molecule decomposed [7]. After exploring several routes for the preparation of these compounds, we developed a simple and high yield preparation. The preparation starts with acetyloxybenzoyl acid, which is converted into the corresponding acid chloride. Then, following the previously described procedure for the benzoyl chloride condensation with barbituric acid in pyridine, the hydroxyl-protected product is produced. The final step involves hydrolysis of the acetyl protecting group, followed by the isolation of pure product upon acidification (Scheme 3).

With these successful developments of synthetic procedures for the preparation of aryl substituted 5-benzoylbarbiturates, we turned our attention to the preparation of the corresponding phenylhydrazones. As mentioned above, the preparation of various Schiff bases between amines and amino acids with acylbarbiturates was previously described and some of these derivatives were used as her-

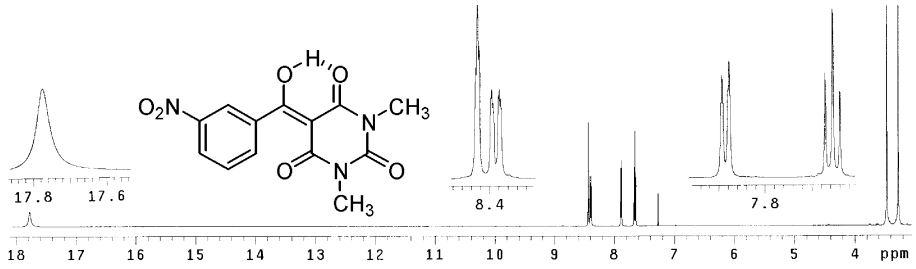
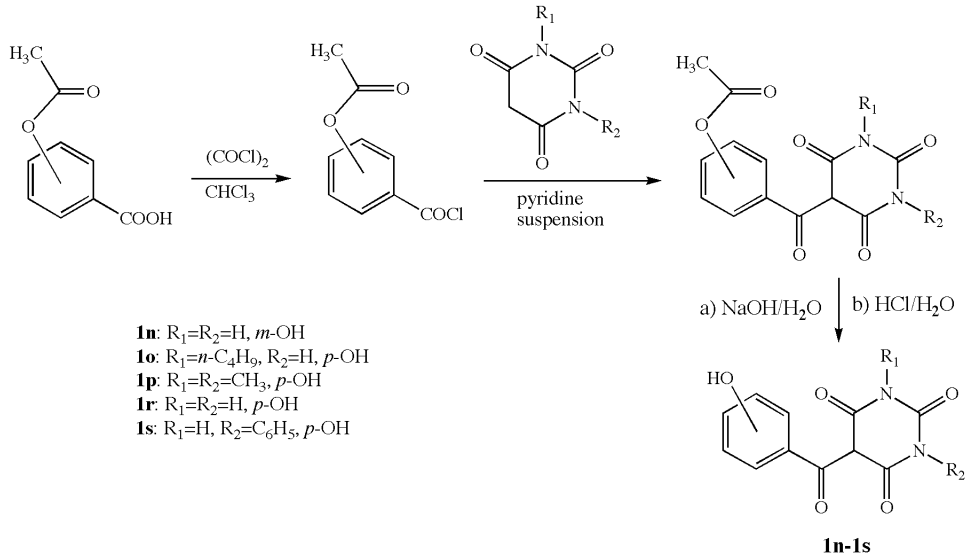


Figure 3. The NMR (500 MHz) spectra of chloroform solution of **1i** at room temperature.

Scheme 3



1n: R_1=R_2=H, *m*-OH
1o: R_1=*n*-C_4H_9, R_2=H, *p*-OH
1p: R_1=R_2=CH_3, *p*-OH
1r: R_1=R_2=H, *p*-OH
1s: R_1=H, R_2=C_6H_5, *p*-OH

Synthetic partway for preparation hydroxybenzoylbarbiturates **1n**-**1s**.

bicides [4]. None of the patented work has focused on 5-benzoylbarbituric phenylhydrazones. Our attempt to apply their synthetic procedures for the preparation of our phenylhydrazones of benzoylbarbiturates was not successful. From these experiments it was obvious that our benzoylbarbiturates are substantially less reactive toward hydrazine condensation reactions. In some instances, products were formed but isolation and purification from the reaction mixture was very difficult. Furthermore, our experiments suggested that both the reactants and the products of the reaction were very sensitive to reaction solvent and the pH of the reaction media. Therefore, we carefully explored reaction conditions to select the optimal reaction conditions for the preparation of these valuable compounds.

In order to find and optimize appropriate reaction conditions for the preparation of phenylhydrazones of benzoylbarbiturates, we performed several NMR reaction-following experiments. A typical ^{1}H-NMR reaction-following experiment for these compounds is demonstrated by the transformation of *p*-nitrophenylhydrazine and 5-(4-methoxybenzoyl)-1,3-dimethyl pyrimidine-2,4,6-trione (**1g**) into 5-{(4-Methoxyphenyl)-[*N*'-(4-nitrophenyl)hydrazino]methylene}-1,3-dimethyl-pyrimidine-2,4,6-trione (**2g**) (Figure 4). The reaction was followed by taking a sample of the reaction mixture [8] (one drop), evaporating the solvent under a nitrogen stream at room temperature and preparing the sample in a DMSO-d_6 solution. *p*-Nitrophenylhydrazine was used in slight excess in the reaction mixture. After the reaction mixture was refluxed for fifteen minutes all benzoylbarbiturate **1g** was consumed. It is obvious that there are two major products of the condensation reaction. When sulfuric acid is added, one of the products is transformed into the other. Prolonged

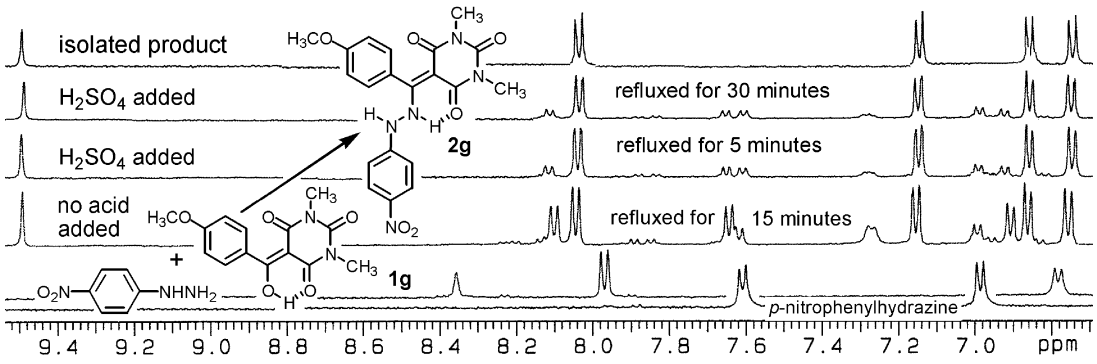


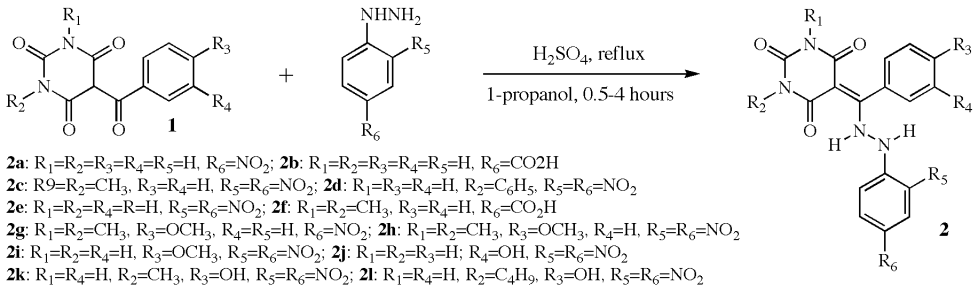
Figure 4. The ^{1}H-NMR (DMSO-d_6, 500 MHz) reactions following for the condensation reaction in 1-propanol without and with sulfuric acid as catalyst.

refluxing of the reaction mixture does not noticeably change the composition of the product. After cooling down the reaction mixture, a solid precipitate containing only one molecular species, compound **2g** (Figure 4) was isolated. Following this synthetic procedure, or by slight modification of this procedure, the phenylhydrazones of benzoylbarbiturates (Scheme 4) were prepared. It is important to mention that for the preparation of these compounds, precipitation of the product from the reaction mixture during the reaction is crucial for obtaining both high yield of the product, as well as high product purity. In some cases, solvents such as methanol and ethanol can be used, but 1-propanol seems to be applicable to almost all reactions performed, and the yields and purities of the products prepared in 1-propanol are high. To obtain better isolated yields for some specific cases of the phenylhydrazones **2**, specific reaction conditions were developed and are mentioned in the experimental section of this paper.

solvents where the other form crystallizes from polar aprotic solvents. For instance, phenylhydrazone **2e** crystallizes from the 1-propanol reaction mixture as the hydrazone with a double bond between nitrogen and carbon (**2eCN**). In pure DMSO solution ^{1}H-NMR shows that the solution actually contains this isomer as a major isomer (Figure 5). After the addition of trifluoroacetic acid, the nitrogen of the C=N is protonated and equilibrium is shifted toward the enamine form **2eCC** (Figure 5). In the DMSO-d_6-CF_3CO_2H solution after one hour **2eCC** is the only detectable isomer. Similar behavior was observed with other prepared hydrazones.

A major problem in the evaluation of biological properties for 5-benzoylbarbiturates comes from the low solubility of these compounds in aqueous media and most common organic solvents. This is even more evident for aryl substituted derivatives. Considering that increasing the size of the aliphatic or aromatic moieties of 5-benzoylbar-

Scheme 4



2a: R_1=R_2=R_3=R_4=R_5=H, R_6=NO_2; **2b**: R_1=R_2=R_3=R_4=R_5=H, R_6=CO2H
2c: R9=R_2=CH_3, R_3=R_4=H, R_5=R_6=NO_2; **2d**: R_1=R_3=R_4=H, R_2=C_6H_5, R_5=R_6=NO_2
2e: R_1=R_2=R_4=R=H, R_5=R_6=NO_2; **2f**: R_1=R_2=CH_3, R_3=R_4=H, R_6=CO_2H
2g: R_1=R_2=CH_3, R_3=OCH_3, R_4=R_5=H, R_6=NO_2; **2h**: R_1=R_2=CH_3, R_3=OCH_3, R_4=H, R_5=R_6=NO_2
2i: R_1=R_2=R_4=H, R_3=OCH_3, R_5=R_6=NO_2; **2j**: R_1=R_2=R_3=H; R_4=OH, R_5=R_6=NO_2
2k: R_1=R_4=H, R_2=CH_3, R_3=OH, R_5=R_6=NO_2; **2l**: R_1=R_4=H, R_2=C_4H_9, R_3=OH, R_5=R_6=NO_2
2m: R_1=R_2=R_4=H, R_3=OH, R_5=R_6=NO_2; **2n**: R_1=C_6H_5, R_2=R_4=H, R_3=OH, R_5=R_6=NO_2
2o: R_1=R_4=H, R_2=CH_3, R_3=OH, R_5=R_6=NO_2; **2p**: R_1=R_2=CH_3, R_3=OH, R_4=H, R_5=R_6=NO_2
2r: R_1=R_2=CH_3, R_3=R_5=R_6=NO_2, R_4=H; **2s**: R_1=R_2=R_4=H, R_3=R_5=R_6=NO_2

Preparation path for phenylhydrazones of benzoylbarbiturates.

As in the cases of 5-benzoylbarbiturates, phenylhydrazones of 5-benzoylbarbiturates have several tautomeric forms. In solution, equilibrium can be reached where several tautomeric forms are present. It is often the case that one tautomeric form can crystallize from nonpolar aprotic

biturates makes these compounds even less water soluble. In order to evaluate their potential pesticide and herbicide activities, it is important to make them water soluble. Both acyl and benzoylbarbiturates have acidic hydrogens in the 5 position of the barbituric acid moiety, making prepara-

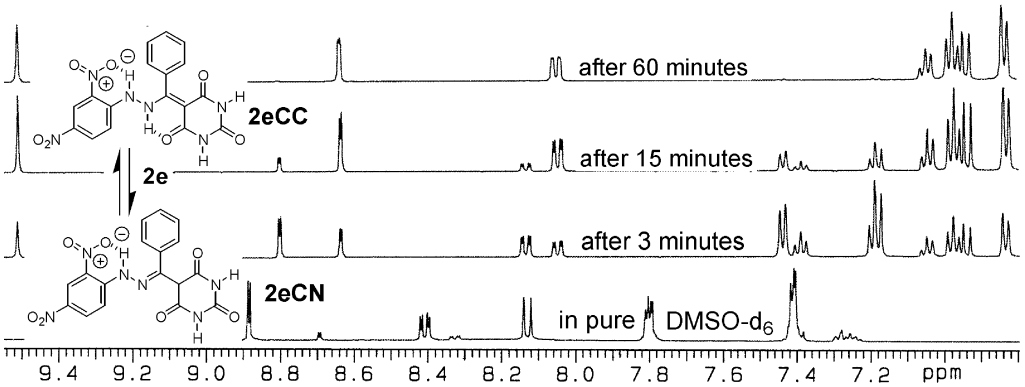
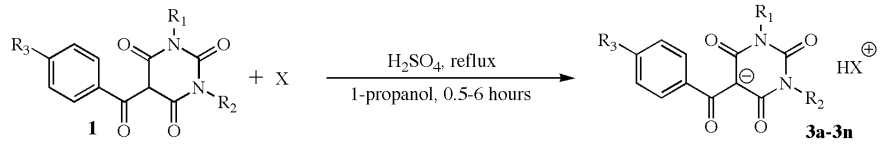


Figure 5. ^{1}H-NMR (500 MHz) isomerization following of **2eCN** transformation into **2eCC** in CF_3CO_2H.

tion of their ammonium salts with secondary amines straightforward. Preparation procedures included mixing benzoylbarbituric acid derivatives with the amine in a solvent, such as tetrahydrofuran or dioxane or even propanol, evaporating the solvent, and finally purification of the product (Scheme 5).

show different ratios of two tautomeric forms, as is demonstrated in Figure 5. To confirm these findings, X-ray structural analysis of **2g** obtained from a 1-propanol solution with a few drops of sulfuric acid was performed (Scheme 6). According to our NMR spectroscopic studies, hydrazones **2** in acidic polar media should be in an

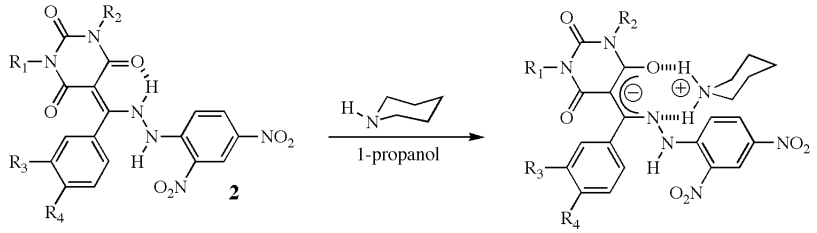
Scheme 5



3a: R_1=R_2=R_3=H, X=$HN(CH_2)_5$; **3b**: R_1=CH_3, R_2=R_3=H, X=$HN(CH_2)_5$
3c: R_1=R_2=H, R_3=OCH_3, X=$NH(CH_2)_5$; **3d**: R_1=R_2=CH_3, R_3=OCH_3, X=$NH(CH_2)_5$
3e: R_1=R_2=H, R_3=NO_2, X=$HN(CH_2)_5$; **3f**: R_1=R_2=H, R_3=NO_2, X=$HN(CH_2CH_2)_2O$
3g: R_1=R_2=H, R_3=NO_2, X=$CH_3N(CH_2CH_2)_2O$; **3h**: R_1=R_2=H, R_3=NO_2, X=$NH_2CH_2CH_2OH$
3i: R_1=R_2=H, R_3=NO_2, X=4-$(CH_3)_2$NPy; **3j**: R_1=R_2=CH_3, R_3=NO_2, X=$HN(CH_2)_5$
3k: R_1=R_2=CH_3, R_3=NO_2, X=$HN(CH_2CH_2)_2O$; **3l**: R_1=R_2=CH_3, R_3=NO_2, X=$CH_3N(CH_2CH_2)_2O$
3m: R_1=R_2=CH_3, R_3=NO_2, X=$NH_2CH_2CH_2OH$; **3n**: R_1=R_2=CH_3, R_3=NO_2, X=4-$(CH_3)_2$NPy

Preparation of substituted ammonium salts of substituted benzoylbarbiturates.

Scheme 6



4a: R_1=R_2=R_4=H, R_3=OH
4b: R_1=R_2=CH_3, R_3=H, R_4=OH
4c: R_1=R_3=H, R_2=C_6H_5, R_4=OH

Preparation of piperidinium salts **4** of phenylhydrazones **2**.

Similar to benzoylbarbiturates, phenylhydrazones also have low solubility in aqueous media. Besides possible herbicide activity, our preliminary results suggest that these compounds might possess anticancer activity through immuno-modulating properties [9]. These compounds are strong carbon acids due to the mobility of hydrogen attached to C-5 of the barbituric acid moiety of compounds **2**. Preparation of the corresponding salts with almost any amine was a straightforward process. Reaction components were dissolved in methanol, ethanol, or 1-propanol, stirred at room temperature for a few hours and the resulting salt was isolated from the reaction mixture (see experimental procedures **G** and **H**).

It is very important to emphasize again that both 5-benzoylbarbiturates **1** and their phenylhydrazones **2** can exist in several different tautomeric forms. Therefore, the NMR spectra of the same compound in different solvents can

enamine form (**2CC**) while in neutral polar media, the Schiff base form (**2CN**) should be present, as it was demonstrated on the NMR equilibrium experiment with hydrazone **2e**. Considering this finding, even if hydrazone **2g** is present in its Schiff base **2gCN** form in neutral solution, in the acidic polar media the enamine isomer **2gCC** (Figure 6) should be a dominant species. This isomer should also be present in the crystalline state if **2g** is crystallized from 1-propanol with sulfuric acid present.

The X-ray structure of **2g** (Figure 7) fully confirms our structural assignment based on the NMR spectroscopy. Compound **2g** is in its enamine form (double bonds are C6C7 and C56C57) with strong hydrogen bonding between the hydrazine hydrogen and the barbituric acid carbonyl (N8-H----O20 and N58-H----O70). Two of the molecular units of **2g** are combined through stacking the nitrophenyl and methoxyphenyl moieties of two

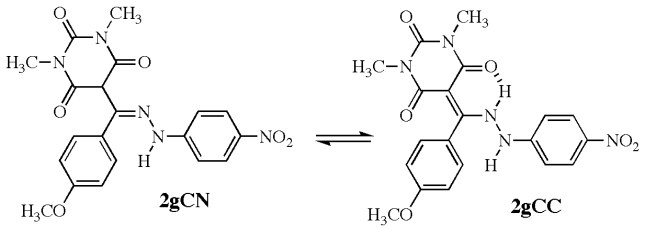


Figure 6. Schiff base **2gCN** and enamine **2gCC** tautomeric forms of **2g** present in solutions.

hydrazones of **2g**, as well as hydrogen bonding between two of these units N9-H-----O66 (Figure 7).

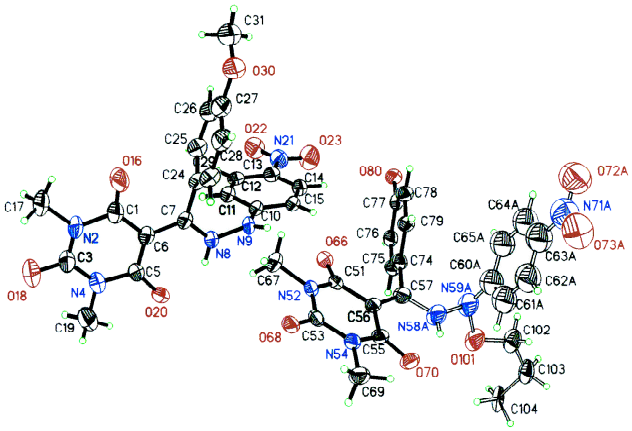


Figure 7. The ORTEP drawing x-ray determined structure of **2g**.

The X-ray structure of piperidinium salt **4b** was obtained from a single crystal grown from acetonitrile as a solvent. The structure is in full agreement with our spectroscopic characterization of this compound. The hydrogen from C6, rather than from O33 of the phenol moiety, is removed by the base to form perfect conjugation throughout entire molecule (Figure 8). Hydrogen bonding no longer exists between the nitrogen of the hydrazone moiety and barbituric acid moiety, as in **2g** due to fact that the

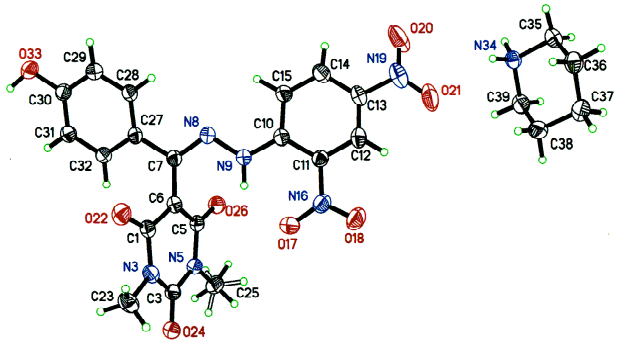


Figure 8. The ORTEP drawing of X-ray determined structure of **4b**.

acidic α-hydrogen of the barbituric acid moiety is removed with piperidene as a base. The negative charge is mostly located on O22 and O26 of the barbituric acid moiety.

At this point it is very interesting to compare structural features of **4** obtained from X-ray experimental data and ones obtained by AM1 semi-empirical modeling of the anion portion of **4b** in the gas phase (Table 1). Both experiment and theory agree that the barbituric acid moiety is almost planar (the bond angles dihedral ring for O22-C1-C6-C5 is close to 180°, Table 1). There is relatively good agreement between experimental and computed structural properties with the biggest discrepancy coming from estimating dihedral angels and hydrogen bond distances. For instance, from x-ray structural studies it is obvious that there is very strong hydrogen bonding between N9H and the nitro O17 oxygen (the O17-H9 bond distance is 1.937 Å, Table 1), while there is little bonding interaction with the barbituric acid carbonyl O26 that bears the partial negative charge. The AM1 estimates fairly well the first hydrogen bond distances, while substantially underestimates the latter one (Table 1). It is obvious that both experimental (X-ray) and computational (AM1) data agree that the hydrogen in the barbituric acid ring is more acidic than the phenolic hydrogen, therefore it is removed by piperidene. The negative charge is localized on two oxygens (O22 and O27) and one carbon (C6) atom of barbituric acid moiety (the AM1 computational studies estimates 1/3 of negative charge being on each of these three atoms). Strong hydrogen bonding between the NH hydrogen and the oxygen of the nitro group of the dinitrophenylhydrazine moiety of **4b** keeps this portion of the molecule in one plane.

Table 1

The X-ray Determined and AM1 Computed Properties for the Anionic Part of **4b** Salt

Atoms	X-Ray	AM1	Atoms	X-Ray	AM1
	Bond distance in Å			Bond angles in (°)	
C1-C6	1.417	1.439	C1-C6-C5	121.5	121.6
C5-C6	1.411	1.433	C1-C6-C7	119.3	118.9
C6-C7	1.483	1.448	C6-C7-N8	123.8	128.7
C7-N8	1.303	1.323	Atoms	Dihedral angles in (°)	
N8-N9	1.373	1.354	O22-C1-C6-C5	-171.2	175.6
O22-C1	1.231	1.253	C1-C6-C7-N8	123.7	131.0
O26-H9	2.740	2.098	C6-C7-N8-N9	-5.7	0.0
O17-H9	1.936	2.116	C32-C27-C7-N8	156.2	130.4

Conclusion.

In conclusion, very efficient synthetic procedures for the preparation of both aryl and barbituric acid substituted derivatives of 5-benzoylbarbiturates and their corresponding phenylhydrazones were developed [11]. Through NMR reaction following experiments, it is possible to direct the reaction for almost quantitative transformation of starting material into desired products.

Due to strong C-H acid properties, several tautomeric forms are present in the solution. Through appropriate choice of solvent as well as temperature, one tautomer structure can be dominant and also crystallize from the solution. This was confirmed by X-ray analysis of one of the compounds. To make 5-benzoylbarbiturates and their phenylhydrazones more soluble in aqueous media these compounds were transferred into their salts using organic amines.

EXPERIMENTAL

All starting materials, reactants, and solvents are purchased from Aldrich and used without prior purification. All NMR spectra were recording on 300, 400, or 500 MHz Varian NMR spectrophotometers. The NMR reaction-following experiments were performed on a UNITY 500 Varian NMR spectrophotometer. Chemical shifts for both ^{1}H-NMR and ^{13}C-NMR are referred to chemical shifts for solvent (for DMSO-d_6 it is 2.50 ppm for proton and 39.51 ppm carbon NMR). Electro-spray mass spectral analyses were performed on a Micromass Quattro 2 Triple Quadropole Masspectrometer. Melting points were determined on Electrothermal 9100 melting point apparatus and they are not corrected. Elemental analyses were performed by Atlantic Microlab Inc. X-ray structure determination was performed on Bruker SMART 1KCCD automated diffractometer. Crystals of compound **2b** were obtained by crystallization from 1-propanol. Semi-empirical computational studies were performed on PC IBM compatible computer with MOPAC [12] computational package with AM1 [13] semi-empirical method for molecules in gas phase.

General Procedure A.

Preparation 5-Benzoyl-1-butylpyrimidine-2,4,6-trione (**1e**).

Benzoyl chloride (14.1 g; 0.1 mol) was slowly added over 10 minutes into a stirring pyridine (60 mL) solution of 1-butylbarbituric acid (18.4 g; 0.1 mol). Resulting reaction mixture was stirred at room temperature for additional two hours. Pyridine reaction mixture was then slowly added over thirty minutes into stirring solution of methanol (60 mL), water (50 mL) and concentrated hydrochloric acid (150 mL). Resulting suspension was stirred at room temperature for additional half an hour and at 0 ºC for an additional hour. Solid precipitate was separated by filtration, washed (3x15 mL) with diluted hydrochloric acid (one part of concentrated hydrochloric acid and nine parts of water). Solid product was dried at 110 ºC for half an hour to afford pure **1e** in 28.0 g (97%). M.p. 138.9-139.7 ºC. ^{1}H-NMR (DMSO-d_6, 500 MHz): δ 11.90 (1H, s), 7.55 (2H, d, *J*=7 Hz), 7.53 (1H, t, *J*=7.5 Hz), 7.43 (2H, t, *J*=7.5 Hz), 3.71 (2H, t, J=7.5 Hz), 1.47 (2H, m), 1.24 (2H, m), and 0.86 ppm (3H, t, *J*=7 Hz); ^{13}C-NMR (DMSO-d_6, 500 MHz): δ 186.9, 164.0, 161.0, 146.0, 131.7, 127.9, 125.0, 124.0, 91.8, 36.0, 26.1, 16.1, and 10.2 ppm. MS-ES$^+$ (CH_3OH) m/z: 289 (M+1+), 311 (M+Na+), 343 (M+CH_3OH+Na$^+$).

Anal. Calcd for $C_{15}H_{16}N_2O_4$ (288.30): C, 62.49; H, 5.59; N, 9.72. Found C, 62.23; H, 5.56; N, 9.88.

Preparation 5-Benzoylpyrimidine-2,4,6-trione (**1a**).

This compound was prepared in 90% isolated yield by following General Procedure A. ^{1}H-NMR (DMSO-d_6, 500 MHz): δ 11.48(2H, s), 7.56(2H, d, *J*=8.7 Hz), 7.53(1H, t, *J*=6.3), and 7.42 ppm (2H, t, *J*=7.5 Hz); ^{13}C-NMR (DMSO-d_6, 500 MHz): δ 186, 163, 145, 131, 128, 125, 123, and 91ppm.

Anal. Calcd for $C_{11}H_8N_2O_4$ (232.05): C, 56.90; H, 3.47; N, 12.06. Found C, 56.81; H, 3.56; N, 11.91.

Preparation 5-Benzyl-1-phenylpyrimidine-2,4,6-trione (**1b**).

This compound was prepared in 83% isolated yield by following General Procedure A. ^{1}H-NMR (DMSO-d_6, 500 MHz): δ 12.09(1H, s), 7.59(2H, d, *J*=7.2 Hz), 7.51(d, 1H, *J*=6.9 Hz), 7.42(5H, m *J*=7.8 Hz), and 7.29 ppm (2H, d, *J*=9.3 Hz); ^{13}C-NMR (DMSO-d_6): δ 186, 164, 161, 145, 131, 131, 127, 125, 125, 124, 124, 123, and 92 ppm.

Anal. Calcd for $C_{17}H_{12}N_2O_4$ (308.08): C, 66.23; H, 3.92; N, 9.09; Found C, 66.11; H, 3.98; N, 10.98.

Preparation of 5-Benzoyl-1-methylpyrimidine-2,4,6-trione (**1c**).

This compound was prepared in 77% yield by following General Procedure A. ^{1}H-NMR (DMSO-d_6, 500 MHz): δ 11.91(1H, s), 7.56(2H, d, *J*=8.1 Hz), 7.44(3H, t+t), and 3.09 ppm (3H, s); ^{13}C-NMR (DMSO-d_6): δ 186, 163, 159, 146, 131, 127, 124, 123, 91, and 23 ppm.

Anal. Calcd for $C_{12}H_{10}N_2O_4$ (246.06): C, 58.54; H, 4.09; N, 11.38; Found C, 58.68; H, 4.01; N, 11.22.

Preparation of 5-(4-Methoxybenzoyl)pyrimidine-2,4,6-trione (**1f**).

This compound was prepared in 87% yield by following General Procedure A. ^{1}H-NMR (DMSO-d_6, 500 MHz): δ 11.41(2H, s), 7.61(2H, d, *J*=8.7 Hz), 6.94 (2H, d, *J*=8.7 Hz), and 3.80 ppm (3H, s); ^{13}C-NMR (DMSO-d_6): δ 185,162, 159, 145, 128, 123, 109, 90, and 51 ppm.

Anal. Calcd for $C_{12}H_{10}N_2O_5$ (262.06): C, 54.97; H, 3.84; N, 10.68; Found C, 54.86; H, 3.92; N, 10.55.

General Procedure B.

Preparation 5-(4-Methoxybenzoyl)-1,3-dimethylpyrimidine-2,4,6-trione (**1g**).

4-Methoxybenzoyl chloride (17g; 0.1 mol) was slowly added to stirring pyridine (60 mL) solution of 1,3-dimethylbarbituric acid (15.6 g; 0.1 mol). Resulting reaction suspension was stirred at room temperatures for four hours and then added into aqueous hydrochloric acid made from water (50 mL) and concentrated hydrochloric acid (150 mL). Resulting suspension was stirred at room temperature for thirty minutes and then at 70 ºC for 30 minutes. After heating, the reaction suspension became a clear water solution. The water solution was extracted (4x100mL) with ethyl acetate. Combined ethyl acetate extracts were dried over anhydrous magnesium sulfate and evaporated to an oily residue. The oily residue was dissolved in ethanol (10 mL) and kept at 0 ºC to form yellow crystals that were separated by filtration, washed with ice cold ethanol (3x 5 mL) and dried on the air to give 26.1 g (90%) of **1g**. M. p. 143.8-145.1 ºC. ^{1}H-NMR (DMSO-d_6, 500 MHz): δ 7.61 (2H, d, *J*=8 Hz), 6.98 (2H, d, *J*=8 Hz), 3.84 (3H, s), and 3.17 ppm (6H, s); ^{13}C-NMR (DMSO-d_6, 500 MHz): δ 188.7, 162.5, 159.0, 150.1, 126.5, 112.8, 94.7, 55.4, and 27.8 ppm. MS-ES$^+$ (CH_3OH) m/z: 291 (M+1$^+$), 313 (M+Na$^+$), 345 (M+CH_3OH+Na$^+$).

Anal. Calcd for $C_{14}H_{14}N_2O_5$ (290.27): C, 57.93; H, 4.86. Found C, 57.83; H, 4.78.

Preparation of 5-Benzoyl-1,3-dimethylpyrimidine-2,4,6-trione (**1d**).

This compound was prepared in 84% yield by following General Procedure B. ^{1}H-NMR (DMSO-d_6, 500 MHz): δ 7.53(3H, d+t, *J*=3.0 Hz), 7.44(2H, t, *J*=8.1 Hz), and 3.17 ppm (s, 6H); ^{13}C-NMR (DMSO-d_6, 500 MHz): δ 185, 163, 146, 131, 127, 124, 124, 92, and 24 ppm.

Anal. Calcd for $C_{12}H_{12}N_2O_4$ (260.25): C, 60.00; H, 4.65; N, 10.76. Found C, 59.91; H, 4.73; N, 10.65.

General Procedure C.

Preparation of 5-(4-Nitrobenzyl)-1,3-dimethylbarbituric Acid (**1k**).

Into tetrahydrofuran solution (200 mL) of 1,3-dimethylbarbituric acid (17.2 g; 0.11 mol) and 4-nitrobenzoyl chloride (18.5 g; 0.1 mol) with stirring *N*-methylmorpholine (15.15 g; 0.15 mol) was added. Color of the reaction mixture immediately changes from yellow to deep red and white precipitate (*N*-methylmorpholinium chloride) starts to form. Tetrahydrofuran was distilled off under atmospheric pressure until the volume of the reaction suspension was ~50 mL. This suspension was poured into ice cooled aqueous hydrochloric acid (800 mL water and 200 mL concentrated hydrochloric acid). Yellow precipitate was separated by filtration and washed with ice water (3x20 mL). Product contains ~3% 4-nitrobenzoic acid. Crude product was added to aqueous sodium bicarbonate (3 g $NaHCO_3$ in 200 mL water) and resulting suspension was stirred at room temperature for one hour. Solid was separated by filtration, washed with ice water and added to aqueous ammonium chloride (4 g =NH_4Cl in 100 mL water). Resulting suspension was refluxed for five minutes, cooled in ice-water. White crystalline product was separated by filtration, washed with ice water (3x15 mL) and dried at 110 ºC for half an hour to afford 27.8 g (91%) pure product. Product decomposes at temperatures above 190 ºC. ^{1}H-NMR (DMSO-d_6, 500 MHz): δ 8.21 (2H, d, *J*=8 Hz), 7.64 (2H, d, *J*=8 Hz), and 3.12 ppm (6H, s); ^{13}C-NMR (DMSO-d_6, 500 MHz) δ 189.1, 163.9, 151.1, 147.7, 128.6, 122.8, 95.2, and 27.4 ppm. MS-ES$^+$ (CH_3OH) m/z: 360 (M+CH_3OH+Na^+), 382 (NaM+CH_3OH+Na^+).

Anal. Calcd for $C_{13}H_{11}N_3O_6$ (305.24): C, 51.15; H, 3.63; N, 13.77; Found C, 51.08; H, 3.71; N, 13.72.

Preparation of 5-(4-Nitro-benzoyl)-pyrimidine-2,4,6-trione (**1h**).

This compound was prepared in 93% isolated yield by following General Procedure C. ^{1}H-NMR (DMSO-d_6, 500 MHz): δ 8,61 (1H, s), 8.46 (1H, d, *J*=11Hz), 8.34 (1H, d, *J*=13Hz), and 7.81 (1H, t, *J*=13 Hz) ppm (6H, s); ^{13}C-NMR (DMSO-d_6, 500 MHz) δ 188.2, 161.4, 154.0, 143.8, 131.3, 128.4, 126.5, 119.6, and 95.5 ppm.

Preparation of 1,3-Dimethyl-5-(4-nitrobenzoyl)pyrimidine-2,4,6-trione (**1i**).

This compound was prepared in 95% yield by following General Procedure C. ^{1}H-NMR (DMSO-d_6, 500 MHz): δ 8.34 (1H, d, *J*=12Hz), 8.33 (1H, s), 7.95 (1H, d, *J*=11Hz), 7.73 (1H, t, *J*=13 Hz), and 3.15 ppm (6H, s); ^{13}C-NMR (DMSO-d_6, 500 MHz): δ 187.3, 164.8, 150.7, 147.3, 137.9, 134.8, 129.8, 125.7, 123.3, 96.2, and 28.0 ppm.

Anal. Calcd for $C_{13}H_{11}N_3O_6$ (305.24): C, 51.15; H, 3.63; N, 13.77. Found C, 51.05; H, 3.76; N, 13.65.

Preparation of 5-(4-Nitrobenzoyl)pyrimidine-2,4,6-trione (**1j**).

This compound was prepared in 93% yield by following General Procedure C. ^{1}H-NMR (DMSO-d_6, 500 MHz): δ 11.64 (2H, s, NH), 8.27 (2H, d, *J*=9.0Hz), and 7.79 ppm (2H, d, *J*=9Hz); ^{13}C-NMR (DMSO-d_6, 500 MHz) δ 188.2, 149.3, 148.6, 141.7, 129.6, 122.8, and 95.8 ppm.

Preparation of 5-(3,5-Dinitro-benzoyl)-pyrimidine-2,4,6-trione (**1l**).

This compound was prepared in 90% yield by following General Procedure C. ^{1}H-NMR (DMSO-d_6, 500 MHz): δ 9.90 (2H, s), 8.79 (1H, s), and 8.42 ppm (2H,s); ^{13}C-NMR (DMSO-d_6, 500 MHz): δ 186.3, 165.4, 151.2, 147.5, 147.2, 127.5, 118.1, and 93.3 ppm.

Preparation of 5-(3,5-Dinitrobenzoyl)-1-methylpyrimidine-2,4,6-trione (**1m**).

This compound was prepared in 93% yield by following General Procedure C. ^{1}H-NMR (DMSO-d_6, 500 MHz): δ 8.78 (1H, s) , 8.41 (2H, s), and 3.05 ppm (6H, s); ^{13}C-NMR (DMSO-d_6, 500 MHz): δ 187.1, 163.2, 152.3, 148.2, 147.4, 127.3, 118.1, 93.4, and 27.1 ppm.

Anal. Calcd for $C_{12}H_8N_3O_8$ (336.21): C, 42.87; H, 2.40; N, 16.66; Found C, 42.78; H, 2.51; N, 16.55.

General Procedure D.

Preparation of 5-(3-Hydroxybenzoyl)barbituric Acid (**1n**).

Chloroform solution (150 mL) of 3-acetoxybenzoic acid (1.8 g; 0.01 mol) and oxalyl chloride (2.5 g 0.02 mol) was stirred at room temperature for four hours. After evaporation of solvent the oily residue was dissolved in carbon tetrachloride (70 mL) and solvent was again evaporated. Chloroform (~30 mL) of this oily residue was slowly added into stirring pyridine (30 mL) suspension of barbituric acid (1.28 g; 0.01 mol). Resulting dark red reaction mixture was stirred at room temperature for additional hour and then added slowly over 20 minutes into stirring aqueous hydrochloride (10 mL water, 20 mL concentrated hydrochloric acid, and 5 mL methanol). Resulting suspension was stirred at room temperature for additional half an hour and kept at 0 ºC for one hour. Solid material was separated by filtration and it contains both 5-(3-acetyloxybenzoyl)barbituric acid and 5-(3-hydroxybenzoyl)barbituric acid (**1n**). To complete the ester hydrolysis solid material was mixed with aqueous sodium hydroxide (0.6 g; 0.015 mol of NaOH in 30 mL water) and heated at 70 ºC for half an hour. Resulting reaction mixture was acidified to pH=2 at ice-water bath temperature. Formed white solid precipitate was separated by filtration, washed with ice-cooled water (3x5 mL) and dried at 110 ºC for 30 minutes. Isolated yield of 5-(3-hydroxybenzoyl)barbituric acid (**1n**) is 91% (2.26 g). Product decomposes at temperatures above 270 ºC. ^{1}H-NMR (DMSO-d_6, 500 MHz): δ, 11.43 (2H, s), 9.65 (1H, s), 7.22 (1H, t, *J*=8 Hz), 6.97 (1H, d, *J*=8 Hz), 6.95 (1H, s), and 6.93 ppm (1H, d, *J*=8 Hz); ^{13}C-NMR (DMSO-d_6, 500 MHz): δ 190.3, 156.6, 149.4, 136.4, 128.8, 119.3, 118.6, 115.3, and 95.1 ppm. MS-ES$^+$ (CH_3OH) m/z: 249 (M+1$^+$), 271 (M+Na^+), 313 (M+2CH_3OH+1$^+$), 519 (2M+Na^+).

Anal. Calcd for $C_{11}H_8N_2O_5$ (248.19): C, 53.23; H, 3.25; N, 11.29; Found C, 53.42; H, 3.34; N, 11.19.

Preparation of 1-Butyl-5-(4-hydroxybenzoyl)pyrimidine-2,4,6-trione (**1o**).

This compound was prepared in 77% isolated yield by following General Procedure D. ^{1}H-NMR (DMSO-d_6, 500 MHz): δ, 11.67(1H, s), 7.51(2H, d, *J*=8.5 Hz), 6.80(2H, d, *J*=8.5 Hz), 3.70 (2H, t, *J*=7.2 Hz), 1.47 (2H, m), 1.25 (2H, m), and 0.86 ppm (3H, t, *J*=7.0 Hz); ^{13}C-NMR (DMSO-d_6, 500 MHz) δ 186, 163, 161, 158, 145, 128, 121, 110, 90, 36, 26, 16, 10 ppm.

Preparation of 5-(4-Hydroxybenzoyl)-1,3-dimethylpyrimidine-2,4,6-trione (**1p**).

This compound was prepared in 85% isolated yield by following General Procedure D. ^{1}H-NMR (DMSO-d_6, 500 MHz): δ 7.51(2H, d, *J*=6.3 Hz), 6.80 (2H, d, *J*=6.9 Hz), and 3.17 ppm (6H, s); ^{13}C-NMR (DMSO-d_6, 500 MHz): δ 185, 161, 158, 146, 128, 121, 110, 90, and 24 ppm.

Anal. Calcd for $C_{13}H_{12}N_2O_5$ (276.24): C, 56.52; H, 4.38; N, 10.14; Found C, 56.45; H, 4.42; N, 10.09.

Preparation of 5-(4-Hydroxybenzoyl)pyrimidine-2,4,6-trione (**1r**).

This compound was prepared in 80% isolated yield by following General Procedure D. ^{1}H-NMR (DMSO-d_6, 500 MHz): δ 11.33 (2H, s), 7.52 (2H, d, *J*=8.0 Hz), and 6.82 ppm (2H, d, *J*=8.5 Hz); ^{13}C-NMR (DMSO-d_6, 500 MHz): δ 186, 162, 158, 145, 128, 121, 110, 90 ppm.

Preparation of 5-(4-Hydroxybenzoyl)-1-phenylpyrimidine-2,4,6-trione (**1s**).

This compound was prepared in 83% isolated yield by following General Procedure D. ^{1}H-NMR (DMSO-d_6, 500 MHz): δ 11.91 (1H, s), 7.55 (2H, d, *J*=8.5 Hz), 7.44 (2H, t, *J*=7.5 Hz), 7.38 (1H, t, *J*=7.0 Hz), 7.28 (2H, d, *J*=8.0 Hz), and 6.78 ppm (2H, d, *J*=8.5 Hz); ^{13}C-NMR (DMSO-d_6, 500 MHz): δ 186, 164, 161, 158, 145, 131, 128, 125, 125, 124, 121, and 110, 90 ppm.

General Procedure E.

Preparation of 5-[[2,4-Dinitrophenyl)hydrozono]-(4-methoxyphenyl)methyl]-1,3-dimethylpyrimidine-2,4,6-trione (**2h**).

To a 1-propanol (20 mL) suspension of 5-(4-methoxybenzoyl)-1,3-dimethylpyrimidine-2,4,6-trione (**1g**) (1.0 g; 3.4 mmol) and 2,4-dinitrophenylhydrazine (0.683 g; 3.4 mmol) one drop of sulfuric acid was added. The reaction mixture was stirred while refluxing and became a clear solution after 30 minutes. The reaction mixture was refluxed for additional four hours and left at 0 ºC for one hour. Resulting orange precipitate was separated by filtration, washed with 1-propanol (3x5 mL), ether (3x10 mL) and dried at 50 ºC for twenty minutes. The isolated yield of pure **2h** is 1.30 g (81%). Mp: 98-99.2 ºC. ^{1}H-NMR(CF_3CO_2H-DMSO-d_6, 500 MHz): δ 9.51(1H, s), 8.62(1H, d, *J*=2.5 Hz), 8.01 (1H, d, *J*=9 Hz), 6.94 (1H, d, *J*=9 Hz), 6.83 (2H, d, *J*=7 Hz), 6.56 (2H, d, *J*=7Hz), 3.44 (3H, s), 2.97(6H, s); ^{13}C-NMR (CF_3CO_2H-DMSO-d_6, 500 MHz): δ 176.2, 165.5, 163.2, 153.1, 146.5, 139.5, 131.2, 128.6, 123.8, 123.4, 114.9, 109.3, 92.1, 55.4, and 28.4 ppm. MS-ES$^+$ (MeOH) m/z 413 (75%), 423 (55%), 493 (M + 23).

Anal. Calcd for $C_{20}H_{18}N_6O_8$ (470.39): C, 51.07; H, 3.86; N, 17.87; Found C, 51.01; H, 3.92; N, 17.82.

Preparation of 5-{[*N*'-(4-Nitrophenyl)hydrazino]phenylmethylene}pyrimidine-2,4,6-trione (**2a**).

This compound was prepared in 73% isolated yield by following General Procedure E. ^{1}H-NMR(CF_3CO_2H-DMSO-d_6, 500 MHz): δ 7.72(2H, d, *J*=8.5 Hz), 7.03(1H, t, *J*=7.8 Hz), 6.96(2H, t, *J*=7.0 Hz), 6.81(2H, d, *J*=8.0 Hz), and 6.38 ppm (2H, d, *J*=9.5 Hz); ^{13}C-NMR (CF_3CO_2H-DMSO-d_6, 500 MHz): δ 177, 166, 152, 151, 141, 131, 129, 129, 126, 126, 112, and 89 ppm.

Preparation of 4-{*N*'-[Phenyl-(2,4,6-trioxo-1-phenylhexahydropyrimidin-5-yl)methylene]-hydrazino}benzoic Acid (**2b**).

1-Propanol (20 mL) mixture of 5-benzoyl-1-phenylpyrimidine-2,4,6-trione (**1b**) (1.0 g; 3.25 mmol) and 4-hydrazino-benzoic acid (0.494 g; 3.25 mmol) were added. To the resulting reaction mixture 1 drop of sulfuric acid was carefully added. The reaction was stirred while refluxing and became a clear solution after 10 minutes. The reaction mixture was allowed to reflux for 4 hours. The resulting reaction mixture was then cooled to room temperature, and a solid yellow precipitate formed. The solid was removed by filtration and washed with ether (3 x 15 mL). The resulting solid was oven dried at 110 ºC for 2 hours. Isolated yield of pure product is 1.1 g (79 %). Product decomposes at temperatures above 200 ºC. ^{1}H-NMR(CF_3CO_2H-DMSO-d_6, 500 MHz): δ 7.57(d, 2H, *J*=4.5, Ar), 7.06(d of t, 3H, *J*=3.0, Ar), 7.01(t, 1H, *J*=7.0, Ar), 6.93(t, 2H, *J*=7.0, Ar), 6.86(d of t, 4H, *J*=3.5, Ar), 6.37(d, 2H, *J*=4.5, Ar): ^{13}C-NMR(CF_3CO_2H-DMSO-d_6, 500 MHz): δ 176, 173, 166, (162, 161, 161, 160 quartet belonging to CF_3CO_2H), 152, 150, 132, 132, 131, 130, 130, 130, 129, 128, 126, 121, (120, 116, 113, 109 quartet belonging to CF_3CO_2H), 113, 90 ppm. MS-ES$^+$ (MeOH) m/z 195(75%), 360(100%), 408(60%), 465 (M + 23). MW=442.42 g/mol + 0.3 molecules H_2O.

Anal. Calcd for $C_{24}H_{18}N_4O_5$: C, 64.36; H, 4.19; N, 12.51. Found C, 64.36; H, 4.21; N, 12.53.

Preparation of 5-{[*N*'-(2,4-Dinitrophenyl)hydrazino]phenylmethylene}-1,3-dimethylpyrimidine-2,4,6-trione (**2c**).

This compound was prepared in 83% isolated yield by following General Procedure E. ^{1}H-NMR (CF_3CO_2H-DMSO-d_6, 500 MHz): δ 9.42(1H, s), 8.55(1H, s), 8.01(1H, d, *J*=9.5 Hz), 7.00(1H, d, *J*=6.5 Hz), 6.9(3H, m), 6.86 (2H, t, *J*=8.0 Hz), and 2.96 ppm (6H, s); ^{13}C-NMR (CF_3CO_2H-DMSO-d_6, 500 MHz) δ 175, 165, 152, 146, 139, 131, 130, 130, 130, 129, 125, 123, 116, 91, and 28 ppm.

Preparation of 5-{[*N*'-(2,4-Dinitrophenyl)hydrazino]phenylmethylene}-1-phenylpyrimidine-2,4,6-trione (**2d**).

This compound was prepared in 88% yield by following General Procedure E. ^{1}H-NMR (DMSO-d_6, 500 MHz): δ 11.51 (1H, s), 10.69 (1H, s), 8.88 (1H, d, *J*=2.4 Hz), 8.37 (1H, d, J_1=12.6 Hz, J_2=2.7 Hz), 8.10 (1H, d, *J*=9.6 Hz),7.83 (2H, d, *J*=9.0 Hz), 7.39 (5H, m), 7.30 (1H, t, *J*=7.2 Hz), and 7.21 ppm (2H, d, *J*=7.8 Hz); ^{13}C-NMR (DMSO-d_6, 500 MHz): δ 157, 157, 150, 147, 140, 134, 133, 132, 126, 125, 125, 125, 124, 124, 124, 123, 119, 113, and 77 ppm.

Anal. Calcd for $C_{23}H_{16}N_6O_7$: C, 56.56; H, 3.30; N, 17.21. Found C, 56.48; H, 3.41; N, 17.09.

Preparation of 5-{[*N*'-(2,4-Dinitrophenyl)hydrazino]phenylmethylene}-pyrimidine-2,4,6-trione (**2e**).

This compounds was prepared in 84% isolated yield by following General Procedure E. ^{1}H-NMR (DMSO-d_6, 500 MHz): δ 11.41 (1H, s), 10.74 (2H, s), 8.87 (1H, d, *J*=2.7 Hz), 8.39 (1H, d, J_1=12.3 Hz, J_2=2.4 Hz), 8.12 (1H, d, *J*=9.9 Hz), 7.79 (2H, t, *J*=9.9 Hz), and 7.39 (3H, *J*=3.2 Hz); ^{13}C-NMR (DMSO-d_6, 500

MHz): δ 158, 148, 147, 140, 133, 133, 126, 125, 125, 124, 123, 119, 113, and 78 ppm.

Preparation of 4-{*N*'-[(1,3-Dimethyl-2,4,6-trioxotetrahydropyrimidin-5-ylidene)phenylmethyl]hydrazino}-benzoic Acid (**2f**).

This compound was prepared in 79% isolated yield by following General Procedure E. ^{1}H-NMR (CF_3CO_2H-DMSO-d_6, 500 MHz): δ 7.55 (2H, d, *J*=8.5 Hz), 7.01 (1H, t, *J*=7.5 Hz), 6.95 (2H, t, *J*=7.5 Hz), 6.81 (2H, d, *J*=7.5 Hz), 6.36 (2H, d, *J*=8.5 Hz), and 2.95 ppm (6H, s); ^{13}C-NMR (CF_3CO_2H-DMSO-d_6, 500 MHz): δ 175, 173, 165, 153, 151, 132, 131, 130, 129, 126, 120, 112, 90, and 28 ppm.

Preparation of 5-{(4-Methoxyphenyl)-[*N*'-(4-nitrophenyl)-hydrazino]methylene}-1,3-dimethylpyrimidine-2,4,6-trione (**2g**).

This compound was prepared in 82% isolated yield by following General Procedure E. ^{1}H-NMR (CF_3CO_2H-DMSO-d_6, 500 MHz): δ 9.51 (1H, s), 8.03 (2H, d, *J*=9.0 Hz), 7.16 (2H, d, *J*=9.0 Hz), 6.86 (2H, d, *J*=9.0 Hz), 6.75 (2H, d, *J*=9.0 Hz), 3.73 (3H, s), and 3.11 ppm (3H, s); ^{13}C-NMR (CF_3CO_2H-DMSO-d_6, 500 MHz): δ 162.8, 158.0, 150.5, 151.6, 149.8, 137.3, 132.6, 128.3, 126.1, 113.1, 110.4, 81.2, 53.4, and 26.5 ppm.

Anal. Calcd for $C_{2o}H_{19}N_5O_6$: C, 56.47; H, 4.50; N, 16.46. Found C, 56.33; H, 4.58; N, 16.38.

Preparation of 5-[[*N*-(2,4-Dinitrophenyl)hydrazino]-(4-methoxyphenyl)methylene]-1,3-dimethyl-pyrimidine-2,4,6-trione (**2h**).

This compound was prepared in 81% isolated yield by following General Procedure E. ^{1}H-NMR (CF_3CO_2H-DMSO-d_6, 500 MHz): δ 9.51(1H, s), 8.62(1H, d, *J*=2.5 Hz), 8.01 (1H, d, *J*=9 Hz), 6.94 (1H, d, *J*=9 Hz), 6.83 (2H, d, *J*=7 Hz), 6.56 (2H, d, *J*=7Hz), 3.44 (3H, s), and 2.97 ppm (6H, s): ^{13}C-NMR (CF_3CO_2H-DMSO-d_6, 500 MHz): δ 176.2, 165.5, 163.2, 153.1, 146.5, 139.5, 131.2, 128.6, 123.8, 123.4, 114.9, 109.3, 92.1, 55.4, and 28.4 ppm.

Preparation of 5-[[*N*-(2,4-Dinitrophenyl)hydrazino]-(4-methoxyphenyl)methylene]-1-methylpyrimidine-2,4,6-trione (**2i**).

This compound was prepared in 81% isolated yield by following General Procedure E. ^{1}H-NMR (DMSO-d_6, 500 MHz) δ 11.32 (1H, s), 11.01 (2H, s), 8.83 (1H, d, *J*=2.7 Hz), 8.33 (1H, d, *J*=6.0 Hz), 8.05 (1H, d, *J*=9.6 Hz), 7.73 (2H, d, *J*=8.7 Hz), 6.93 (2H, d, *J*=9.0 Hz), and 3.76 ppm (3H, s). ^{13}C-NMR (DMSO-d_6, 500 MHz) δ 163, 158, 157, 147, 140, 133, 126, 125, 125, 119, 113, 110, 109, 78, and 51 ppm.

Preparation of 5-[[*N*'-(2,4-Dinitrophenyl)hydrazino]-(3-hydroxyphenyl)methylene]-1-methylpyrimidine-2,4,6-trione (**2j**).

This compound was prepared in 88% isolated yield by following General Procedure E. ^{1}H-NMR (DMSO-d_6, 500 MHz): δ 11.37 (1H, s), 10.76 (2H, s), 8.87 (1H, d, *J*=2.1 Hz), 8.41 (1H, d, *J*=12.0 Hz), 8.06 (1H, d, *J*=9.5 Hz), 7.24 (1H, t, *J*=7.5 Hz), 7.17 (2H, d), and 6.79 ppm (1H, d, *J*=10.0 Hz): ^{13}C-NMR (DMSO-d_6, 500 MHz): δ 158, 153, 148, 147, 140, 135, 133, 126, 125, 125, 119, 114, 113, 112, 110, and 78 ppm.

Preparation of 5-[[*N*-(2,4-Dinitrophenyl)hydrazino]-(4-hydroxyphenyl)methylene]-1-methylpyrimidine-2,4,6-trione (**2k**).

This compound was prepared in 88% isolated yield by following General Procedure E. ^{1}H-NMR (DMSO-d_6, 500 MHz): δ 11.44 (1H, s), 10.34 (1H, s), 8.86 (1H, d, *J*=1.5 Hz), 8.33 (1H, d, *J*=6.0 Hz), 8.04 (1H, d, J=4.5 Hz), 7.60 (2H, d, *J*=4.0 Hz), 6.75 (2H, d, *J*=4.5 Hz), and 3.03 ppm (3H, s); ^{13}C-NMR (DMSO-d_6, 500 MHz): δ 158, 157, 155, 153, 149, 140, 132, 126, 126, 125, 124, 120, 113, 111, 77, and 22 ppm.

Preparation of 1-Butyl-5-[[*N*-(2,4-dinitrophenyl)hydrazino]-(4-hydroxyphenyl)-methylene]pyrimidine-2,4,6-trione (**2l**).

This compound was prepared in 80% isolated yield by following General Procedure E. ^{1}H-NMR (DMSO-d_6, 500 MHz): δ 11.34 (1H, s), 10.98 (1H, s), 8.86 (1H, d, *J*=2.5 Hz), 8.36 (1H, d, *J*=12.0 Hz), 8.05 (1H, d, *J*=9.5 Hz), 7.63 (2H, d, *J*=8.5 Hz), 6.79 (2H, d, *J*=8.5 Hz), 3.72 (2H, t, *J*=7.5 Hz), 1.50 (2H, m), 1.26 (2H, m), and 0.86 ppm (3H, t, *J*=7.5 Hz); ^{13}C-NMR (DMSO-d_6, 500 MHz): δ 157, 156, 155, 149, 147, 140, 133, 126, 125, 125, 124, 119, 113, 111, 78, 26, 26, 16, and 10 ppm.

Preparation of 5-[[*N*-(2,4-Dinitrophenyl)-hydrazino]-(4-hydroxyphenyl)methylene]-pyrimidine-2,4,6-trione (**2m**).

This compound was prepared in 91% isolated yield by following General Procedure E. ^{1}H-NMR (DMSO-d_6, 500 MHz): δ 11.36 (1H, s), 10.79 (2H, s), 8.85 (1H, d, *J*=2.1 Hz), 8.36 (1H, d, *J*=10.5 Hz), 8.04 (1H, d, *J*=9.9 Hz), 7.63 (2H, d, *J*=8.7 Hz), and 6.78 ppm (2H, d, *J*=9.0 Hz); ^{13}C-NMR (DMSO-d_6, 500 MHz): δ 158, 156, 147, 147, 140, 133, 126, 126, 125, 123, 118, 113, 111, and 78 ppm.

Anal. Calcd for $C_{17}H_{12}N_6O_8$: C, 47.67; H, 2.82; N, 19.62. Found C, 47.55; H, 2.93; N, 19.54.

Preparation of 5-[[*N*'-(2,4-Dinitrophenyl)hydrazino]-(4-hydroxyphenyl)methylene]-1-phenylpyrimidine-2,4,6-trione (**2n**).

This compound was prepared in 83% isolated yield by following General Procedure E. ^{1}H-NMR (DMSO-d_6, 500 MHz): δ 11.52 (1H, s), 10.37 (1H, s), 8.87 (1H, d, *J*=2.7 Hz), 8.33 (1H, d, *J*=12.0 Hz), 8.03 (1H, d, *J*=9.9 Hz), 7.67 (2H, d, *J*=9.0 Hz), 7.38 (2H, t, *J*=7.4 Hz), 7.28 (1H, t, *J*=7.5 Hz), 7.19 (2H, d, *J*=8.4 Hz), and 6.76 ppm (2H, d, *J*=8.4 Hz); ^{13}C-NMR (DMSO-d_6, 500 MHz): δ 158, 157, 156, 149, 147, 140, 133, 132, 126, 126, 125, 125, 125, 124, 124, 119, 113, 111, and 79 ppm.

Preparation of 5-[[*N*'-(2,4-Dinitrophenyl)hydrazino]-(4-hydroxyphenyl)methylene]-1-methylpyrimidine-2,4,6-trione (**2o**).

This compound was prepared in 84% isolated yield by following General Procedure E. ^{1}H-NMR (DMSO-d_6, 500 MHz): δ 11.40 (1H, s), 10.34(1H, s), 8.85 (1H, d *J*=3.0 Hz), 8.33 (1H, d, J_1=12.5 Hz, J_2=3.0 Hz), 7.99 (1H, d, *J*=9.5 Hz), 7.61 (2H, d, *J*=8.5 Hz), and 6.75 ppm (2H, d, *J*=8.5 Hz); ^{13}C-NMR (DMSO-d_6, 500 MHz): δ 158, 157, 155, 153, 149, 140, 132, 126, 126, 125, 124, 119, 112, 111, and 78, 24 ppm.

Preparation of 5-[[*N*'-(2,4-Dinitrophenyl)hydrazino]-(4-hydroxyphenyl)methylene]-1,3-dimethylpyrimidine-2,4,6-trione (**2p**).

This compound was prepared in 91% isolated yield by following General Procedure E. ^{1}H-NMR (DMSO-d_6, 500 MHz): δ 11.40 (1H, s), 10.35 (1H, s), 8.34 (1H, d of d, J_1=16 Hz, J_2=4 Hz), 8.00 (1H, d, *J*=16 Hz), 7.61(2H, d of d, J_1=11 Hz, J_2=4 Hz), and 6.70 ppm (2H, d of d, J_1=11 Hz, J_2=3 Hz); ^{13}C-NMR (DMSO-d_6, 500 MHz): δ 157.1, 155.6, 153.7, 149.1, 140.4, 132.5, 126.3, 126.2, 125.2, 124.9, 120.0, 113.0, 111.4, 78.2, and 23.8 ppm.

Preparation of 5-[[(2,4-Dinitrophenyl)hydrazono]-(4-nitrophenyl)methyl]pyrimidine-2,4,6-trione (**2r**).

To a 250 mL round bottom flask charged with 20 mL propanol, 5(4-nitro-benzoyl)-pyrimidine-2,4,6-trione (**1b**) (0.277 g; 1.00

mmol), 2,4-dinitrophenylhydrazine (0.198 g; 1.00 mmol), and drop of sulfuric acid was stirred with refluxing for six hours. After cooling to room temperature orange solid product was separated by filtration, washed with 1-propanol (1 x10 mL), ether (3x15 mL) and dried at 110ºC for two hours. The yield of pure product was 0.409 g (89%). Product decomposes at temperatures above 275 ºC. ^{1}H-NMR(DMSO-d_6, 500 MHz): δ 11.51 (1H, s, NH), 10.59 (2H, s, NH), 8.87 (1H, d, *J*=1.0 Hz), 8.40 (1H, d, *J*=5.5 Hz), 8.20 (2H, d, *J*=4.5 Hz), 8.14 (1H, d, *J*=5.0 Hz), 8.00 (2H, d, *J*=4.5 Hz); ^{13}C-NMR (DMSO-d_6, 500 MHz): δ 159, 147, 146, 143, 140, 140, 133, 126, 126, 125, 119, 119, 113, 78 ppm. MS-ES$^+$ (MeOH) m/z 408(100%).

Anal. Calcd for $C_{17}H_{11}N_7O_9$: C, 44.65; H, 2.42; N, 21.44. Found C, 44.65; H, 2.54; N, 21.20.

Preparation of 5-[[*N*-(2,4-Dinitrophenyl)hydrazino]-(4-nitrophenyl)methylene]pyrimidine-2,4,6-trione (**2s**).

This compound was prepared in 91% isolated yield by following General Procedure E. ^{1}H-NMR (DMSO-d_6, 500 MHz): δ 11.51 (1H, s), 10.59 (2H, s), 8.87 (1H, d, *J*=2.5 Hz), 8.40 (1H, d, *J*=11.5 Hz), 8.20 (2H, d, *J*=8.5 Hz), 8.14 (1H, d, *J*=10.0 Hz), and 8.00 ppm (2H, d, *J*=9.0 Hz); ^{13}C-NMR (DMSO-d_6, 500 MHz): δ 159, 147, 146, 143, 140, 140, 133, 126, 126, 125, 119, 119, 113, and 78 ppm.

General Procedure F.

Preparation of 5-(4-Nitrobenzoyl)-1,3-dimethylpyrimidine-2,4,6-trione Morpholinium Salt (**3k**).

Tetrahydrofuran (200 mL) solution of 5-(4-nitrobenzoyl)-1,3-dimethylpyrimidine-2,4,6-trione (**1k**) (610 mg; 2 mmol) and morpholine (191 mg; 2.2 mmol) was stirred at room temperature for half an hour. The solvent was evaporated and the solid residue was mixed with ether (100 mL), and resulting suspension was stirred at room temperature for ten minutes. Solid product was separated by filtration, washed with ether (3x15 mL) and dried at 110 ºC for half an hour. The yield of product is 740 mg (94%). Product decomposes at temperatures above 220 ºC. ^{1}H-NMR (DMSO-d_6, 500 MHz): δ 8.12 (2H, d, *J*=8.5 Hz), 7.52 (2H, d, *J*=8.5 Hz), 3.77 (4H, m) , 3.13 (4H, m), and 3.06 ppm (6H, s); ^{13}C-NMR (DMSO-d_6, 500 MHz): δ 191.0, 163.0, 152.2, 151.4, 146.9, 127.9, 122.6, 93.7, 63.4, 43.1, and 26.9 ppm.

Anal. Calcd for $C_{17}H_{20}N_4O_7$ (392.36) C, 52.04; H, 5.14; N, 14.28. Found C, 51.96; H, 5.12; N, 14.15.

Preparation of 5-Benzoylpyrimidine-2,4,6-trione Piperidinium Aalt (**3a**).

This compound was prepared in 80% isolated yield by following General Procedure F. ^{1}H-NMR (DMSO-d_6, 500 MHz): δ 7.47 (2H, d, *J*=7.0 Hz), 7.36 (1H, t, *J*=7.5 Hz), 7.30 (2H, t, *J*=7.5 Hz), 2.97 (4H, t, *J*=5.5 Hz), 1.61 (4H, m), and 1.51 ppm (2H, m); ^{13}C-NMR (DMSO-d_6, 500 MHz): δ 190, 162, 148, 139, 126, 125, 124, 90, 41, 19, and 18 ppm.

Preparation of 5-Benzoyl-1-methylpyrimidine-2,4,6-trione Piperidinium Aalt (**3b**).

This compound was prepared in 95% isolated yield by following General Procedure F. ^{1}H-NMR (DMSO-d_6, 500 MHz): δ 9.69 (1H, s), 8.52(2H, s), 7.45 (2H, d, *J*=9.9 Hz), 7.28 (3H, m) 3.01 (4H, t, *J*=6.0 Hz), 2.99 (3H, s), 1.64 (4H m), and 1.54 ppm (2H, m); ^{13}C-NMR (DMSO-d_6, 500 MHz): δ 189, 160, 159, 148, 140, 125, 124, 123, 89, 40, 22, 18, and 18 ppm.

Preparation of 5-(4-Methoxybenzoyl)pyrimidine-2,4,6-trione Piperidinium Salt (**3c**).

This compound was prepared in 88% isolated yield by following General Procedure F. ^{1}H-NMR (DMSO-d_6, 500 MHz): δ 9.70 (2H, s,), 8.58 (2H, s), 7.51 (2H, d, *J*=8.7 Hz), 6.83 (2H, d, *J*=8.7 Hz), 3.76 (3H, s), 2.98 (4H, t, *J*=5.4 Hz), 1.61 (4H, m), and 1.51 ppm (2H, m); ^{13}C-NMR (DMSO-d_6, 500 MHz): δ 188, 161, 157, 147, 131, 127, 108, 89, 51, 40, 18, and 18 ppm.

Preparation of 5-(4-Methoxybenzoyl)-1,3-dimethylpyrimidine-2,4,6-trione Piperidinium Salt (**3d**).

This compound was prepared in 93% isolated yield by following General Procedure F. ^{1}H-NMR (DMSO-d_6, 500 MHz): δ 8.40 (2H, s), 7.52 (2H, d *J*=8.7 Hz), 6.85 (2H, d, *J*=8.7 Hz), 3.77 (3H, s), 3.07 (6H, s), 3.00 (4H, t, *J*=5.4 Hz), 1.63 (4H, m), and 1.54 ppm (2H, m); ^{13}C-NMR (DMSO-d_6, 500 MHz): δ 188, 159, 157, 148, 130, 127, 109, 89, 51, 40, 23, 18, and 18 ppm.

Preparation of 5-(4-Nitrobenzoyl)pyrimidine-2,4,6-trione Piperidinium Salt (**3e**).

This compound was prepared in 95% isolated yield by following General Procedure F. ^{1}H-NMR (DMSO-d_6, 500 MHz): δ 9.65 (2H, s), 8.50 (2H, s), 8.12 (2H, d, *J*=8 Hz), 7.51 (2H, d, *J*=8 Hz), 3.00 (4H, m), 1.61 (4H, m), and 1.52 ppm (2H, m); ^{13}C-NMR (DMSO-d_6, 500 MHz): δ 190.5, 165.3, 151.5, 151.3, 147.1, 128.3, 122.8, 93.6, 44.1, 22.3, and 21.8 ppm.

Preparation of 5-(4-Nitrobenzoyl)pyrimidine-2,4,6-trione Morpholinium Salt (**3f**).

This compound was prepared in 90% isolated yield by following General Procedure F. ^{1}H-NMR (DMSO-d_6, 500 MHz): δ 9.75(2H, s), 8.11(2H, d, *J*=8.0 Hz), 7.52 (d, 2H, *J*=8.0), 3.74 (4H, m), and 3.09 ppm (4H, m); ^{13}C-NMR (DMSO-d_6, 500 MHz): δ 190.9, 165.6, 151.5, 151.2, 147.2, 128.4, 122.9, 93.9, 63.5, and 43.3 ppm.

Preparation of 5-(4-Nitrobenzoyl)pyrimidine-2,4,6-trione *N*-Methylmorpholinium Salt (**3g**).

This compound was prepared in 91% isolated yield by following General Procedure F. ^{1}H-NMR (DMSO-d_6, 500 MHz): δ 9.68 (2H, s), 8.12 (2H, d, *J*=8 Hz), 7.52 (2H, d, *J*=8 Hz), 3.80 (4H, m), 3.20 (4H, m), and 2.79 ppm (3H, s); ^{13}C-NMR (DMSO-d_6, 500 MHz): δ 190.5, 165.3, 151.4, 151.0, 147.2, 128.4, 122.8, 93.7, 63.6, 53.0, and 40.0 ppm.

Preparation of 5-(4-Nitrobenzoyl)pyrimidine-2,4,6-trione Ethanolammonium Salt (**3h**).

This compound was prepared in 98% isolated yield by following General Procedure F. ^{1}H-NMR (DMSO-d_6, 500 MHz): δ 9.62 (2H, s), 8.12 (2H, d, *J*=8 Hz), 7.79 (3H, s), 7.52 (2H, d, *J*=8 Hz), 3.67 (2H, m), and 2.85 ppm (2H, m); ^{13}C-NMR (DMSO-d_6, 500 MHz): δ 190.3, 165.2, 151.5, 151.0, 147.2, 128.4, 122.8, 93.5, 57.6, and 41.5 ppm.

Preparation of 5-(4-Nitrobenzoyl)pyrimidine-2,4,6-trione 4-Dimethylaminopyridinium Salt (**3i**).

This compound was prepared in 97% isolated yield by following General Procedure F. ^{1}H-NMR (DMSO-d_6, 500 MHz): δ 9.50 (2H, s), 8.17 (2H, d, *J*=7 Hz), 8.11 (2H, d, *J*=8 Hz), 7.51 (2H, d, *J*=8 Hz), 6.95 (2H, d, *J*=7Hz), and 3.16 ppm (6H, s); ^{13}C-NMR (DMSO-d_6, 500 MHz): δ 190.1, 165.0, 157.1, 151.5, 151.3, 147.1, 139.3, 128.4, 122.8, 107.1 93.3, and 39.8 ppm.

Preparation of 5-(4-Nitrobenzoyl)1,3-dimethylpyrimidine-2,4,6-trione Piperidinium Salt (**3j**).

This compound was prepared in 92% isolated yield by following General Procedure F. ^{1}H-NMR (DMSO-d_6, 500 MHz): δ 8.13 (2H, d, *J*=8.5 Hz), 7.52 (2H, d, *J*=8.5 Hz), 3.07 (6H, s), 3.03 (4H, m), 1.65 (4H, m), and 1.54 ppm (2H, m); ^{13}C-NMR (DMSO-d_6, 500 MHz): δ 191.0, 163.0, 152.2, 151.5, 146.9, 127.9, 122.6, 93.7, 44.0, 26.3, 22.3, and 21.8 ppm.

Preparation of 5-(4-Nitrobenzoyl)1,3-dimethylpyrimidine-2,4,6-trione *N*-Methylmorpholinium salt (**3l**).

This compound was prepared in 89% isolated yield by following General Procedure F. ^{1}H-NMR (DMSO-d_6, 500 MHz): δ 8.13 (2H, d, *J*=8.5 Hz), 7.54 (2H, d, *J*=8.5 Hz), 3.81 (4H, m), 3.22 (4H, m), 3.08 (6H, s), and 2.80 ppm (3H, s); ^{13}C-NMR (DMSO-d_6, 500 MHz): δ 191.2, 163.1, 152.1, 151.4, 146.9, 127.9, 122.6, 93.8, 63.5, 52.9, 43.1, and 26.9 ppm.

Preparation of 5-(4-Nitrobenzoyl)1,3-dimethylpyrimidine-2,4,6-trione *N*-Ethanolammonium Salt (**3m**).

This compound was prepared in 92% isolated yield by following General Procedure F. ^{1}H-NMR (DMSO-d_6, 500 MHz): δ 8.31 (2H, d, *J*=8 Hz), 7.56 (2H, d, *J*=8 Hz), 3.48 (2H, m), .3.06 (6H, s), and 2.98 ppm (2H, m); ^{13}C-NMR (DMSO-d_6, 500 MHz): δ 170.1, 150.9, 147.4, 141.3, 128.0, 123.6, 89.3, 59.2, 47.3, and 27.3 ppm.

Preparation of 5-(4-Nitrobenzoyl)1,3-dimethylpyrimidine-2,4,6-trione *N*-4-Diemethylaminopyridinium Salt (**3n**).

This compound was prepared in 93% isolated yield by following General Procedure F. ^{1}H-NMR (DMSO-d_6, 500 MHz): δ 8.22 (2H, d, *J*=8 Hz), 8.11 (2H, d, *J*=8.5 Hz), 7.52 (2H, d, *J*=8.5 Hz), 6.97 (2H, d, *J*=8.0 Hz), 3.18 (6H, s), and 3.04 ppm (6H, s); ^{13}C-NMR (DMSO-d_6, 500 MHz): δ 190.4, 162.5, 156.9, 152.4, 151.4, 146.9, 139.2, 128.1, 122.6, 106.9, 93.1, and 26.8 ppm.

General Procedure G.

Preparation of Piperidinium Salt of 5-[[2,4-Dinitrophenyl)hydrazono]-(4-hydroxyphenyl)methyl]-1,3-dimethyl-pyrimidine-2,4,6-trione (**4b**).

1-Propanol (20 mL) suspension of 5-[[2,4-dinitrophenyl)-hydrazono]-(4-hydroxyphenyl)methyl]-1,3-dimethyl-pyrimidine-2,4,6-trione (**2p**) (0.50 g; 1.09 mmol) and piperidine (1.3 mL; 0.111 g; 1.30 mmol) was stirred at room temperature for 2 hours. Reaction suspension was diluted with ether (50 mL) and solid precipitate was separated by filtration, washed with ether (3 x 15 mL), and dried at 110 ºC for 2 hours to give 0.535 g (98%) of pure product. Product decomposes at temperatures above 250 ºC. ^{1}H-NMR(DMSO-d_6, 500 MHz): δ 11.48 (1H, NH), 8.85 (1H, d, *J*=3.5 Hz), 8.31 (1H, d, *J*=11.0 Hz), 8.03 (1H, d, *J*=16 Hz), 7.56 (2H, d, *J*=14 Hz), 6.72 (2H, d, J=14 Hz), 3.10 (6H, s), 2.98 (4H, t, J=9 Hz), 1.61 (4H, m), and 1.54 ppm (2H, m); ^{13}C-NMR (DMSO-d_6, 500 MHz): δ 157.1, 155.0, 153.8, 149.5, 140.4, 132.1, 126.3, 126.1, 125.9, 124.5, 120.0, 113.0, 111.2, 77.2, 40.3, 23.5, 18.7, and 18.1 ppm. MS-ES$^+$ (CH_3COOH) m/z 360 (100%).

Anal. Calcd for $C_{24}H_{27}N_7O_8$•0.3 H_2O: C, 52.71; H, 5.09; N, 17.93. Found C, 52.82; H, 5.07; N, 17.97.

Preparation of Piperidinium Salt of 5-[[2,4-Dinitrophenyl)hydrazono]-(3-hydroxyphenyl)methyl]pyrimidine-2,4,6-trione (**4a**).

This compound was prepared in 93% isolated yield by following General Procedure G. ^{1}H-NMR (DMSO-d_6, 500 MHz): δ 11.48(1H, s), 10.31 (2H, s), 8.87 (1H, d, *J*=2.7 Hz), 8.37 (1H, d, *J*=12.3 Hz), 8.05 (1H, d, *J*=9.6 Hz), 7.24 (1H, t, *J*=7.8 Hz), 7.16 (2H, m. *J*=7.8), 6.76(1H, d, *J*=10.2 Hz), 2.91(4H, t, J=5.1 Hz), 1.57(4H, m), and 1.48 ppm (2H, m); ^{13}C-NMR (DMSO-d_6, 500 MHz) δ 159.2, 153.7, 150.6, 148.2, 140.6, 135.9, 133.0, 126.5, 125.5, 125.2, 119.9, 115.0, 113.1, 112.9, 111.1, 78.0, 40.4, 18.7, and 18.2 ppm.

Preparation of Piperidinium Salt of 5-[[2,4-Dinitrophenyl)hydrazono]-(4-hydroxyphenyl)methyl]-1-phenylpyrimidine-2,4,6-trione (**4c**).

This compound was prepared in 81% isolated yield by following General Procedure G. ^{1}H-NMR (DMSO-d_6, 500 MHz): δ 8.89 (1H, d, *J*=2.7 Hz), 8.31(1H, d, *J*=12.3 Hz), 8.04 (1H, d, *J*=10.2 Hz), 7.65 (2H, d, *J*=8.7 Hz), 7.37 (2H, t, *J*=7.5 Hz), 7.27 (1H, t, *J*=7.5 Hz), 7.19 (2H, d, *J*=8.1 Hz), 6.75 (2H, d, *J*=8.4 Hz), 2.91 (4H, t, J=5.2 Hz), 1.56 (4H, m), and 1.50 ppm (2H, m); ^{13}C-NMR (DMSO-d_6, 500 MHz): δ 158.4, 158.2, 155.1, 153.3, 148.6, 140.4, 133.8, 132.2, 126.3, 126.1, 126.0, 125.9, 124.6, 124.5, 123.3, 120.0, 113.1, 111.2, 77.1, 40.4, 18.8, and 18.2 ppm.

Preparation of Methyl L-Lysine Salt of 5-{(4-Methoxyphenyl)[2-(4-nitrophenyl)hydrazino]methylene}pyrimidine-2,4,6-trione (**4d**).

Methanol (500 mL) suspension of 5-{(4-methoxyphenyl)[2-(4-nitrophenyl)hydrazino]methylene}pyrimidine-2,4,6-trione (397 mg; 1 mmol) and *L*-lysine (146 mg; 1 mmol) was stirred at 50 ºC for ten minutes until reaction mixture becomes solution. Solvent was evaporated to solid residue. Solid residue was mixed with ether (50 mL). Solid was separated by filtration from resulting suspension, washed with ether (3x20 mL) and dried at 110 ºC for ten minutes to give 525 mg (97%) of **4d**. Product decomposes at temperatures above 200 ºC. ^{1}H-NMR (DMSO-d_6, 500 MHz): δ 10.09 (1H, s), 9.44 (2H, s), 8.06 (2H, d, *J*=9.5 Hz), 7.56 (2H, d, *J*=9 Hz), 7.14 (2H, d, *J*=7.5 Hz), 6.84 (2H, d, *J*=7.0 Hz), 3.76 (3H, s), 3.26 (1H, t, *J*=6 Hz), 2.74 (2H, d, *J*=7 Hz), 1.65 (2H, m), 1.51 (2H, m), and 1.37 ppm (2H m); ^{13}C-NMR (DMSO-d_6, 500 MHz): δ 171.4, 163.6, 159.1, 152.4, 151.6, 149.6, 137.1, 132.6, 128.3, 126.0, 113.0, 111.5, 81.7, 55.1, 53.5, 38.5, 30.1, 26.6, and 21.7 ppm. MS-ES$^+$ (CH_3OH), m/z: 381 (M-H_2O-Lysine, 100%), 632 (MNa_3 +Na$^+$), 654 (MNa_4 + Na$^+$), 676 (MNa_5 + Na$^+$), 708 (MNa_5 + CH_3OH + Na$^+$), 984 (2MNa-Lysine).

Anal. Calcd for $C_{24}H_{31}N_7O_8$ (545.22): C, 52.84; H, 5.73; N, 17.97; Found C, 52.82; H, 5.07; N, 17.97.

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REFERENCES AND NOTES

[1] For instance see: [a] B. G. Katzung, "Basic & Clinical Pharmacology" eighth edition, McGrawHill, New York, 2001; [b] J. Y. De Belin, M.-R. Romero-Martin, P. W. Fin, L. G. Sayers, N. M. Law, D. Billington, S. Ryley and S. Bhattacharya, "Barbituric Acid Analogs as Therapeutic Agents" International Patent WO 01/93841A2; *Chem. Abstr.*, 31669, **136** (2001) and references therein.

[2a] I. Watanabe, T. Andoh, R. Furuya, T. Sasaki, Y. Kamiya and H. Itoh, *Anesthesia & Analgesia* (Baltimore) **88**, 1406 (1999); [b] J. M. J. Gonzales, *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, "Methods for treating or preventing viral infections and associated diseases using barbituric acid and thiobarbituric acid derivatives" *International* Patent WO 13708(2000); *Chem. Abstr.*, 203127, **132** (200); [b] R. I. Ashkinazi, "Salts of 5,5'-arylidenebis[barbituric acids] and 5,5'-arylidenebis[2-thiobarbituric acids] having antibacterial, antichlamydial, antiviral and immuno-modulating activity" International Patent WO 25699 (1999); *Chem. Abstr.*, 5267, **131** (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).

[4a] D. L Lee and C. G. Carter, "Herbicidal Method and Composition Utilizing Certain 5-(2-Substituted Benzoyl)-Barbituric Acids" United States Patent 4,797,147 (1989); *Chem. Abstr.*, 148889, **111** (1989); [b] I. T. Kay, F. C. Peacock and W. S. Waring, "5-Acyl Barbituric Acid Derivatives" United State Patent 3,828,043 (1974); *Chem. Abstr.*, , 72545, **76** (1972); [c] Y. Hirono, H. Ishikawa, I. Iwataki, M. Sawaki and O. Nomura, "Herbicidal Barbituric Acid Derivatives" German Patent DE 252478 (1975); *Chem. Abstr.*, 121891, **84** (1975).

[5] For instance see: [a] B. S. Jursic and D. M. Neumann, *Tetrahedron Lett.*, **42**, 4103 (2001); [b] B. S. Jursic and D. M. Neumann, *Tetrahedron Lett.*, **42**, 8435 (2001); [c] D. M. Neumann, B. S. Jursic and K. L. Martin, *Tetrahedron Lett.*, **43**, 1603 (2002); [d] B. S. Jursic, F. Douelle, K. Bowdy and E. D. Stevens, *Tetrahedron Lett.*, **43**, 2002 (2002); [e] B. S. Jursic and E. D. Stevens, *Tetrahedron Lett.*, **43**, 5681 (2002); [f] B. S. Jursic, *J. Heterocyclic Chem.* in press; [g] Jursic, B. S.; Stevens, E. D. in press.

[6] For preparation of barbituric acid derivatives by simple condensation of malonic esters with substituted urea see: (a) Vogel "Text-Book of Preparative Organic Chemistry", Third Edition, John Wiley, New York, 1966 (a) Buzz, Recreational Drugs, Loompanics Unlimited, 1989.

[7] For methods oftransformation of methyl aryl ethers into phenole derivatives (deprotetion of phenol OH group) see: T. W. Greene and P. G. M. Wuts, Protective Groups in Organic Synthesis 3rd Ed., John Wiley & Sons, Inc., New York, 1999.

[8] Reaction was carried under conditions described in General Procedure E.

[9] L. R. Morgan, B. S. Jursic, C. L. Hooper, D. M. Neumann, K. Thangaraj and B. LeBlanc, *Bioorg. Med. Chem. Lett.*, **12**, 3407 (2002).

[10] In X-ray study of these compounds it was determined that in about 5% there was a presence of a cocrystal between a new derivative of **2g** as well as **2g** by itself. The derivative was formed by elimination of methyl from the methoxy group and by substitution of a hydrazone hydrogen with 1-propyloxy group. It is our speculation that this product was formed by crystallization of **2g** from propanol with traces of sulfuric acid. In this unique reaction alcohol is added to the NN double bond of the hydrazone moiety and in this way a very exciting new compound with NOR moiety was formed. This reaction mechanism and outcome requires further studies and results will be published elsewhere.

[11] Patent application in preparation.

[12] All calculations were carried out with MOPAC version 6.0. Quantum Chemistry Program Exchange (QCPE), Program Number 455.

[13] M. J. S. Dewar, E. G. Zoebisch, E. F. Healy and J. J. P. Stevart, *J. Am. Chem. Soc.*, **107**, 3902 (1985); M. J. S. Dewar and E. G. Zoebisch, *J. Mol. Struct. (Theochem)*, **180**, 1 (1988).