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The Design and Synthesis of Novel Barbiturates of Pharmaceutical Interest

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THE DESIGN AND SYNTHESIS OF NOVEL BARBITURATES OF PHARMACEUTICAL INTEREST

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by

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Dedicated to:

My daughter, Madeline Megan Jenkins

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ABSTRACT

Barbituric acids have been historically classified as compounds that act on the central nervous system, and as such provide therapeutic uses as anxiolytics, sedatives, hypnotics, and anti-convulsants. Recent investigations of barbituric acid derivatives have provided scientists with information that barbituric acids may have applications in antibacterial, anti-chlamydial, anti-viral, as well as anti-cancer treatments. Additionally, recent literature accounts have indicated that barbituric acid derivatives may also act as immune modulators.

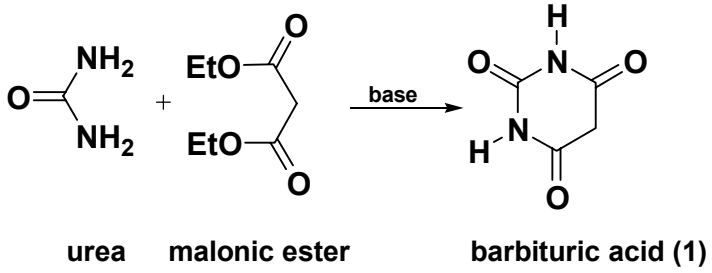
The recent explorations of barbiturates and their potential anti-cancer and immune modulating properties are the subject of this work. Novel synthetic approaches to the development of new barbituric acid derivatives were explored thoroughly, and the mechanisms of these novel syntheses were detailed by experiment and spectroscopic characterizations. In many cases the reaction procedures were designed for large scale, efficient syntheses, that are directly applicable to pharmaceutical production of these potentially valuable therapeutic compounds.

Several new products unique to barbituric acid reactions were characterized spectroscopically. Barbituric acid derivatives were the subject of biological evaluation, and the results are reported in this work. Overall, unique synthetic approaches to the production of novel barbituric acid derivatives were accomplished to create several new classes of barbiturates with potential applications in cancer treatment.

INTRODUCTION

Ia. History of Barbituric Acid

In 1864, German chemist Adolph von Bayer, future founder of Bayer Pharmaceuticals, discovered one of the most notorious therapeutics known to chemists, malonylurea, more commonly known as barbituric acid **(1)**.[1] During the scientific era of Bayer, chemists had none of the tools available to modern day scientists, and analyses of compounds thought to possess biological activity were routinely characterized by taste, giving chemists first hand knowledge of the physiological effects of potential therapeutics. Curiously, after this routine analysis was performed, barbituric acid in itself was determined to be without therapeutic significance.[1] However, the discovery of barbituric acid subsequently led to the introduction of many other barbiturate derivatives, fueling the discoveries of a broad new class of therapeutics that would quickly dominate both the medical and social circles in the early 20th century.[1]



urea **malonic ester** **barbituric acid (1)**

Figure I.1: Synthesis of barbituric acid **(1).**

Ia.1 Modifications to original barbituric acid

Among the early derivatives of barbituric acid was 5,5'-diethylbarbituric acid. In 1903 Fischer and von Mering synthesized the first therapeutically active derivative of barbituric acid, done by replacing the *C*-5 hydrogens of the barbituric acid ring with ethyl substituents.[1] Upon administration of this new barbiturate derivative, human subjects fell into a state of hypnosis, or deep sleep. This new diethyl barbiturate, commonly called Veronal **(3) (Figure I.2)**, is the first known active derivative of hypnotics derived from barbituric acid.[1,2]

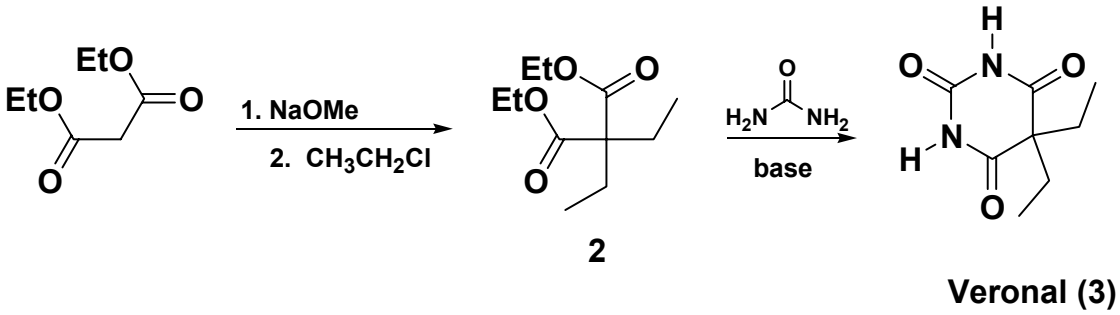
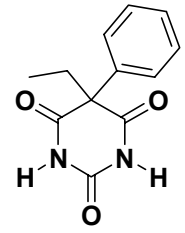


Figure I.2: Original synthesis of Veronal (5,5'-diethylbarbituric acid) **(3).**

Even in the early 20th Century, chemists realized that there was a serious problem with the metabolic degradation of Veronal. The hypnotic drug was slow to take effect, and very slowly metabolized. According to early scientific accounts, human subjects administered this compound would sleep for several days, unable to be roused from the coma-like state induced by the drug.[1,2] From this point on, medicinal chemists have been exploring the therapeutic effects of barbituric acids, barbituric acid derivatives and new substitutions and derivations of barbituric acids as compounds with therapeutic value. Since the synthesis of Veronal, improvements have been made to this class of

therapeutics, which in turn elicited new structures belonging to perhaps one of the most valuable medicinal classes of compounds known to date.[1]

Early advances in the structure-activity relationship of barbiturates and their therapeutic effects produced, in 1912, the active drug Phenobarbital [1] **(4) (Figure I.3)**. Phenobarbital has been classically described as a medicinal compound possessing hypnotic and anticonvulsant activity, and given twice daily, keeps epileptic seizures under control.[2]



phenobarbital (4)

Figure I.3: Structure of the active anti-epileptic Phenobarbital **(4)**.

Subsequent research pertaining to the structure-activity relationship of barbiturates produced further understanding that the lack of drug activity and subsequent metabolism of the earlier derivatives, such as original barbituric acid **(1)** and Veronal **(3)**, existed due to the same physical property, namely negligent passage across tissues lining the gastrointestinal tract (GI) of the human body. This negligent passage inhibited the drugs' passage into the circulatory system. These early scientific discoveries led to the production of barbiturates that contained larger hydrocarbon groups, similar to those in the fatty tissue of the gastrointestinal tract.[1,2]

Ia.2 Effects of subsequent barbituric acid modification

The modifications of barbiturates led to the yield of lipophilic compounds able to quickly pass through both the GI tract and the blood-brain barrier (BBB), enabling the transformation of barbiturates into widely used anesthetics, anxiolytics, and sedatives. Functional substitutions of the original barbituric acid stem from either *C*-5 substitutions or *C*-2 substitutions, each producing compounds with varying activities. For example, manipulations of the *C*-5 position have resulted in the production of amobarbital **(5)**, pentobarbital **(6)**, secobarbital **(7)** and hexobarbital **(8)**. Substitutions at *C*-2 have resulted in the production of the short acting barbiturates, thiopental **(9)**, and thiamylal **(10) (Figure I.4).**[1,2]

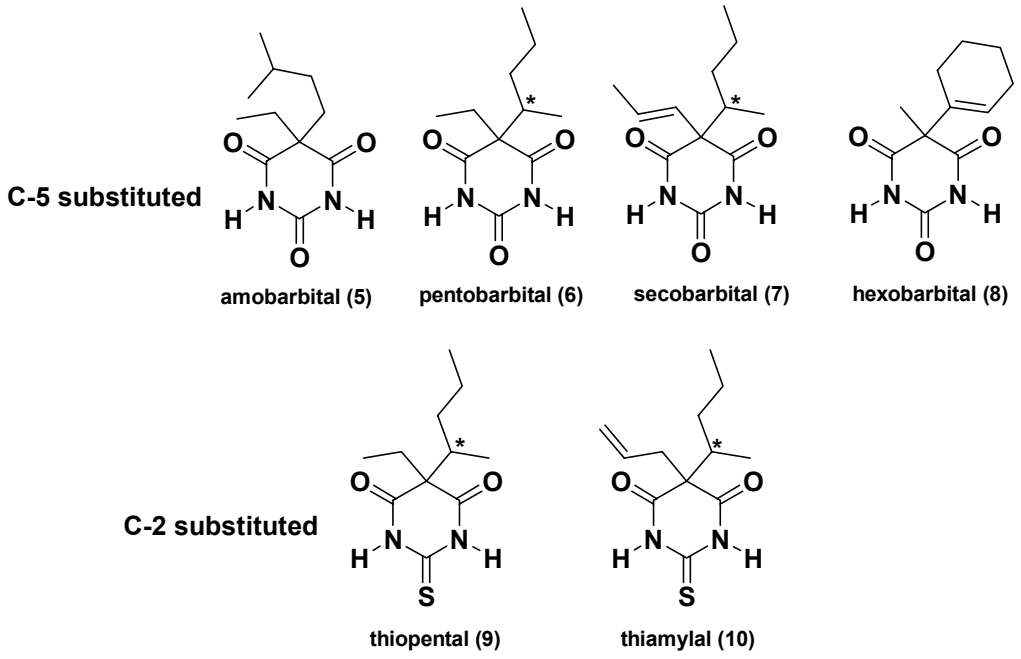


Figure I.4: Substitutions of the original barbituric acid at either *C*-5 or *C*-2.

Ib. Classifications of Barbiturates

Barbituric acids and their subsequent derivatives are broken down into four classes, and are classified according to their metabolic degradation and tissue deposition.[2] The duration of the effects of barbiturates as well as the protein binding affinity of barbiturates are directly proportional to the chain length of the hydrocarbon attached to the *C-5* position of the barbituric acid ring.[2] For example, the classes include the following:

1) *Ultra short-acting barbiturates.* Include compounds that are metabolized rapidly and are highly lipid soluble. These are typically used as intravenous anesthetics. Examples include hexobarbital **(8)**, thiopental **(9)**, thiamylal **(10),** all of which have *C-5* substituents that are hydrocarbons of four or more carbon units.[2]
2) *Short-acting barbiturates.* Include compounds that are lipid soluble and bind to proteins. Renal clearance of these derivatives is very low and they are generally used as hypnotics for patients who need help falling asleep. These compounds typically have a half life of about three hours, and are advantageous because they do not cause next-day drowsiness. While these are compounds with similar structures of ultra-short acting counterparts, they lack the additional *C-2* substitution. Several examples of short acting barbiturates include pentobarbital **(6)** and secobarbital **(7).**[2]
3) *Intermediate-acting barbiturates.* These derivatives are typically used as hypnotics for persons waking in the middle of the night. They generally have a half life of three to six hours, and cause next-day drowsiness. Several examples in this class include butabarbital and amobarbital **(5).**[2]

4) *Long acting barbiturates.* These compounds exert a hypnotic effect for longer than six hours, causing sedation and subsequent drowsiness. They are traditionally used for anti-convulsant effects rather than hypnotic effects, due to the side effects. Examples include Phenobarbital **(4)** and veronal **(3).** [2]

Ic. Physical Properties of barbituric acids

Barbituric acids and the active derivatives of barbituric acid are considered both hydrophilic, due to the 2,4,6-pyrimidinetrione ring system, and lipophilic, depending on the nature of the 5,5'-substituents. Barbituric acid in itself is a strong acid, having a p*K*a of 4.01 in water.[3a] It is partially soluble in polar solvents, such as methanol and water, and in these solvents retains its acidic properties, as well as be converted into the corresponding salt when treated with a base.[3b] Generally speaking, barbiturate derivatives having at least one unsubstituted NH hydrogen retain their acidic properties, but the relative acidity of barbituric acid derivatives depends not only on the *N*-substitution, but the *C*-5 substitution as well (**Figure I.5).**[3b]

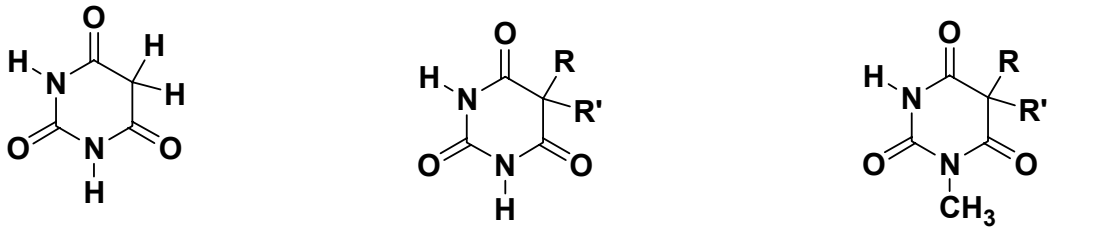


Figure I.5: Acidic properties of barbituric acids.[3]

The barbituric acid ring itself contains one sp^3 hybridized carbon atom, and is treated as an achiral ring system unless the 5,5'-substituents differ from one another and one of the NH moieties is substituted.[3b]

Id. Pharmacological effects of barbiturates and barbituric acids as building blocks for large heterocycles with pharmaceutical value

Historical literature accounts describe barbituric acids as exhibiting a primary mode of action on the central nervous system. The primary binding site of barbiturates is the GABAa-ion receptor complex, which will be described in further detail. Once bound to this ion-receptor complex, barbiturates elicit effects that can be manifested in several ways:[2,3]

1) hypnosis and anesthesia.
2) Anti-convulsant
3) Miscellaneous, including analgesic, autonomic nervous system actions, respiratory effects etc.

While traditional roles of barbiturates in medicinal chemistry have been identified as GABAa-ion receptor complex, [3] there have been more recent literature documentation that barbiturates can exhibit biological activities in other areas, such as anti-bacterial, anti-fungal, possess anti-cancer activity, anti-osteoporosis activity to name just a few.[4]

Id.1 The traditional barbiturate target: the GABAa-ion Receptor Complex

The human nervous system is composed of specialized cells known as neurons. Communication between neurons *via* chemical synapses is vital to the normal function of both the central and peripheral nervous systems.[5] Neurons are separated from one another by a space called the synaptic cleft, which effectively prohibits direct communication between adjacent neurons. Instead, neurotransmitters that bind to specific receptors present in post-synaptic terminals are used as a means of communication between two neurons.[5] Neurotransmitters can be of two types; excitatory or inhibitory. Excitatory neurotransmitters act by depolarizing the next cell, which increases the probability that an action potential will be fired. Inhibitory neurotransmitters act by causing the next cell to hyperpolarize, which decreases the probability that an action potential will be fired.[5,6]

The main inhibitory neurotransmitter in the central nervous system (CNS) is gamma-aminobutyric acid (GABA). Release of this neurotransmitter into the synaptic cleft allows the interaction with the corresponding post-synaptic ligand gated GABAa receptor.[5,6] Chloride channels are then activated and the rapid influx of chloride ions into the neuron makes the intracellular charge negative, and in turn depresses the excitatory depolarization of that neuron, making it less likely to fire an action potential.[5,6] The release of GABA and its subsequent post-synaptic recognition by the corresponding GABAa receptor essentially inhibits the excitatory responses that result from fear or anxiety and ensures a tranquilizing effect. In this respect, GABA can be deemed one of the most important neurotransmitters in the CNS, ensuring a level of homeostasis of neuron firing in the CNS.[5,6]

The GABAa receptor has a structure common to most ligand-gated receptors. The receptor is made up of five protein subunits of approximately 50 kD, arranged in a circle, labeled α, β, or γ, which forms a channel that traverses the cell membrane (**Figure I.6**).[5-7]

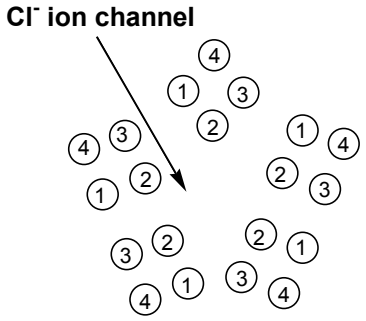


Figure I.6: Cartoon of the GABAa receptor.[7]

This channel remains closed until GABA binds to the site of recognition of the receptor and causes several conformational changes, including the rotation of the five subunits until the diameter of the channel is widened. This widening of the channel allows for the passage of the chloride ion into the neuron. Each protein subunit is a string of amino acids that pass both in and out of the cell membrane as a trans-membrane 4 helix bundle. The extracellular end, the N-terminus, is traditionally described as the mediator of the interaction between GABA and the GABAa receptor **(Figure I.7)**.[5-7]

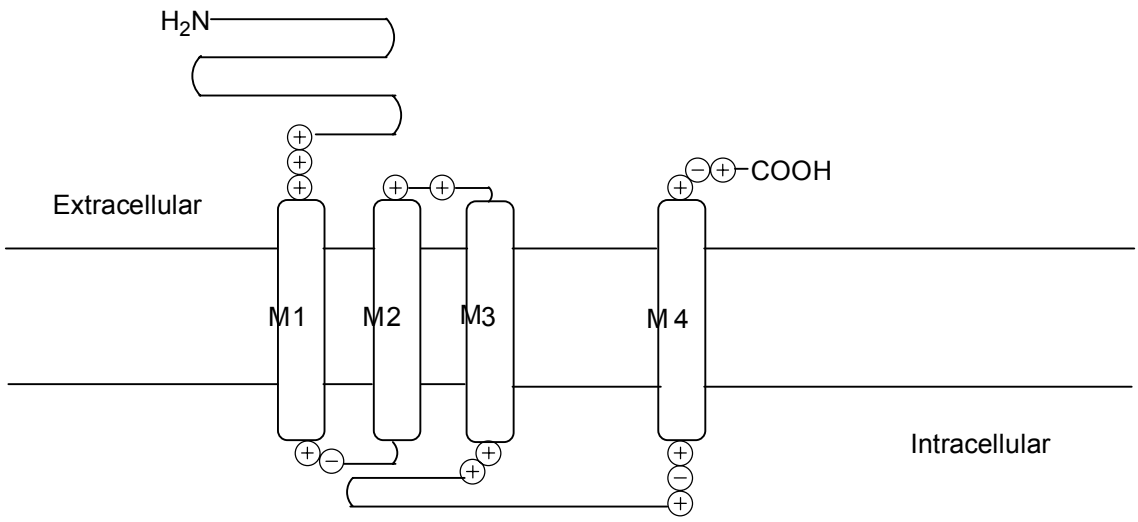


Figure I.7: Cartoon of protein subunits of GABAa that traverse the cell membrane.

GABAa receptors are common targets for many therapeutic drugs, including anti-epileptic drugs, general anesthetics, barbituric acids and benzodiazepines. When certain chemical structures, such as barbituric acid, bind to the GABAa-ion receptor complex associated with the neuron, the chloride current, activated by GABA, is enhanced.[5,6] Barbituric acids bind to the β-subunit of the GABAa-ion receptor complex and cause a conformation in the ion channel which allows more chlorine ions into the intracellular matrix of the cell. The mediating factor of barbituric acid activity within the human body is the ability of the compound to pass through the blood brain barrier.[5,6] Therefore, most barbiturate derivatives that are lipophilic enough to pass the blood brain barrier do enhance the chloride ion influx into the cell, and inhibit the firing of the action potential to the next cell.

Id.2 Discovery of Benzodiazepines

The vast research surrounding barbiturates has indirectly led to the discovery of another potent class of anxiolytic compounds known and benzodiazepines. The benzodiazepine family consists of a large class of compounds that have a variety of substitutions on a basic tricyclic ring structure. Among these are clinically used chlorodiazepoxide **(11)**, flurazepam **(12),** triazolam **(13)**, diazepam (valium) **(14),** lorazepam **(15)**, and nitrazepam **(16) (Figure I.7a)**.[5,6]

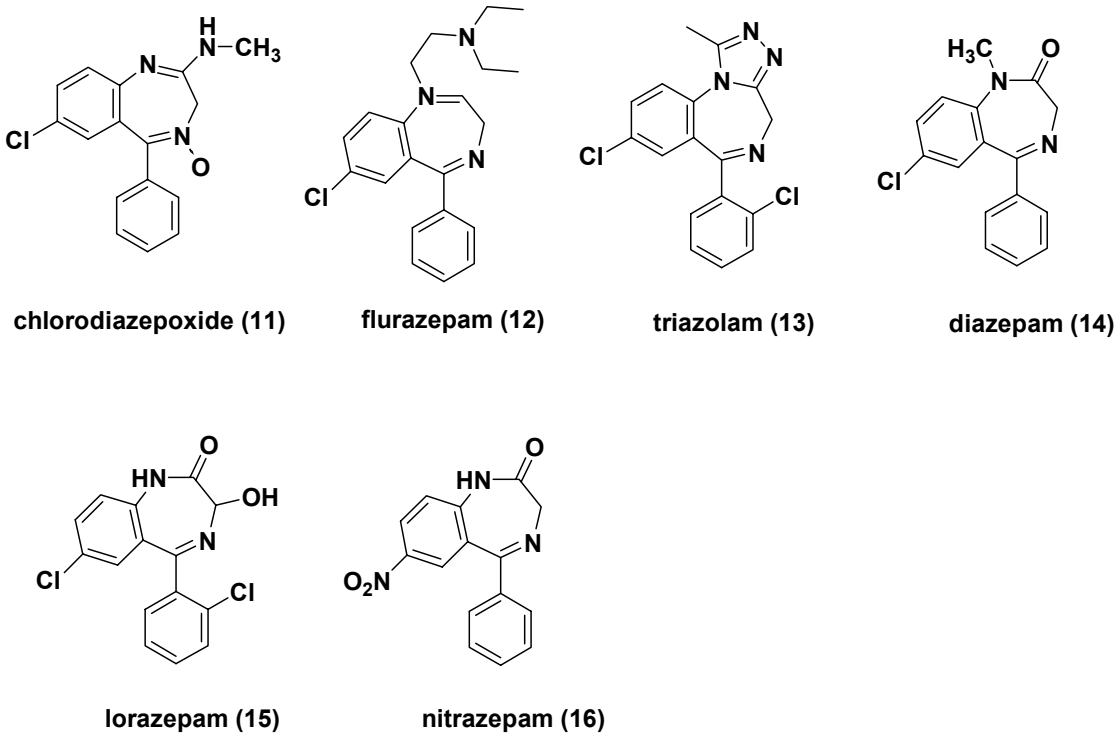


Figure I.7a: Benzodiazepines commonly used today.

The structural changes on the tricyclic ring are responsible for the widely variant half-lives of each compound.[8] Benzodiazepines act as sedatives, anxiolytic, muscle relaxants, and anti-convulsants, and do so with a moderate degree of selectivity.[5] However, each of

the physiological characteristics elicited by benzodiazepines typically are a result of the same action. Benzodiazepines tend to enhance the inhibitory activity of GABA at the GABAa receptors.[5,6] Once bound to the GABAa receptor-ion complex, benzodiazepines cause an allosteric change in the receptor, which ultimately increases the number of chloride channels opened at once.[5-7] One other advantage to using benzodiazepines as therapeutics is that they exhibit a much lesser degree of toxicity than do their barbiturate counterparts.[5] While accidental overdoses of persons using barbiturates became a serious problem for the medical community, this problem is almost non-existent with the use of benzodiazepines. To this end, benzodiazepines have largely replaced barbiturates in the pharmaceutical marketplace.[5]

Id.3 Other possible physiological targets for barbiturates: Histone deacetylase enzymes

Chromatin is classically defined as a complex of protein/DNA material within a given cell. Nucleosomes are the basic units of chromatin within the cell, and they consist of an octamer of core histones. These histones, labeled H2A, H2B, H3, and H4 wrap 1.8 turns of DNA and form a compact structure within the cell. Localized changes within the chromatin structure are one of the main components of transcriptional gene regulation.[8]

Several of the localized changes in the chromatin structure are a consequence of post-translational modifications of the histone tails. These modifications include acetylation, methylation, phosphorylation, ubiquitination and poly-ADP-ribosylation, all playing important roles in gene regulation (**Figure I.8**).[9] Perhaps one of the best studied post-translational histone modifications is histone acetylation and deacetylation.

Acetylation of histones generally occurs at lysine residues, and there are two classes of enzymes involved in determining the degree of acetylation of histones. These enzymes are histone acetylases (HATs) and histone deacetylases (HDACs).[12] Generally, **hyper**acetylated histones are associated with transcriptional permissiveness, and **hypo**acetylated histones mediate gene repression.[10] Histone deacetylases (HDAC) are enzymes found in association with large protein complexes that are involved in gene expression.[12] HDACs both regulate gene expression by deacetylating transcription factors and participate in cell cycle regulation.[12] Compounds that inhibit HDAC increase histone acetylation by preventing deacetylation, and regulating a small subset of genes (approximately 2%).[10]

Figure I.8: Cartoon of targets for post-translational histone modification *via* acetylation of lysine residues (**K**).[11]

There are several known compounds that act as histone deacetylase inhibitors (HDACIs). Among these are sodium butyrate, phenylbutyrate, **P**hthalimido**C**aproyl **H**ydroxamic **A**cid (**PCHA**) **(17),** trichostatin A **(18)**, **S**uberoyl**A**nilide **H**ydroxamic **Acid** (**SAHA**) **(19),** apicidin **(20),** and trapoxin **(21) (Figure I.9)**.[10,12]

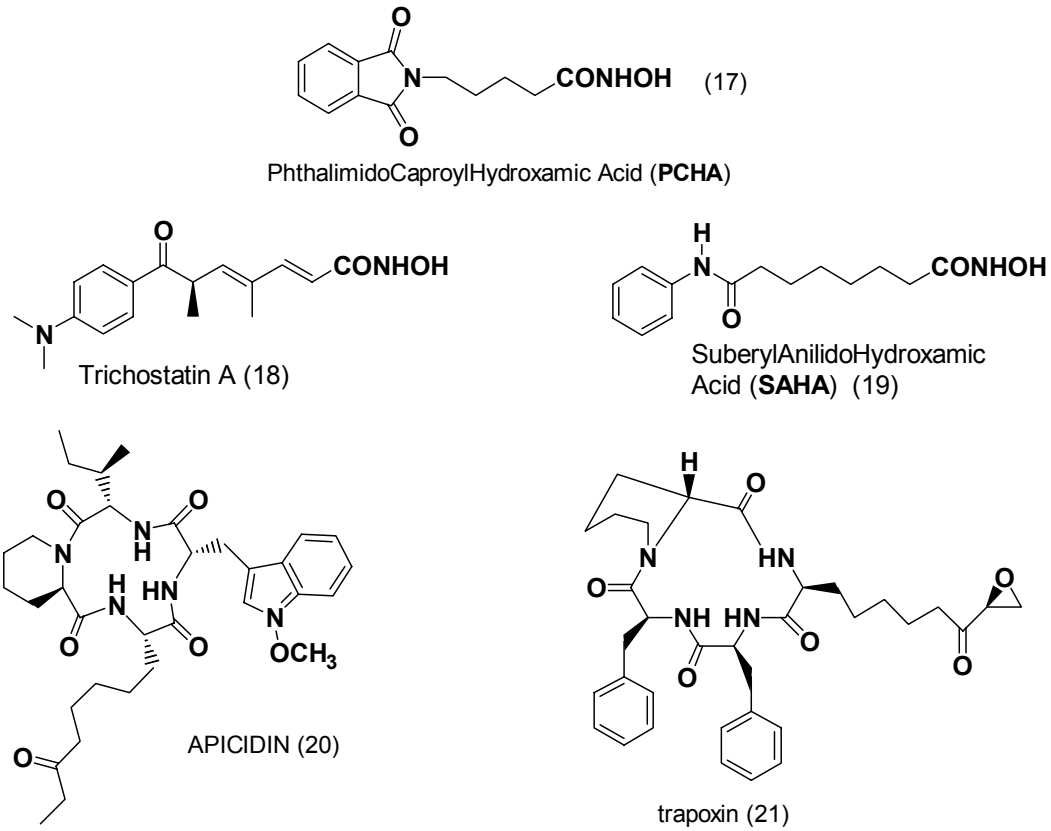


Figure I.9: Several known histone deacetylase inhibitors.

In cellular cultures, the physiological effects of each of these compounds include cell growth inhibition, cell differentiation, apoptosis (programmed cell-death), as well as inhibition of cancer cell growth in animal models.[12] Development through the cell cycle requires that gene expression be synchronized to the activities of proteins.[10,13] Several small polar hydroxamic acids act as HDAC inhibitors and mediate cell growth, arrest and/or differentiation. SAHA **(19)** and PCHA **(17)** are in fact two of those compounds. SAHA (**19**), perhaps one of the most widely studied hydroxamic acid HDACI's, has been shown both *in vitro* and *in vivo* to increase the accumulation of acetylated histones in both tumor tissue and normal tissue, however, the growth suppression and apoptotic activity of SAHA appears to be limited to only transformed (cancerous) cells.[12,14]

Treatment of normal cells with these small polar compounds causes no growth inhibition or apoptosis, even though the increases of histone acetylation are detected in both normal and transformed cells.[14a]

Recent advances have been made with respect to the active site of the HDAC. For instance, scientists have been able to analyze the enzyme active site of an HDAC-like protein (HDLP) isolated from a species of anaerobic bacteria. Through these studies, it was shown that the catalytic site of the enzyme has a tubular pocket with a zinc binding site at the base of the pocket and two Asp-Histadine charge relay systems.[12] The hydroxamic acid part of SAHA was shown to bind with the zinc atom (**Figure I.10).**[12] Furthermore, these hydroxamic acid HDACI's have been shown to bind directly to the enzyme active site, thereby blocking the substrate access, and causing an accumulation of acetylated proteins.[14b]

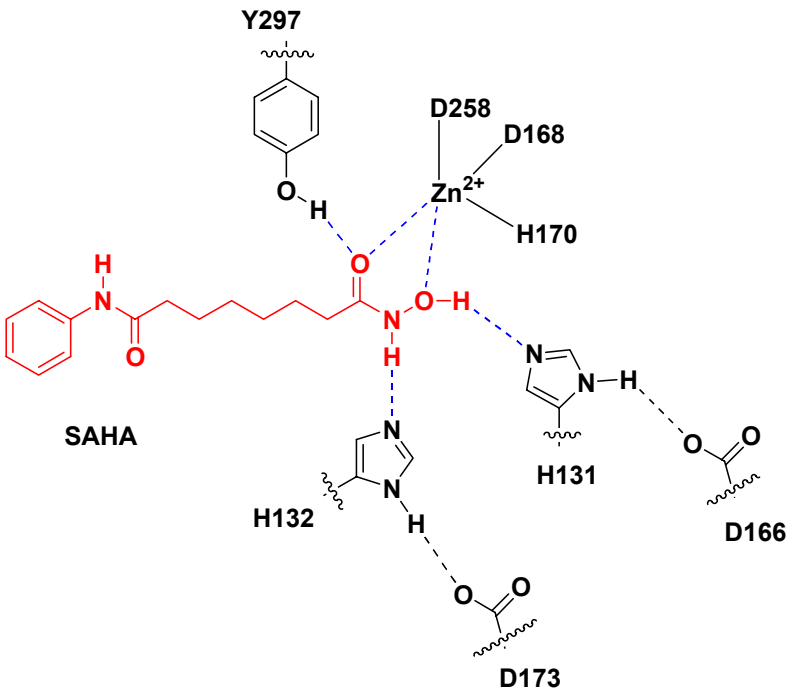


Figure I.10: HDLP Enzyme catalytic site with suberylanilido hydroxamic acid (19) bound.[14b]

The ensuing pharmacophore developed using this model consists of a metal binding domain that actively interacts with the catalytic binding site, a linker domain that occupies the tubular channel of the protein, and a surface recognition domain that interacts with the residues on the rim of the active site (**Figure I.11**).[14b] Since HDACI's have been shown to cause growth arrest, differentiation, and apoptosis in a wide variety of *in vitro* cell cultures, including neuroblastoma, melanoma, leukemia, breast, prostate, lung, ovarian, and colon cancers,[12] we felt that exploration of the potential HDAC inhibition effects of novel barbiturates structured to resemble in many ways both SAHA and PCHA, were ideal starting points for the discovery of novel compounds that could mediate cell differentiation, or arrest tumor cell division by acting as HDACI's, while maintaining some structural resemblance of the previously described pharmacophore.

For instance, that can be accomplished by replacing the aromatic moiety of SAHA or PCHA with the barbituric acid moiety. In doing so, we would effectively increase the number of hydrogen bonding interactions between the new inhibitor and the targeted enzyme. Based on this logic, our hypothesis was that barbituric acid analogs could be designed to retain the pharmacophore of potent HDACIs by either utilizing barbituric acid as the metal binding moiety of the pharmacophore or the surface recognition moiety of the pharmacophore and in turn create a new class of HDACIs with ideally the same biological activity as observed in SAHA and PCHA.

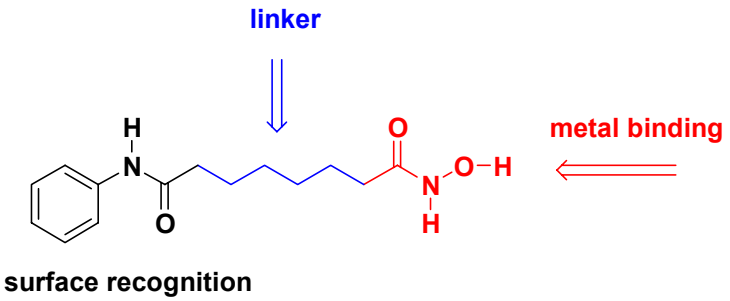


Figure I.11: Pharmacophore of potential histone deacetylase inhibitors.

Id.4 Barbiturates as Potential Immuno-Modulating Compounds

From an immunological point of view, cancer cells can be defined as cells that have somehow escaped the normal cell growth regulatory mechanisms, producing non-functional cells.[15] These non-functioning cells then give rise to clone cells which are constantly replicating, leading to the development of a tumor.[15] While the human immune system has genes and cells that have many functions, including maintaining homeostasis of normal tissue by regulating cellular proliferation and cell death, it is clearly indicated by the number of annual cancer deaths worldwide that the level of

effectiveness of the immune response to tumor cells is often inadequate or poorly expressed. Because of this, scientists have been increasing focus on the exploration of the immune system response to the regulation and destruction of cancer cells, designing vaccines as well as molecular systems that enable the reactivation of human immune responses to cancer cells.[15]

Overview of the Immune System

An effective immune response involves two cellular groups. These groups are known as lymphocytes and antigen-presenting cells. There are many types of lymphocytes, and these cells are produced as white blood cells from bone marrow. Once the lymphocyte leaves the bone marrow, it circulates in the blood and the lymphatic systems, and finally resides in lymphoid organs in the body. Lymphocytes have antigen (foreign body) binding cell surface receptors that mediate immunological responses, such as specificity, diversity, memory, and self-nonself recognition.[15]

T lymphocytes leave the bone marrow and travel to the thymus to mature. Here, these cells differentiate to express a unique antigen binding molecule, the T-cell receptor, on its membrane. These T-cell receptors can only recognize antigens bound to cell membrane proteins, known as major histocompatibility complex (MHC) molecules. MHCs function in recognition, termed "antigen presentation" in which the recognition occurs between the molecule and glycoproteins found on cell membranes.[15]

Dendritic cells (DC) are antigen-presenting cells of the human immune system that are involved in the initiation of the immune response.[16a] DCs are responsible for the acquisition of antigens or cancer cells, and their subsequent transport to T-lymphocyte

rich areas. They are present in lymphatic tissues and lymphoid organs. Once the DCs interact with antigens and become activated, they are able to derive specific immune responses. Secondary lymphoid organs, such as the skin, recruit both naive T-lymphocytes and antigen-stimulated DCs into T-cell rich lymphoid areas, and the co-localization of these early immune response constituents is representative of T-cell activation. [16a] Effective anti-tumor responses elicited from the immune system require the presence of both antigen presenting cells and T lymphocytes.[16b]

In order for a T-cell to become activated, which in turn initiates the immune response of antigen destruction, a T-cell activation signal is required. This signal is triggered by the recognition of the peptide-MHC molecular complex by the T-cell receptor as well as by a co-stimulatory signal. The co-stimulatory signal is usually triggered by an interaction between cell surface glycoproteins of the antigen presenting cell and the T-cell (**Figure I.12)**.[15] Because tumor cells express low levels of MHCs and lack necessary co-stimulatory molecules, both necessary to initiate the proliferation of T-cells, they are not effective modulators of antigen presenting cells.[15, 16c] Without sufficient antigen presenting cells in the vicinity of a tumor, T-cells receive only partial activating signals, and tumors are allowed to proliferate.[15]

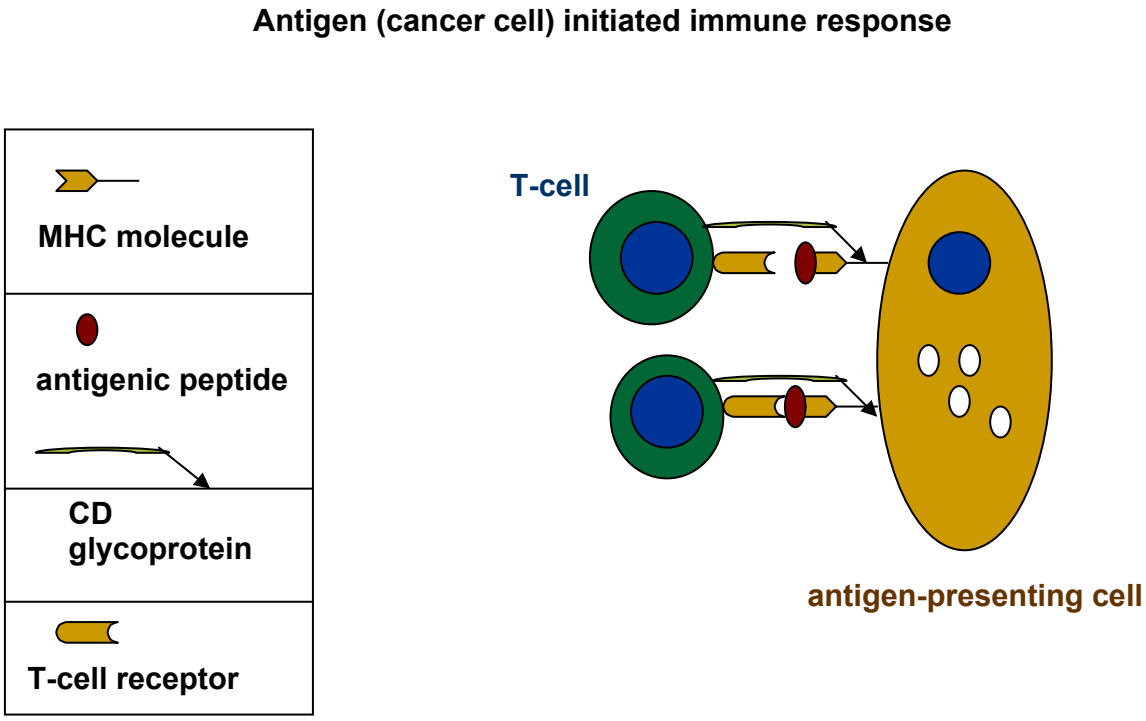


Figure I.12: Antigen initiated human immune response.

Immunotherapy is an approach in cancer treatment that attempts to supplement the natural immune defenses of the human body.[15] To that end, one compound that has been clinically shown to demonstrate significant anticancer activities is 4,4'-dihydroxybenzophenone-2,4-dinitrophenylhydrazone (**A-007 (22) Figure I.13**).[17] X-ray crystallography data revealed that **A-007 (**as monoclinic crystals) exists as two unique

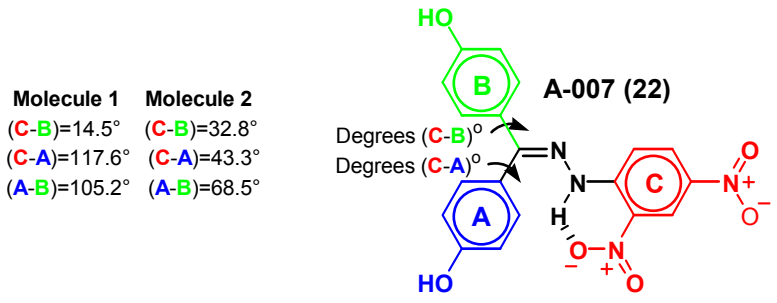


Figure I.13: Structural crystallography characteristics of **A-007 (22).** [18]

rotamers. These rotamers differ only in the orientation of the bis-diphenylmethane group, where the rings are approximately perpendicular to each other and rotated approximately 90^{o} from the orientation of the rings in each rotamer (**Figure I.13**).[18a] Both rotamers show strong intramolecular hydrogen bonds between the -NH of the -HN-N=C- moiety and an oxygen of the *o*-nitro group. Examining the structure of **A-007,** one can see that there are three unique functional moieties present in **A-007** that may contribute to its overall biological activity. These three moieties are the dihydroxy-bis-diphenylmethane rings, the hydrazone moiety and the dinitrophenyl moiety. However, despite **A-007's** high electrophilicity, it has no chemical reactivity with cell surface glycoproteins, making this compound and analogs of this compound promising new anti-cancer treatments.[18b]

A-007 and its structural analogs appear to act as T-cell activators *via* CD45+ surface receptors on lymphoendothelial cells, and in particular with dendritic cells. Thus far, thirty-three people have been treated with topical **A-007 (22)** (as a 0.25% gel) in the Phase I study, and of these subjects, 31% objective remissions have been observed with two complete responses.[17] During the Phase I study, it was discovered that **A-007** was not acting through a cytotoxic mechanism. There was no local or systemic toxicity noted, and histochemical reviews of biopsies of human skin topically treated with **A-007** revealed that increased infiltrates of T-lymphocytes containing the membrane glycoproteins CD4+ (T-helper cells), CD3+(T-cytotoxic cells), CD8+(T-cytotoxic cells), and CD45+ had occurred after treatment.[17] Increased skin infiltrates of CD11c+ dendritic cells (function as antigen presenters to T-helper cells) were also observed in treated areas.[19] Further immunohistochemical studies suggested that immune modulation had occurred *in vitro* and *in vivo* following exposure to **A-007.**[17,19]

A-007 is a simple organic molecule that appears to act as an antigen, possibly due to the unique electronic properties associated with this molecule. It has been hypothesized by Morgan, et al. that up-regulation of the CD45+ receptor is an initiation site for the **A-007**-induced immune modulations that are being observed in patients with cancer.[19] Our hypothesis is that if this is in fact the initiation site for up-regulation of receptor glycoproteins involved in immune modulation, then other structural analogs of **A-007** should be able to elicit the same, or greater responses.

CD45+ is expressed on dendritic cells, lymphocytes, monocytes, and leukocytes, as well as some neoplastic cells, as a protein tyrosine phosphatase (PTP), which together with other members of the PTPs, are responsible for phosphorylating tyrosine residues.[16d] Blocking the CD45+ sites with anti-CD45 antibodies has been shown to inhibit T-cell activation and prevent mitogen (lectin) activation of naïve T-cells.[20a] CD45+ receptor surfaces contain the amino acid residues of arginine, serine/threonine, and cysteine, and these residues can bind to or transfer natural ligands to the surface of antigen presenting cells and hydrolyze tyrosyl phosphates.[20b] Morgan et al. hypothesized that **A-007** does not inhibit or block CD45+, but up-regulates lymphocytes and dendritic cells (to antigen presenting cells) *via* electrostatic and/or non-covalent binding with the Arg, Cys, Ser/ Threo residues, as depicted in **Figure I.14**.[19] Furthermore, **A-007**-activated DCs are capable of initiating mitotic events with naïve human blood peripheral mononuclear cells (PBMC) and up-regulating both CD45+ and CD11c+ receptors in human peripheral dendritic cells,[20c] all exemplifying the fact that **A-007** is not an inhibitor of CD45+, but rather an up-regulator or modulator of the molecular sites (**Figure I.14**). The influence that functional group substitutions may have on **A-007**'s intra-/inter-molecular hydrogen

bonding and electrostatic interactions is presented below (This figure illustrates several possible interactions, and is not meant to illustrate the fact that all interactions occur).

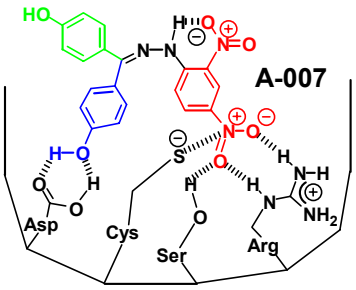


Figure I.14: Postulated possible interactions of **A-007** with the CD45 receptor (modified from Ref. 16d).

Considering this, we felt that one possibility of a moiety that would elicit the same up-regulation of CD receptors was the barbituric acid moiety. Since the possibility exists for barbituric acid to make the same types of non-covalent interactions as **A-007** with the active site of the CD45 receptor, and was a versatile functional group in itself, we chose barbituric acid as the starting point for our explorations into the possibility of designing new and more potent immune modulating compounds. Outlined through the remaining portion of this thesis are our synthetic and spectroscopic studies outlining the designed barbituric acid derivatives. While several classes of compounds were selected and designed for future *in vitro* studies as HDACI's, (namely those compounds designated in chapters **IIa-d** of this dissertation**)** several other classes were outlined as potential immune modulating compounds (chapters **IId-i)**. In both cases, the explorations of the reaction procedures, spectroscopic characterizations of the intended

products, and explorations of the reaction mechanisms are thoroughly outlined. All obtained *in vitro* results are also included in the subsequent chapters of this dissertation.

RESULTS AND DISCUSSION

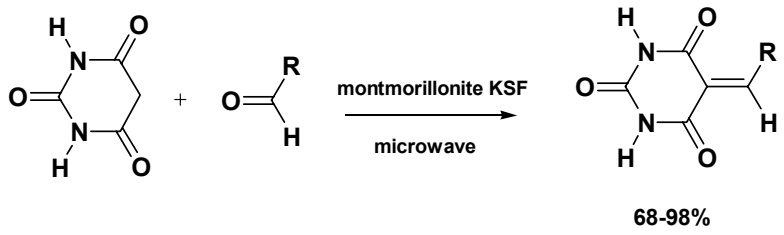
IIa. Condensation Products

IIa.1 Preamble

Because barbituric acid has an active methylene group located at the *C*-5 position the molecule is easily involved in condensation reactions with aldehydes or ketones that do not contain an α-hydrogen. This general type of reaction is known as the Knoevenagel condensation reaction.[21] The reaction of barbituric acid with carbonyl compounds was studied as early as 1864, traditionally using urea and derivatives of malonate, and the isolated products obtained from these reactions were typically the mono *C*-5 or *C*-5,5'-disubstituted products (**Figure I.4**).[22] However, to perform such reactions, the acid chloride of the alkyl substituent was necessary and due to the nature of the reaction, this procedure was applicable to a limited variety of reagents.

Benzylidene barbituric acids are generally considered important biologically active compounds. Benzylidene barbituric acids are useful as potential organic oxidizers,[23] as building blocks in the preparation of oxadeazaflavines,[24] and for the unsymmetrical synthesis of disulfides.[25] Other applications have been reported, such as several studies indicating that benzylidene barbiturates could be used as nonlinear optical materials.[26] Considering the discussed uses of benzylidene barbiturates, we felt that a straightforward and simple synthesis of a large variety of these compounds was virtually essential for both the scientific and pharmaceutical marketplaces.

To achieve the formation of the *mono* condensation product between aromatic aldehydes and barbituric acid, various methods utilizing acid or base catalyzed reactions have been previously employed such as clay mediated catalysis, radiation, and reactions without solvents just to name a few.[27-33] There are some drawbacks to using previously described literature procedures. For example, in basic conditions, the product of the reactions between barbituric acids and alkyl or aryl halides is not only the *C*-5 substituted alkyl or aryl product, but the *N, N*'-disubstituted alkyl or aryl products as well. Even so, literature accounts dictate several very interesting approaches utilized for obtaining high yields of benzylidene barbituric acids as a product of condensation. For instance, Villemin and Labiad microwaved a mixture of barbituric acid, aromatic aldehydes, and clay (Montmorillonite KSF) without solvent.[29] The product of the condensation was obtained in high yield after extraction from the solid reaction residue using the solvent DMF (**Figure IIa.1**).



R= 3,4-dimethyloxybenzaldehyde, 3,4,5-trimethoxybenzaldehyde, 4-dimethylaminobenzaldehyde, 4-chlorobenzaldehyde, thiophene-2-carboxaldehyde, 2-furaldehyde, 3-(2-furyl)acrolein, 5-nitro-2-furaldehyde

Figure IIa.1: Villemin *et.al.* preparation of Knoevenagel condensation products.[29]

Another interesting approach to the preparation of Knoevenagel condensation products utilized a solid state reaction using clay and infrared radiation to obtain relatively high yields of the desired product (**Figure IIa.2**).[34-35]

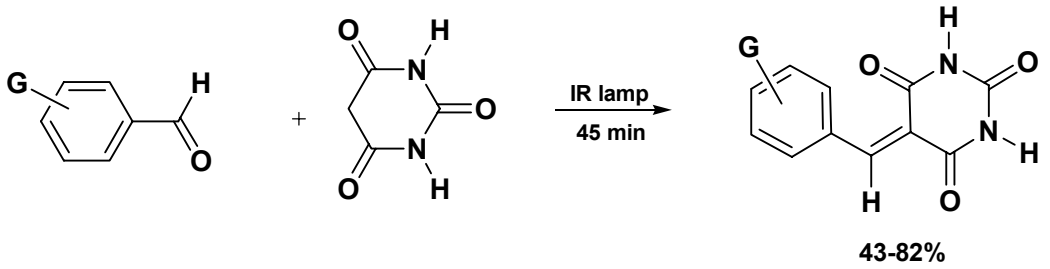


Figure IIa.2: Formation of Knoevenagel products from solid state reactions.[35]

While both of these methods provided the mono-condensation products of benzaldehydes and barbituric acid in adequate yields, the cost and availability of the necessary instruments and acidic clay catalysts provided a limitation for the production of large quantities of these compounds, therefore there was still a need for the development of a better synthetic procedure for our future studies utilizing these derivatives.

IIa.2 Results and Discussion

The synthetic procedure that we subsequently developed proved to be exceptionally simple and allowed the Knoevenagel condensation between aromatic and α,β-conjugated aromatic aldehydes with both *N,N'*-disubstituted and unsubstituted barbituric acids in methanol solution. The reaction was performed utilizing the barbituric acids ability for self-catalysis in the case of unsubstituted barbituric acid to ensure the formation of the product. In the case of *N,N'*-disubstituted barbituric acids, such as 1,3-

dimethylbarbituric acid, a catalytic amount of either sulfuric acid or formic acid was used to ensure reactant conversion. The general procedure involved mixing aldehydes with barbituric acid in a sufficient amount of alcohol to dissolve both reactants. Based on the reactivity of the aldehydes used as reactants, the reaction was allowed to stir at room temperature for several hours to one full day (**Figure IIa.3**). While typically, the reactions were performed at room temperature, we determined that in some cases, namely in the case of reactive aromatic aldehydes, the reaction mixtures could also be refluxed in methanol to give quantitative yields of the respective products in shorter time periods (~1-2 h). However, when refluxing conditions are used, care must be taken with the length of the reaction time. After extended refluxing time (12 h), we observed spectroscopically the products of decomposition in the reaction mixture solution, the formation of which hinders the isolation and purity of the desired product.

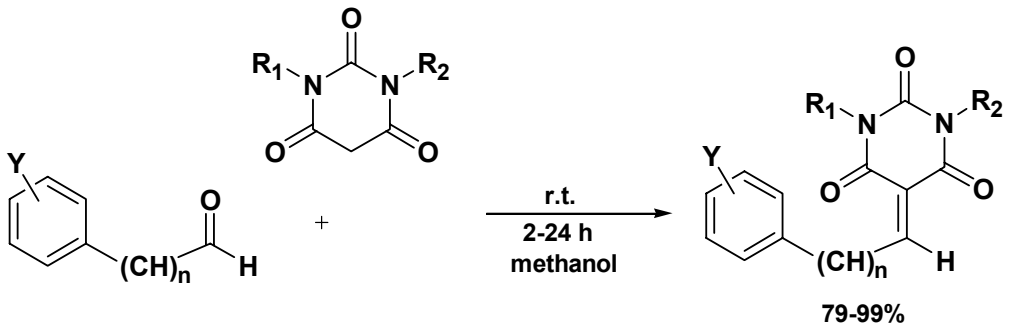


Figure IIa.3: General procedure for obtaining Knoevenagel condensation products.

Our experiments indicated that aldehydes possessing electron-donating substituents, such as OH, and $N(CH_3)_2$ react much faster, and the condensation product, visually observable by the change in color (darker) of the reaction mixture due to extended conjugation of the product, was detected as early as one minute after the

reaction progression. Similarly, *trans*-cinnamaldehyde and its counterparts reacted with similar reaction rates as did the electron-donating aldehydes. For example, the α,β-conjugated aromatic aldehydes such as *trans*-cinnamaldehyde and *trans*-3-(2-furyl)acrolein produced a dark solid precipitate after a few minutes in methanol at room temperature, and was subsequently characterized spectroscopically as the condensation product.

The products generally had a very low solubility in methanol, and the separation of the product from the reactants was done by simple filtration and ensuing washes with cold methanol, which provided highly pure condensation products. The products of condensation were thermally sensitive and decomposed rapidly at temperatures exceeding 260º C in the solid state. In solution, the products of condensation were even more thermally sensitive, and purification by hot crystallization was deemed not a preferred method of purification for these products.

To obtain a 90% conversion in the less reactive aldehydes such as unsubstituted benzaldehydes, a longer reaction time was typically required. Generally, the reaction could be performed in 1-2 days in methanol at room temperature. Careful monitoring of the reaction was needed, because once the volume of alcohol decreased, starting materials as well as our condensation products precipitated from the methanol solution, determined through ^{1}H-NMR spectroscopy in DMSO-d_6 of the solid precipitate present after evaporation of methanol occurred. In our spectral analyses, there were clear differences in the chemical shift for the NH signals of the Knoevenagel condensation product (~11.25 and 11.35 ppm) and the starting barbituric acid (11.11 ppm). The ratios of these signals were used to determine the percentage of reaction conversion, which, depending

on the time elapsed varied from 50%-80% conversion. To prevent obtaining impure products, the reactions with less reactive aldehydes were subsequently performed in closed flasks as opposed to open beakers.

As previously mentioned, crystallization using hot liquid was not a preferable method of purification, due to low thermal stability of the products in solution, for any of the desired products. Purification of the product from the starting material using solvents such as ethyl acetate or petroleum ether slightly improved the isolated yield, but elimination of unreacted barbituric acid was not accomplished. It was also necessary to perform the purification procedures several times, which ultimately lowered the yields of the condensation products. Our best purification procedure involved the evaporation of methanol at reduced pressure and room temperature to a solid residue. Elimination of barbituric acid was accomplished by adding water to the resulting solid residue and after stirring at room temperature for 30 minutes, the solid was separated by filtration. To eliminate any starting aldehydes and to remove traces of water, the solid was washed with ether, providing highly pure (> 98%) products of condensation obtained in high yields.

Our reaction procedure was only applicable to aromatic and α,β–conjugated aromatic aldehydes (**Table IIa.1**). All attempts to isolate the Knoevenagel condensation product of aliphatic aldehydes, such as hexanal, and barbituric acid were unsuccessful. Following the reaction by ^{1}H-NMR spectroscopy in methanol-d_4 (CD_3OD) as a solvent, we observed the formation of 5-10% of the condensation product (**23, Figure IIa.4)**. This was done by monitoring the intensity of the olefinic (C**H**=C) proton in the spectra (typically appearing around 8 ppm). The reaction conversion ratio remained the same

after several days at room temperature. One can assume that the preparation of the aliphatic *C-5* substituted compounds could have been facilitated by using different solvents or elevated temperatures. However, the formed products were exceptionally sensitive to both high temperatures and acidic solvents, and decomposed rapidly. If the reaction was carried out for several days in a closed flask at room temperature, then traces of other products, including the Aldol condensation product **(24)** were detected by spectroscopy (**Figure IIa.4**). This was also the case when the reaction was attempted using aliphatic or aromatic ketones. For instance, when acetophenone was used as the carbonyl source we were unable to detect even a trace of the condensation product in the reaction mixture.

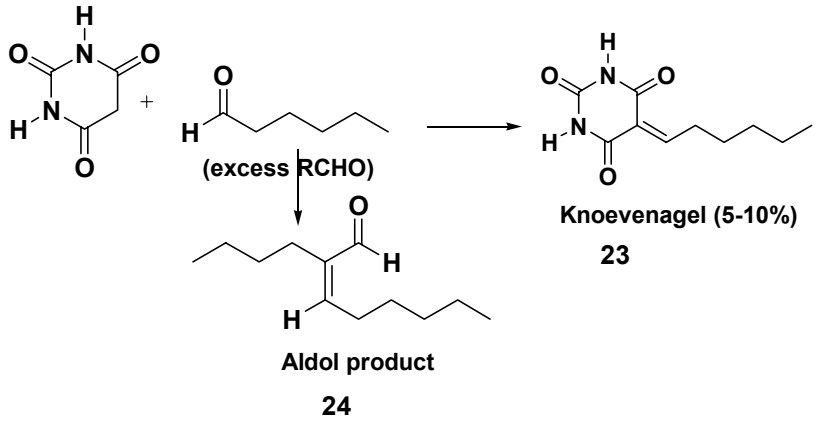


Figure IIa.4: Spectroscopically detected products in reaction between barbituric acid and aliphatic aldehydes.

Likewise, performing the reaction with aromatic aldehydes containing electron-withdrawing substituents, such as NO_2, COOH, or pyridinium moieties was unsuccessful in producing the desired Knoevenagel products of condensation. While literature reports

indicated that it would be possible to form the Knoevenagel condensation product using 5-nitro-2-furaldehyde and barbituric acid,[35] our own results suggested that the nature of the condensation product was not the single addition, but the products of double condensation, and the products obtained from these reactions will be discussed in further detail in **IIe** of this dissertation.

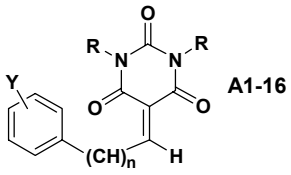


Figure IIa.5: Products of described reactions in **Table IIa.1**.

Table IIa.1: Description of Knoevenagel condensations.

Product	Y	R	n	Procedure	Yield (%)
A1	4-Me_2N	H	**0**	A	**98**
A2[#]	H	H	**2**	A	**95**
A3[#]	4-Me_2N	H	**2**	A	**99**
A4[#]	4-OH	H	**0**	A	**95**
A5*[#]	$C_5H_4O_2$	H	**0**	B	**81**
A6[#]	H	H	**0**	B	**85**
A7	3,4-$(CH)_4$	H	**0**	B	**83**
A8	2,4-OH	H	**0**	B	**85**
A9**[#]	C_9H_7NO	H	**0**	B	**96**
A10	2-OH	H	**0**	B	**80**
A11	2,4,6-OCH_3	CH_3	**0**	C	**81**
A12	2,3,4-OCH_3	CH_3	**0**	C	**79**
A13	4-OH	CH_3	**0**	C	**80**
A14	2,4-OH	CH_3	**0**	C	**79**
A15	H	CH_3	**2**	C	**81**

**2-furaldehyde used for this relation; **2-indoylaldehyde used for this reaction. Procedure A: reactions stirred at room temperature overnight. Procedure B: stirred at room temperature in closed reaction vessels over several days. Procedure C: additional acid catalyst used. # Indicate compounds synthesized by Jursic.*

IIb. Reductive C-5 alkylation and C-5 benzylation of barbituric acids

IIb.1 Preamble

The majority of barbituric acid derivatives available for pharmaceutical use consist of compounds that are *C-5* mono or *C-5* dialkylated or benzylated barbituric acids. Several examples of these include common sedatives such as veronal **(3)**, pentobarbital **(6)**, and phenobarbital **(4)**. Considering the availability and use of these compounds by the pharmaceutical industry, it seems logical that there would be a simple general procedure for the production of derivatives of such widely used compounds. Surprisingly, there is no simple synthetic procedure for preparing many derivatives of these compounds in the literature, and the methodology used to prepare mono and di-*C-5* substituted barbiturates has changed little from the century old method that uses malonic esters and urea as starting materials.[36-38]

Also noteworthy, mono *C*-alkylated and benzylated barbiturates are highly important intermediate compounds necessary for the production of assymmetrical barbiturates of pharmacological importance. Typically, chiral barbiturates can be classified in one of two categories, one in which chirality is associated with the heterocyclic ring system making *C-5* a prochiral center if R_1 is not equal to R_2 (Type I, **Figure IIb.1**), and the other in which chirality exits outside the ring system, wherein R_3 or R_4 have optical activity (Type II, **Figure IIb.1)**.

Figure IIb.1: Examples of asymmetric barbiturates

All chiral barbiturates currently marketed are in the racemic form, even though it has been classically shown that different enantiomers of chiral barbiturates exhibit different physiological effects.[39] In 2000, Trost et al. described experimental work performed toward the palladium catalyzed asymmetric allylic alkylation reaction (**AAA**) as an advancement toward the production of enantioenriched barbituric acid derivatives, a feat not yet accomplished by literature accounts. In these experiments the mono *C*-5 alkylated intermediate **(25)**, Pd_2dba_3-$CHCl_3$ and a chiral ligand **(26)** were utilized in producing several chiral barbiturates **(e.g. 27)** of pharmaceutical value obtained as enantioenriched products (**Figure IIb.2**).[39]

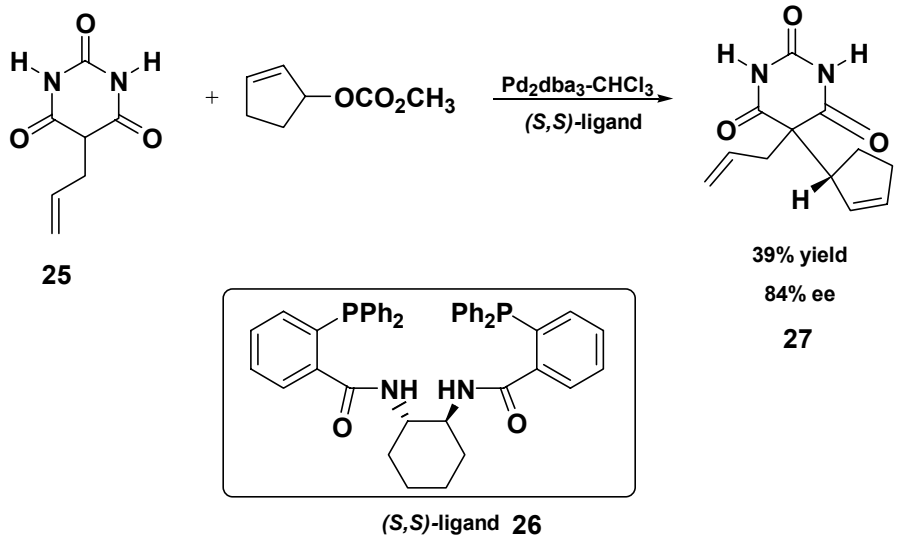


Figure IIb.2: Trost utilization of mono *C-5* alkylated barbiturates.[39]

While the isolated yields of Trost's experiments are less than desirable (39%),[39] the initial results of enantioenriched products prepared open an avenue of barbituric acid chemistry that has been under explored to date. Given these current advancements, we felt it clearly relevant explore reaction conditions necessary to develop new methodology that would enable the mono *C*-5 alkylated and benzylated products to be produced by a synthetically simple method in large scale quantities.

IIb.2 Results and Discussion

IIb.2.1 Alkylation

The preparation of both mono and di-*C*-5-alkylated barbituric acids was done using catalytic reductive alkylation procedures. While our developed procedures remain general and almost all 5-alkyl and 5,5'-dialkyl products were prepared easily, some of the analog preparations required different solvents, catalysts, and order of reactant mixing. Through our experimentation, we determined that the best catalysts for these reactions

was 5 wt% (dry basis) Pd or Pt on active carbon with the water content normally 50%. Combining the catalyst with a specific order of addition of reactants as well as monitoring solvent selection, the selective mono and di-*C*-5-alkylation and benzylation of three classes of barbituric acids were achieved, utilizing unsubstituted (barbituric acid), *N*-substituted (1-phenylbarbituric acid), and *N,N'*-disubstituted (1,3-dimethylbarbituric acid) derivatives.

Based on our previous experiments described in section **IIa** of this dissertation, we hypothesized that the first step of the reductive alkylation process between aliphatic aldehydes and ketones would be the formation of the Knoevenagel condensation product (~5% conversion), which would immediately yield upon catalytic hydrogenation of the newly formed C=C bond our desired mono *C-5* substituted barbiturate. Through experimentation, our initial hypothesis appeared correct, and we were able to perform the selective mono *C*-alkylation of barbituric acids with aliphatic aldehydes and ketones under described catalytic reductive alkylation conditions. The initial condensation reactions were catalyzed by acid, either by auto-catalysis of barbituric acid (R_1 or R_2 = H), or by the addition of an acid catalyst such as concentrated HCl (several drops to 1 mL). The reactions were carried out as one pot syntheses in either methanol or ethanol as a reaction media (**Figure IIb.3)**. In cases where the carbonyl reagent in the reaction was used in high excess as a solvent and a reactant, such as in the case of acetone, the mono *C-5* alkylated product was the only detectable product. Despite our previous experiments' indications of only a small conversion of reactants to the Knoevenagel condensation products, both aliphatic aldehydes and ketones were excellent alkylating agents. Additionally, there were no apparent structural restrictions on the aldehydes or

ketones, with the exception being that there can be no reductive hydrogenation sensitive functionalities on any reactant (**Table IIb.1)**.

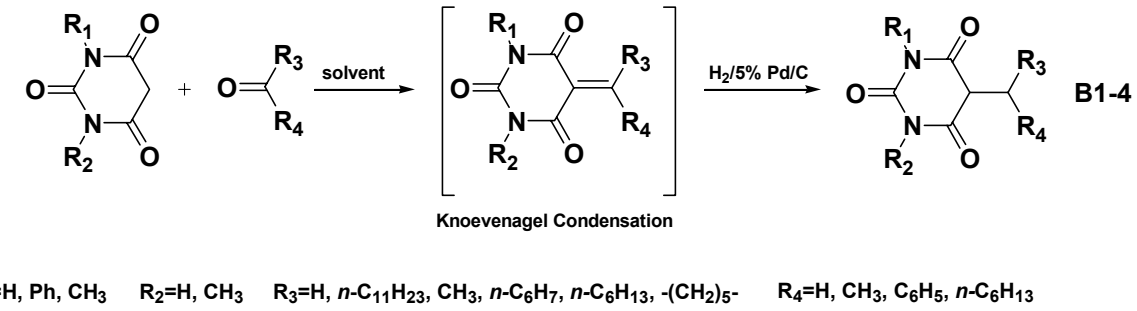


Figure IIb.3: General reaction for synthesis of mono *C-5* alkylated barbiturates.

Table IIb.1: Selected representative mono *C*-alkylated products (**General Procedure D**)

Product	R_1	R_2	R_3	R_4	Solvent	Yield (%)
B1	H	C_6H_5	CH_3	H	Acetic Acid	96
B2	CH_3	CH_3	CH_3	CH_3	Acetic Acid	97
B3	H	H	-$(CH_2)_5$-		Methanol	95
B4	H	H	*n*-C_6H_{13}	H	Methanol	97

If R_1 or R_2 of the barbituric acid was not hydrogen, then acidic conditions were required to perform the reaction. In such cases, the solvent for the reaction was acetic acid, and a few drops of sulfuric acid were sufficient to catalyze the initial condensation reaction.

IIb.2.2 Benzylation

We determined through experiment that it was not possible to utilize the one-pot synthesis for the monobenzylated products due to the fact that even when one equivalent of the aldehyde was used, we obtained the di-*C-5* benzylated product. We hypothesized that this was due to the additional stability provided by the aromatic ring to the intermediate formed *in situ,* which subsequently facilitated the second aldehyde addition. Nevertheless, the mono *C*-benzylation of barbituric acid with aromatic aldehydes seemed to be a particularly straightforward process that afforded the mono *C*-benzylated products in high yields. The first step consisted of the synthesis of the Knoevenagel condensation product between the barbiturate and corresponding aromatic aldehyde. The second step was the catalytic reduction of the condensation product using catalytic amounts of Pd/C (50% water content). Extended conjugation on the aromatic aldehydes or electron donating groups, such as methoxy and dimethylamino, substantially decreased the reaction time. For instance, the condensation reaction between 4-(dimethylamino)benzaldehyde and barbituric acid was complete in several seconds in hot methanol (60º C). The catalytic reduction of this compound was carried out in the same reaction mixture without isolation of the condensation product.

Our initial experiments determined that the conjugated double bonds of the condensation product hydrogenated first, as determined by ^{1}H-NMR of the reaction mixture after 20 minutes hydrogenation at 15 psi. However, both Pt and Pd catalysts produced total aromatic hydrogenation when the benzaldehydes used possessed an electron donating substituent, such as -OCH_3, -OH, or –$N(CH_3)_2$,. For example, while reduction of the double conjugated bond of these derivatives was complete after 2 hours

at relatively low hydrogen pressure (15 psi), stopping the reaction this time provided a reaction mixture containing both the desired reduced product **(B10)** and the corresponding product of aromatic hydrogenation (**28, Figure IIb.4**).

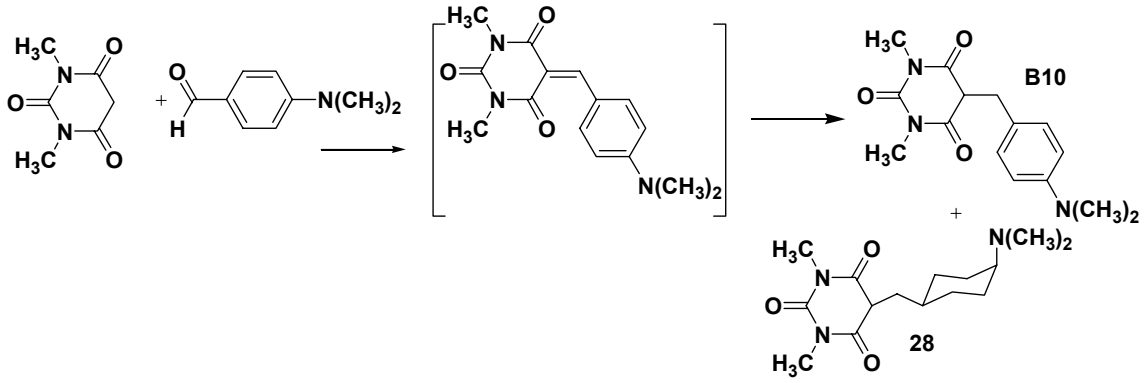


Figure IIb.4: Products of mono *C*-5 benzylation after hydrogenation

Searching the literature for ideas to overcome this problem, we came across one reference that indicated that one method utilized to eliminate the reduction of the aromatic ring of a molecule was to use benzylic alcohols as a solvent.[40] We utilized this method to avoid obtaining the mixture of products, using 4-methoxybenzyl alcohol as the reaction media. However, several of our condensation products were not sufficiently soluble in 4-methoxybenzyl alcohol, and through further experiments we determined that using benzene as a co-solvent eliminated the aromatic ring reduction upon catalytic hydrogenation, even at higher pressures. Therefore, all electron-rich aromatic aldehydes were subjected to reductive benzylation conditions using benzene as a co-solvent (**Figure IIb.5)**. In such cases the only isolated products were the mono-*C*-benzylation products (**Table IIb.2)**.

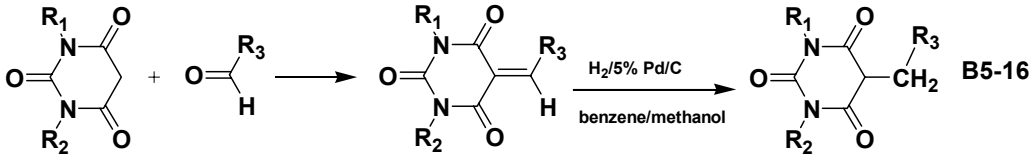
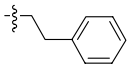
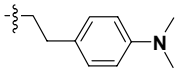
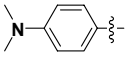
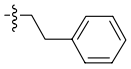
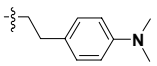
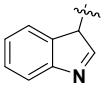
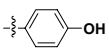
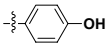


Figure IIb.5: General synthesis of mono *C*-5-benzylated products.

Table IIb.2: Representative mono *C*-5-benzylated products (**General Procedure E**)

Compound	R_1	R_2	R_3	Yield (%)
B5	**H**	**H**		**85**
B6	**H**	**H**		**90**
B7	**H**	**H**		**92**
B8	**H**	**H**		**89**
B10	**CH_3**	**CH_3**		**97**
B11	**CH_3**	**CH_3**		**91**
B12	**CH_3**	**CH_3**		**94**
B13	**CH_3**	**CH_3**		**95**
B14	**CH_3**	**CH_3**		**91**
B15	**H**	**H**		**94**
B16	**H**	**H**		**75**

IIb.2.3 *C-5* dibenzylation of barbituric acid

We experimentally determined that by using an excess of reactive aromatic or conjugated aldehydes and varying the reaction conditions slightly, it was possible to obtain the double benzylation product of barbituric acid *C*-5 benzylation in quantitative yields **(Figure IIb.6)**. In these cases, it seemed that the addition the excess of the reactive aldehydes served as an inhibitor to aromatic reduction, thereby replacing the role of benzene as a co-solvent. Isolation procedures for the *C-5* di-benzylated products were very simple, and produced the desired compounds in high yields. As determined previously, auto-catalysis by barbituric acid was a sufficient acid catalyst for the initial condensation reaction, and no additional acid was needed for the reaction to proceed. Likewise, catalytic amounts of sulfuric acid were needed to produce the Knoevenagel condensation products when *N,N'*-disubstituted barbituric acids were used as reactants.

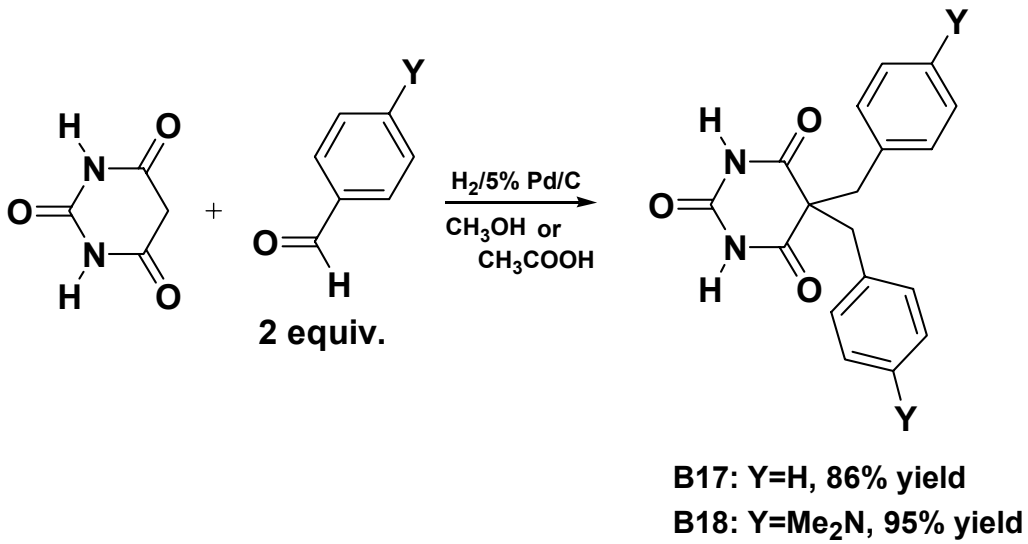
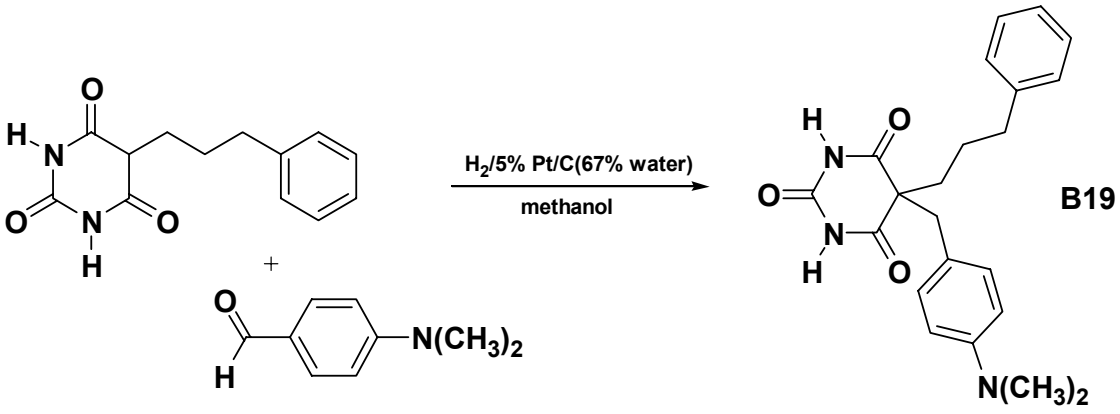


Figure IIb.6: Two representative structures of barbituric acid *C-5* dibenzylation (General Procedure F).

IIb.2.4 Unsymmetrical *C-5* alkylation of barbituric acid

Finally, we explored the possibility of producing the unsymmetrical *C-5* dibenzylation of barbituric acids. We experimentally determined that *C-5* -benzylation can also be performed on mono *C-5* alkylated or benzylated barbituric acids through reductive alkylation with aromatic aldehydes. Utilizing the products of mono *C*-alkylation, which were described above, we successfully benzylated the mono *C*-alkylated barbiturates to yield the desired unsymmetrical alkylated barbituric acid derivative (**B19, Figure IIb.7)**. When R_1 and R_2 of the barbituric acid were not equal, then the racemate was obtained. However, we were unsuccessful in producing the second alkylation when aliphatic aldehydes or ketones were used as the second alkylating agent. Therefore, in the cases where unsymmetrical double alkylation products having one C-5 substituent of aliphatic nature are necessary, aliphatic alkylation must be the first step of the reaction.



barbituric acids=barbituric acid, 1-phenylbarbituric acid, 1,3-dimethylbarbituric acid
C5-monosubstitutions=$CH(CH_3)_2$, $C_6H_5(CH_2)_3$
aromatic aldehydes=C_6H_5, *p*-$CH_3C_6H_4$, *p*-$CH_3OC_6H_4$, *p*-$(CH_3)_2NC_6H_4$, *p*-$(CH_3)_2NC_6H_4CH{=}CH$

Figure IIb.7: Representative synthesis of unsymmetrical double alkylation products. (General Procedure G).

IIc. Development of 5-cyclohexylmethyl barbituric acids-Precursors for Asymmetric Synthesis

IIc.1 Preamble

In our literature searches for the preparation of new barbituric acid derivatives, it also came as a surprise that there were no available methods for the preparation of other simple mono *C-5* substituted barbituric acid derivatives, such as 5-cyclohexylmethyl barbiturates. This came as a surprise because *C-5*-monoalkylated barbiturates could potentially be very important intermediates in the preparation of asymmetric biologically active barbituric acid derivatives. Given the fact that generally barbiturates containing lipophilic substituents tend have biological activity associated with them,[1,2] we focused our attention on the development of a model reaction to produce new types of derivatives, namely those with a cyclohexylmethyl substituent in the *C*-5 position of the barbituric acid ring.

IIc.2 Results and Discussion

Our previous research led to the synthetic procedures developed to produce not only mono *C*-alkylated products, but mono *C*-benzylated products as well, both potentially valuable precursors for asymmetric synthesis of barbiturates if the barbituric acid in itself is prochiral.[39, 41-44] However, while during the course of these studies we were able to selectively hydrogenate the activated aromatic rings of compounds such as **B10 and B14 (Table IIb.1)**, we were unsuccessful in producing the corresponding derivative with unactivated aromatics, such as benzaldehyde and naphthaldehyde.

To be able to thoroughly explore the area of asymmetric synthesis with respect to barbiturates, we reasoned that it would be pertinent to begin not only with our previously synthesized mono *C-5* alkylated products, but cyclohexylmethyl barbiturates as well. To perform our future studies, various derivatives of 5-cyclohexylmethyl barbiturates must be readily synthesized in order to utilize this potentially important moiety for later generations of new and more potent chiral barbiturates. Based on the previously discussed successful results with reductive *C*-alkylation of barbituric acids, we tailored our synthesis for the desired cyclohexylmethyl derivatives.

Electron-donating substituents increased the reactivity of the aldehydes and due to the ease of the preparation of the mono *C-5* benzylated products, one would assume that the synthesis of 5-cyclohexylmethyl derivatives would be a straightforward process under the optimal reaction conditions. We predicted that -OH and $–OCH_3$ substituted benzaldehydes would be the ideal precursors for the preparation of our targeted compounds. Our assumption was based on the fact that in either water or methanol the OH or OCH_3 substituent would be easy to remove from the cyclohexane ring after ring reduction, utilizing the reactivity of the substituent to be protonated.

Depicted in **Figure IIc.1** is our methodological development for the synthesis of *C-5* cyclohexylmethyl barbiturates. Condensation of both *para* hydroxybenzaldehyde and *para* methoxybenzaldehyde with barbituric acids in methanol requires only several minutes in refluxing methanol to produce compounds **2a**. The product precipitates from the methanol solution and the isolated yields for each of the reactions should be almost quantitative (> 90%). Reduction of these condensation products, either with 5% wt (dry

basis) Pd-C or Pt-C with 50% water content, in methanol and benzene as a co-solvent generate product **2b** with reduction of only the double bond, and not the aromatic ring.

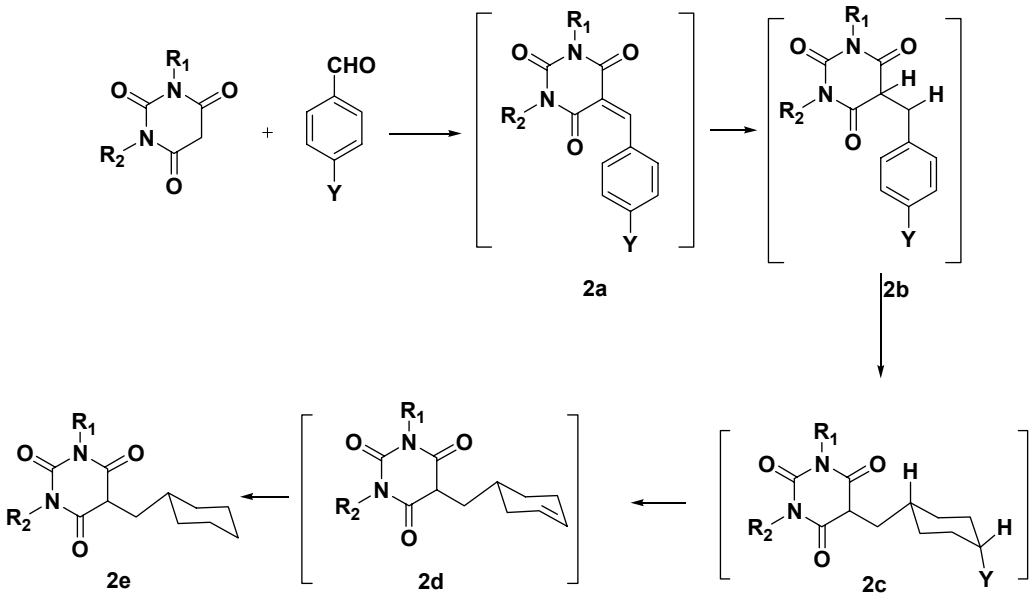


Figure IIc.1: Reaction methodology for 5-cyclohexylmethyl barbiturates.

Using this method, product **2b** can be isolated in quantitative yields. If the reduction is performed in a 0.01 M methanol suspension with PtO_2 as a catalyst at 80 psi hydrogen pressure at 70º C for several days, then the product of hydrogenation, product **2c** is generated. In our experimental studies, we were able to isolate product **2c** when both R_1 and R_2 of the barbituric acid ring were CH_3 and Y was OH. To confirm the product identity, we crystallized a small amount of **2c,** which was subjected to X-ray analysis. The ratio of the *cis* to *trans* isomer was 4:1, as determined through ^{1}H-NMR spectroscopy. From this point we hypothesized that in acidic media, compound **2c** should be transformed to compound **2d,** which would be further reduced under catalytic reduction to our targeted product, compound **2e**.

To avoid having to isolate and characterize each of these intermediates and to increase the overall isolated yield of the respective reactions producing cyclohexylmethyl derivatives of barbiturates, we thoroughly explored the possibility of performing the reactions as a one-pot synthesis. Reactions were performed in various acidic solvents, such as acetic acid, methanol-dilute sulfuric acid, methanol-trichloroacetic acid, aqueous hydrochloric acid, and methanol-hydrochloric acid. The combination of methanol-hydrochloric acid as a solvent system gave the best results, and was subsequently chosen as the media. In retrospect, the solvent system was logical, considering the low solubility of condensation product **2a** in many solvents could potentially hinder the reaction progression. The optimal solvent ratios were determined experimentally to be 1:1. While the methanol-HCl solvent mixture was determined to be the optimal media for performing this reaction, it should also be noted that in several other solvent mixtures, some amount of the desired product **2e** could be detected in the reaction mixture if 5% Pd-C with 50% water was used. Limited reactant conversion and subsequent product isolation hampered the outcome of the reaction in these cases. Our best results were obtained when 5% Pt-C 50% water with methanol-HCl (1:1) were used as a catalyst and reaction media (**Figure IIc.2)**, in which case the product of the reaction was obtained almost quantitatively in a one-pot synthesis **(Table IIc.1)**.

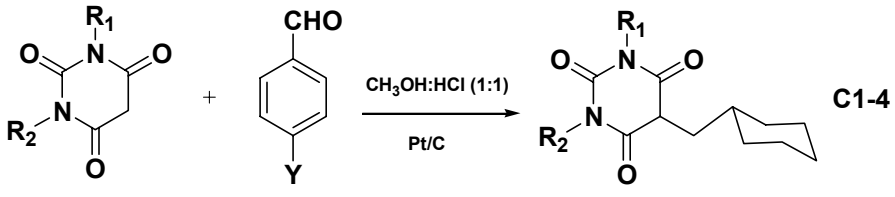


Figure IIc.2: One pot synthesis of 5-cyclohexylmethyl barbiturates.

Table IIc.1: Aromatic hydrogenation of selected barbituric acid benzylidenes.

Product	**R_1**	**R_2**	**Y**	Yield (%)
C1	H	H	OCH_3	**89**
C2	H	CH_3	OH	**84**
C3	H	C_6H_5	OCH_3	**93**
C4	CH_3	CH_3	OH	**88**

To fully confirm the structure of our compounds, one compound **C4** was the subject of X-ray structural analysis. The monoclinic $P2_{1/c}$ crystals were grown from a methanol solution by allowing methanol to slowly evaporate at room temperature. The X-ray determined structure of 5-(cyclohexylmethyl)-1,3-dimethylbarbiturate is presented in **Figure IIc.3**. Both amide nitrogens of the barbituric acid ring are blocked with methyl groups, therefore the strong hydrogen bonding generally present in crystalline barbituric acid derivates cannot be observed in this instance. The barbituric acid ring is almost planar, and almost perpendicular to the cyclohexane ring, which is in the chair conformation.

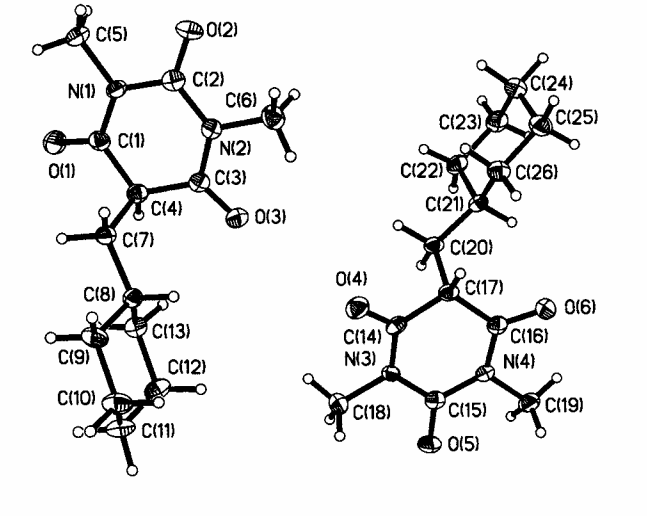


Figure IIc.3: Ortep drawing of compound **C4 (***courtesy of Prof.s E. D. Stevens and K. L. Martin*)**.**

IId. Preparation of 5-Formyl and 5-Acetyl Barbiturates and Corresponding Schiff Base Products

IId.1 Preamble

Many new drugs can be envisioned using the small 5-formyl or 5-acetyl barbiturates as a primary building block. Synthetic procedures for the preparation of 5-acetylbarbiturates with acyl groups containing phenyl as well as long alkyl groups are well documented in literature.[45-46] Direct pharmaceutical and other industrial applications for the uses of these derivatives have also been documented in the literature, and while the applications exist,[46-47] unfortunately, there are no good synthetic procedures for the preparation of simple acylbarbiturates, such as formyl and acetyl barbiturates.

There are several very efficient ways of introducing the formyl group to organic molecules.[48-49] The general methods for the introduction of a masked formyl group can be divided into three classes, according to the nature of the reactant (**C, -C, or +C**). The first group, **C**, belong to the Inanaga SmI_2-induced masked formylation of carbonyl compounds.[50] This reaction has a limited synthetic scope because strong oxidants or SmI_2 must be used **(Figure IId.1)**.

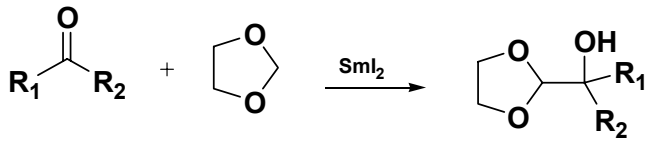


Figure IId.1: Inanaga method for introduction of a masked formyl group.[50]

On the other hand, using a masked nucleophile **(-C)** to introduce the formyl group is probably the most widely developed method today **(see 31, Figure IId.2)**, but not applicable to our system due to the fact that the C-5 of barbituric acid is a (**-C**) nucleophile.[51-54]

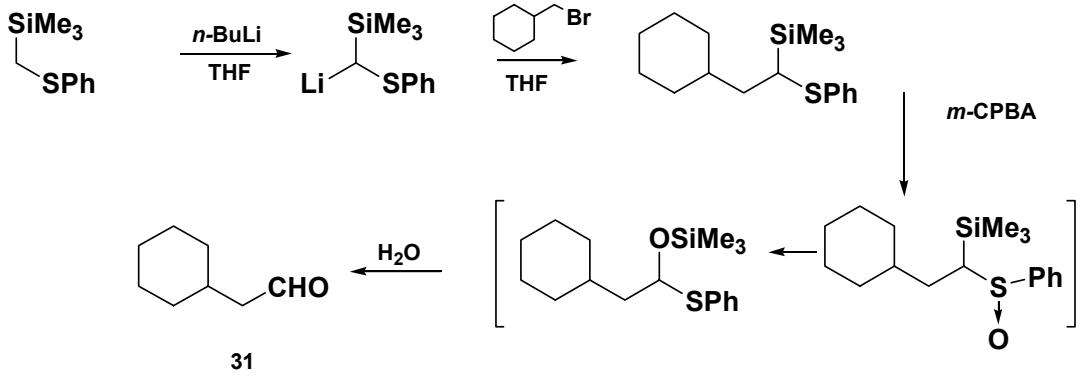


Figure IId.2: Example of (**–C**) masked nucleophile to introduce formyl group.[54]

Other classical examples of the formylation include using cation (**+C**) equivalents in reactions of alkyl orthoformates with organometallics.[55-57] Direct formylation of organic compounds is also well established in organic chemistry. The Vilsmeier or Vilsmeier-Haack reaction is the most common method for the direct formylation of reactive aromatic rings, such as anilines or phenols **(Figure IId.3).**[58-60]

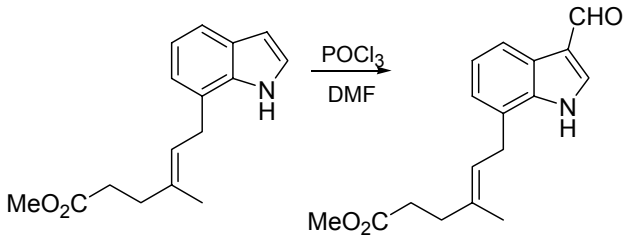


Figure IId.3: Example of direct formylation *via* Vilsmeier-Haack reaction.[60b]

Another direct formylation that can be applied to phenols and certain heterocyclic compounds, such as pyrroles and indoles, is the Reimer-Tiemann reaction.[61-63] This reaction is performed in basic solution and the yields are generally low, seldom overcoming 50%.[64] This methodology was employed previously by Panteleimonov and Madrik in their preparation of 5-formylbarbituric acid in 30% yield.[65]

IId.2 Results and Discussion

By modifying the Reimer-Tiemann reaction procedure, we simplified the reaction procedure and obtained a higher purity and higher yield of 5-formylbarbiturates **(Figure IId.4)**. By following the course of the reaction through ^{1}H-NMR spectroscopy, it was apparent that 80% of the barbituric acid was converted to the corresponding formyl compound. Unfortunately, the solubility of barbituric acid and 5-formylbarbituric acid in both water and methanol are very similar, and a large quantity of product was lost during the purification process. When phenyl or methyl substituted barbituric acids were used

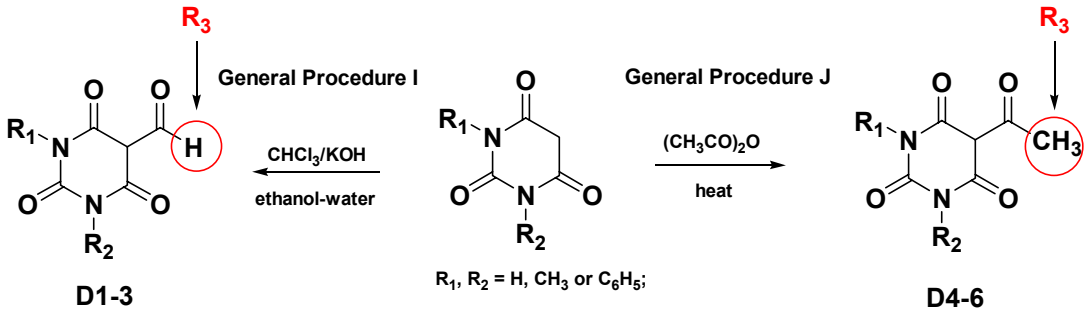


Figure IId.4: Synthesis of 5-formyl and 5-acetyl barbiturates (General procedures I and J).

the isolated yields obtained were much higher (**Table IId.1**). To our surprise we were unable to find in the literature a reliable procedure for the preparation of 5-acetylbarbiturates as well, although the preparation of some *N*-substituted 5-acetlybarbiturates is known.[66] If 5-acetylbarbiturates are to be used as precursors in the preparation of valuable pharmaceuticals, they should be inexpensive and available in high yields. To meet these requirements, a simple, preferably one-pot synthesis should be prepared using readily available starting materials. Our resulting developed procedure adheres to these requirements, utilizing acetic anhydride as a reagent for introducing the acetyl substitution in the 5-position of barbituric acids **(Table IId.1)**.

Table IId.1: 5-Formyl and 5-acetyl barbiturates.

Product	R_1	R_2	R_3	Yield (%)
D1	CH_3	CH_3	H	**75**
D2	H	H	H	**45**
D3	C_6H_5	H	H	**67**
D4	H	H	CH_3	**95**
D5	C_6H_5	H	CH_3	**65**
D6	CH_3	CH_3	CH_3	**92**

IId.3 Preparations of ω-aminoalkanoic acid Schiff Base Products

Schiff-base products of 5-formyl and 5-acetylbarbituric acids have been reported as showing some interesting biological properties, therefore, the need for the preparation of these compounds in larger quantities using simple and effective synthetic procedures

was evident.[67-70] Based on our previous experience, we felt especially valuable biologically active compounds could come as a result of a Schiff base reaction between formylated or acetylated barbituric acids and ω-aminoalkanoic acids. Based on previously performed structure-activity relationship studies with already known histone deacetylase inhibitors as anticancer compounds, such as **PCHA (17)** and **SAHA (19)**, we hypothesized that our Schiff base products of barbituric acid derivatives and ω-aminoalkanoic acids , designed to structurally resemble these inhibitors, might also be active anticancer compounds **(Figure IId.5)**.[71-73]

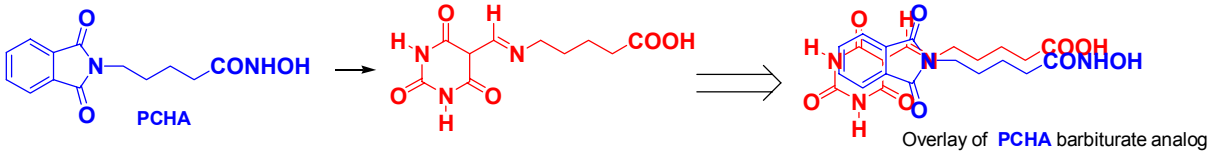


Figure IId.5: Formyl barbiturates designed as potential histone deacetylase inhibitors.

Our ensuing procedure used to develop these potentially valuable compounds involved the one-pot synthesis of the condensation of the two reactants (barbiturate and ω-aminoalkanoic acid) in methanol **(Figure IId.6)**. The products had physical properties that easily set them apart from both starting materials, as well as made them an easy

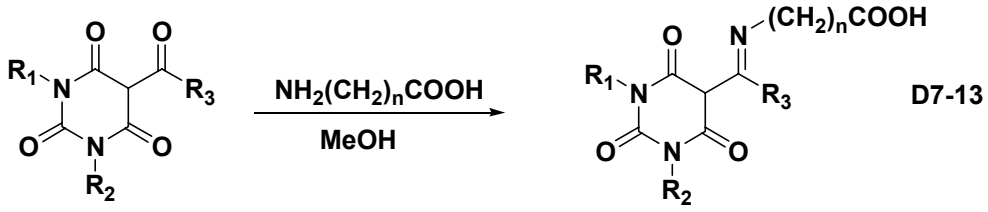


Figure IId.6: Synthesis of ω-aminoalkanoic acid Schiff bases (General Procedure K).

subject of biological evaluation, being highly water soluble, and having similar structures as zwitterionic amino acids. Furthermore, considering the nature of the physical properties of the products, our isolated yields were very high **(Table IId.2)**.

Table IId.2: ω-aminoalkanoic acid and barbituric acid Schiff base products.

Product	**R_1**	**R_2**	**R_3**	**n**	Yield (%)
D7	**CH_3**	**CH_3**	**H**	**5**	90
D8	**H**	**H**	**H**	**3**	95
D9	**H**	**H**	**H**	**5**	91
D10	**C_6H_5**	**H**	**H**	**3**	80
D11	**H**	**H**	**CH_3**	**3**	89
D12	**H**	**H**	**CH_3**	**5**	87
D13	**H**	**H**	**CH_3**	**2**	90

IId.3.1 Physical properties of Schiff base products with ω-aminoalkanoic acid

The positions of the double bonds in the Schiff base product strongly varied with the nature of the solvent and temperature applied. It is commonly interpreted that Schiff bases are compounds that have a carbon-nitrogen double bond,[74] which can move throughout the molecule to produce the more thermally stable isomer. This double bond isomerization occurs *via* either proton exchange in solvent, or proton exchange with another molecule of the Schiff base product. Our barbituric acid Schiff bases were perfect examples of this type of equilibrium. The equilibrium was temperature sensitive and the two isomers, one containing a **C-N** double bond, and the other containing a **C-C**

double bond had substantially different proton ^{1}H-NMR chemical shifts, as demonstrated in the ^{1}H-NMR spectrum of **D13 (Figure IId.7)**. **D13** was highly soluble in water and dimethyl sulfoxide (DMSO), but only slightly soluble in methanol. At room temperature, more than 90% of compound **D13** had a **C-C** double bond **(Figure IId.7 A)**. This structural assignment was based on the chemical shift for β-alanine as a standard in DMSO-d_6. β-alanine is slightly soluble in DMSO, and all hydrogens on the nitrogens are exchanged with deuterium from the solvent, therefore two triplets, one at 2.789 ppm (J= 4.5 Hz) for –N**CH_2**- of β-alanine and the other at 2.060 ppm (J= 4.5 Hz) for –C**H_2**CO- of β-alanine were observed. With the assumption that the chemical shift for –N**CH_2**- of **D13** in the **C-C** double bond isomer is similar to the chemical shift of our standard, β-alanine, we assigned the 2.973 ppm peak to the –N**CH_2**- of the **D13 C-C** double bond isomer **(Figure IId.7 A)**. The chemical shifts at 3.632 and 3.616 ppm were assigned to –NHC**H_2** in the **D13 C-N** double bond isomer **(Figure IId.7 A)**. By refluxing a methanol-water solution for 5 minutes, the ratio of the isomers does not change to a discernable degree, as determined by ^{1}H-NMR spectroscopy.

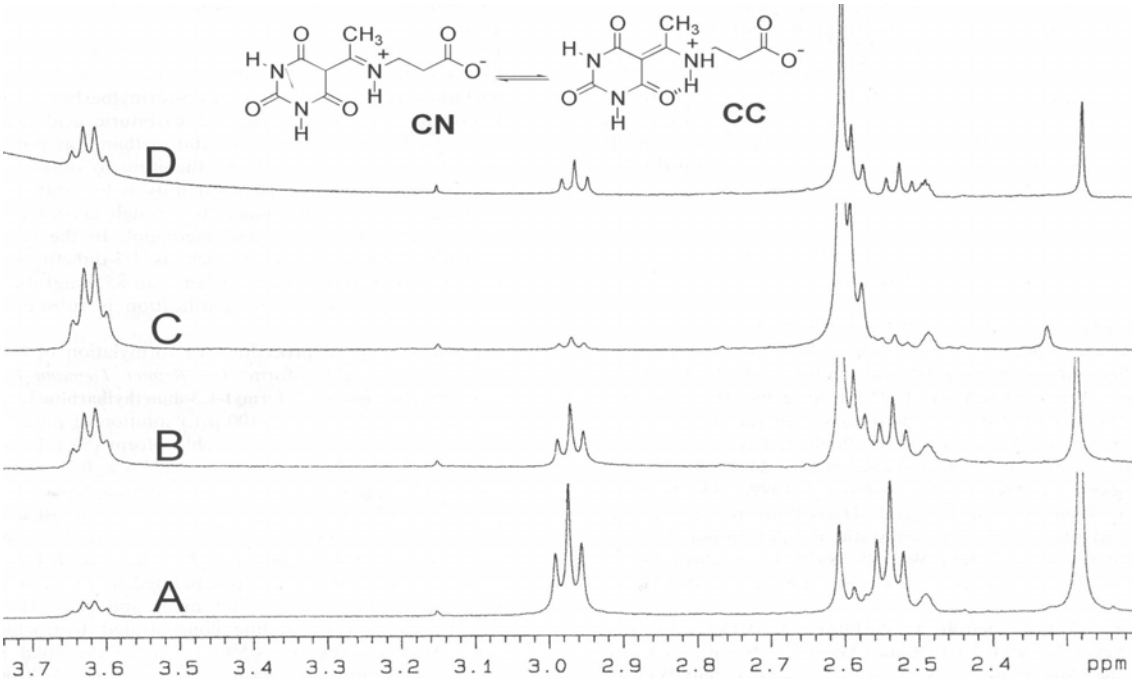


Figure IId.7: Spectroscopic following by ^{1}H-NMR (DMSO-d_6) of the change in the ratios of the two structural isomers of **D13.** (A) two isomers isolated from the methanol reaction mixture; (B) ratio of isomers after heating DMSO-d_6 solution for 1 min; (C) 3 min heating; (D) 5 min heating then standing at room temperature for 8 h.

It seemed obvious that due to the low boiling point of each of these solvents, the temperature necessary to induce the isomerization of **D13** could not be reached using methanol and water. On the other hand, DMSO has a boiling point of 189º C, and its heat capacity is much higher than that of methanol and water, thus a higher temperature can be reached in this refluxing solvent. By heating the DMSO solution and allowing the solvent to reflux for one minute, the amount of the **C=N** isomer in solution increased from 18% to 61% **(Figure IId.7 B)**. With prolonged heating the **C=N** isomer ratio increased to 89% **(Figure IId.7, C)**, and after 5 minutes, the **C=N** isomer was practically the only observed isomer spectroscopically. Upon standing at room temperature for

several hours, the **C=C** isomer begins to re-establish, however not to the ratio previously observed in spectrum **A (Figure IId.7 D)**. From this study, it can be stated that the **C=C** isomer is probably the kinetic product of the reaction, while the **C=N** isomer is probably the thermodynamically favored product. When the Schiff base product **D13** was purified by crystallization, only the **C=C** isomer was present in the isolated material.

IId.4 Preparations of Phenylhydrazones of 5-Formyl and 5-Acetyl barbiturates

It was demonstrated that simple nitrophenylhydrazones of 4-hydroxybenzophenone have strong anticancer properties.[75] With respect to the binding capabilities to biomolecules, the barbituric acid moiety should be superior to phenols, due to the larger number of hydrogen bonds that can be formed during non-bonding interactions. Because of this rationale, we felt it of interest to develop the phenylhydrazones of the simple 5-formyl and 5-acetyl barbiturates previously described with the intent to do biological evaluation of these derivatives. Several methods for this synthesis were explored. The simplest and most effective methods were the direct condensation of the corresponding phenylhydrazine with the 5-formyl or 5-acetyl barbiturates in methanol at elevated temperatures **(Figure IId.8)**.

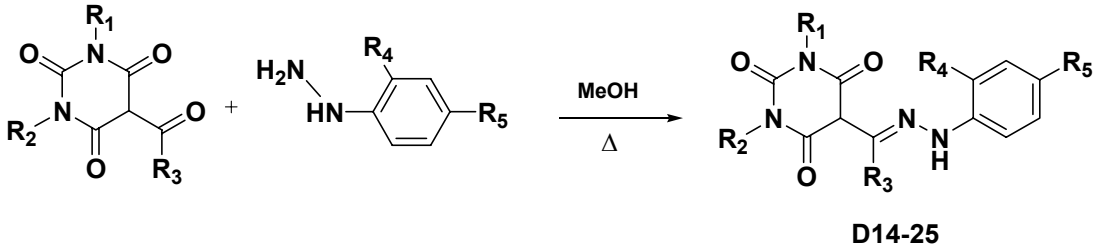


Figure IId.8: Synthesis of traditional Schiff bases of phenylhydrazines and barbituric acids (General Reaction L).

After the reaction was completed, the isolation of the product was dependent on the physical properties of the compound; however the products generally tended to be only slightly soluble in reduced volumes of methanol. The optimized isolated yields of several derivatives are presented in **Table IId.3**.

Table IId.3: Schiff base products of phenylhydrazines and barbiturates.

Product	R_1	R_2	R_3	R_4	R_5	Yield (%)
D14	H	H	H	H	NO_2	80
D15	H	H	H	NO_2	NO_2	88
D16	Ph	H	H	H	NO_2	92
D17	Ph	H	H	H	COOH	93
D18	CH_3	CH_3	H	H	NO_2	95
D19	CH_3	CH_3	H	H	COOH	91
D20	H	H	CH_3	H	NO_2	73
D21	H	H	CH_3	NO_2	NO_2	86
D22	Ph	H	CH_3	H	NO_2	84
D23	Ph	H	CH_3	NO_2	NO_2	81
D24	CH_3	CH_3	CH_3	H	NO_2	63
D25	CH_3	CH_3	CH_3	NO_2	NO_2	84

IIe. Aromatic-dibarbiturates- Pyridine and Quinoline Derivatives

IIe.1 Preamble

There are some molecular systems that are capable of modulating immune responses, effectively opening an avenue for new and innovative treatments that combat terrible diseases such as AIDS and cancer.[76-78] Until recently, barbiturates were mostly used as sedative and anesthetic drugs.[79-81] However, there are a few recent literature reports that suggest that some aromatic-dibarbiturates may also possess modulating activity, and initiate the human immune response.[82-83] One could argue that the reason that aromatic dibarbiturates have not yet been thoroughly explored is due to the lack of availability of these derivatives. Additionally, even in the few cases reported, once the derivatives were prepared, the low water solubility of these synthetic compounds hampered further the biological evaluation of their immune modulating activities. One can propose that both of these problems can be eliminated if the aromatic moieties of the dibarbiturates are substituted with either a pyridine or quinoline moiety, thereby providing aromatic heterocycles that are more water soluble than corresponding benzene or naphthalene derivatives. Unfortunately, procedures for the preparation of aromatic and heterocyclic dibarbiturates were not available at the time of our initial literature searches, indicating that we would need to devise our own synthetic design to produce these analogs in sufficient quantities for future testing.

IIe.2 Results and Discussion

We hypothesized that the ideal starting materials for the preparation of these types of barbiturate analogs would be aromatic and heteroaromatic aldehydes and nitrogen substituted barbituric acids (**Figure IIe.1**). In general, barbituric acid condenses

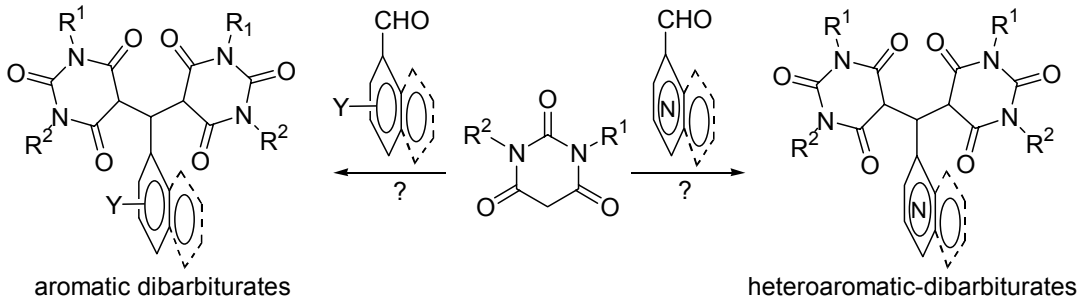


Figure IIe.1: Possible starting materials for the preparation of heterocyclic dibarbiturates.

with aromatic aldehydes to form Knoevenagel condensation products.[84] However, the outcome of these types of condensations is not always the simple arylidenebarbiturate. Some very interesting condensation products can be formed by simply varying either the nature of the aldehydes or the position of the heterocyclic atom of the aldehyde. In general, the nature of the condensation product is determined by the 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 (**Figure IIe.2**), which will be discussed at length in subsequent chapters of this manuscript. When barbituric acid is used instead of 1,3-dimethylbarbituric acid the reaction outcome is different. For example, in trifluoroacetic acid (TFA) the condensation product between

2-pyridinecarboxaldehyde and barbituric acid is 2-pyridinemethylenedibarbiturate **i** rather than the corresponding dipyridine-dibarbituric acid ylide **ii** (**Figure IIe.2**). This is not true for all reaction conditions. Even with barbituric acid as a starting material (R=H) the reaction conditions can be optimized in such way that ylide **ii** (R=H) becomes the major product of the condensation. This finding suggests that through careful exploration of the reaction conditions, a variety of aromatic-dibarbiturates can be prepared from the same starting materials, and specific reaction conditions required to produce the desired bis barbiturate must be thoroughly explored.

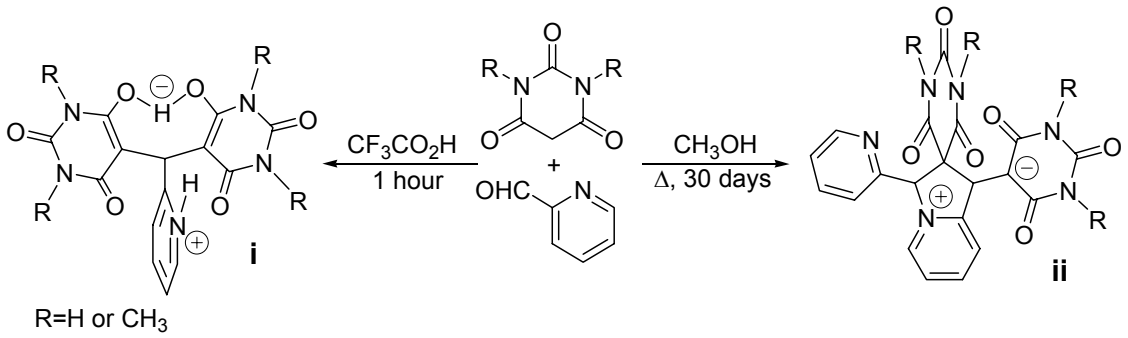


Figure IIe.2: Two different products of barbituric acid (R=H) and 1,3-dimethylbarbituric acid (R=CH_3) condensation with 2-pyridinecarbaldehyde.

Therefore, we outlined and performed a systematic study of aromatic and heteroaromatic aldehydes in condensation with barbituric acids, with the target being to prepare both aromatic and heteroaromatic-dibarbiturates. The fact that the major product of the Knoevenagel condensation between aromatic aldehydes and barbituric acid is the 5-arylidenebarbituric acid was perfectly demonstrated in our ^{1}H-NMR spectra, recorded throughout the course of the reaction of the condensation between 1-naphthaldehyde and

barbituric acid (**Figure IIe.3**). Regardless of the nature of the reaction media (neutral, acidic, or basic) only one product of the reaction was detected and isolated, and that product was 5-naphthalen-1-ylmethylenebarbituric acid (**A7)**. This reaction could be performed 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, each giving the respective Knoevenagel condensation product. In acidic solvents, such as trifluoroacetic acid, the reaction was practically over in two hours at room temperature. Even when the reaction was conducted using a ten-fold molar excess of barbituric acid and higher temperatures (~70-120º C) overnight, we were not able to obtain the double barbituric acid addition product with 1-naphthaldehyde. Furthermore, the same reaction outcome was obtained when the reaction was carried out with benzaldehyde instead of naphthaldehyde, indicating that the nature of the formation of the bis-barbiturate required some other stabilization, not found in the unsubstituted aromatic aldehydes.

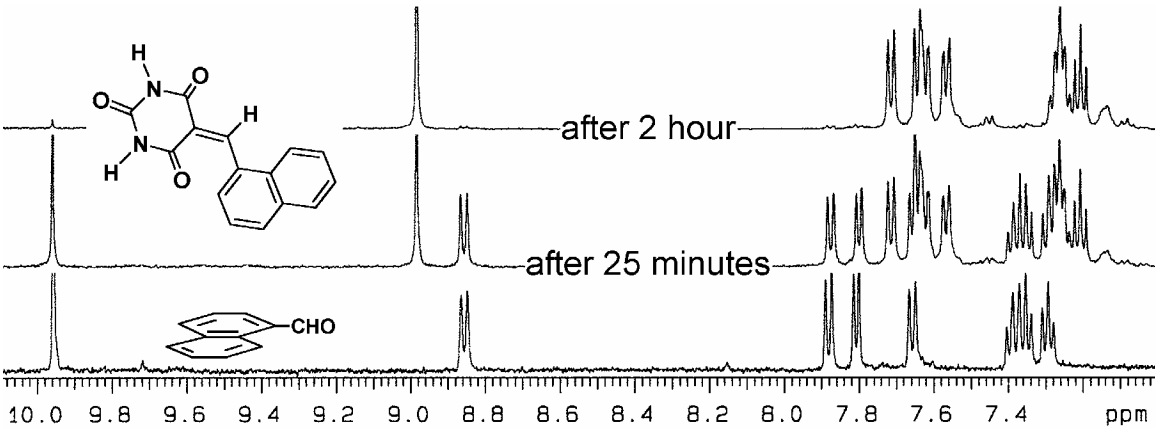


Figure IIe.3: ^{1}H-NMR (500 MHz) reaction following for 1-naphthaldehyde (1 mM) condensation with barbituric acid (5 mM) in CF_3COOH to produce **A7**.

Through the course of our experiments, we were also able to demonstrate the influence of both the solvent and the nature of the substituents attached to benzaldehyde on the outcome of the condensation reaction. For instance, in our previous studies, outlined in Chapter **IIa**, we demonstrated that benzaldehydes with electron donating substituents, such as the dimethylamino or hydroxyl groups, form the Knoevenagel condensation product easily. The reaction was completed and the product isolated as quickly as one hour after refluxing in methanol, or several hours stirring at room temperature. The same product can be detected if the condensation reaction is performed in dimethyl sulfoxide as a reaction media, therefore, we chose to use dimethyl sulfoxide as the reaction media for our ^{1}H-NMR spectroscopic studies of the reaction progression for several reasons. In both methanol and DMSO, the initial reaction mixture is a solution, but when methanol is used as a reaction media the condensation product precipitates from the reaction mixture. Due to this precipitation, we were unable to determine through ^{1}H-NMR the existence of any product in solution. In DMSO the Knoevenagel condensation reaction was completed after fourteen hours at room temperature (**Figure IIe.4**). In our ^{1}H-NMR spectra following the reaction, we could not detect traces of the double barbituric acid addition product **E1**. One can argue that this is due to the fact that the addition of the second barbituric acid to the condensation product **A1** 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, and[85] to be able to perform this reaction it would be necessary to utilize a strong nucleophile. Consequently, the second addition of barbituric acid could only be accomplished with the

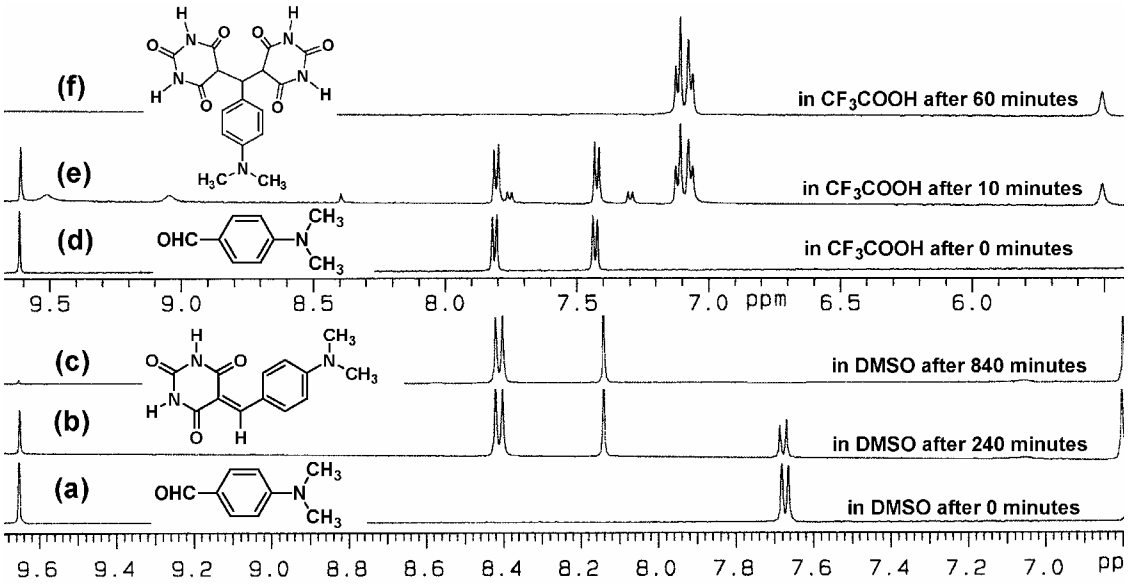


Figure IIe.4: The ^{1}H-NMR (500 MHz) reaction following of 4-dimethylaminobenzaldehyde condensation with barbituric acid in DMSO (a, b, and c) to yield **A1** and CF_3COOH (d, e, and f) to yield **E1**.

enol form of barbituric acid. In such a case, we hypothesized that strong acidic media would be the required reaction media in order to perform the double addition reaction with barbituric acid acting as a nucleophile.

Through our ^{1}H-NMR spectroscopic monitoring of the reaction progression using acidic media, such as D_2O-HCl, CH_3CO_2H, H_2SO_4, CF_3CO_2H, CF_3SO_3H, and H_2SO_4, we noted that we obtained the best results for the formation of the double addition products using CF_3CO_2H as our strong acid. The reaction was practically complete in one hour, and the formation of the Knoevenagel condensation product **A1** was observed spectroscopically (**Figure IIe.4-spectrum e**) during the course of the reaction. This intermediate was a very good α,β-unsaturated carbonyl compound that facilitated the second barbituric acid addition in CF_3CO_2H, which resulted in the dibarbituric acid

adduct **E1** (**Figure IIe.4 spectra e and f**). We were able to fully convert 4-dimethylaminobenzaldehyde into the double barbituric acid adduct **E1**. At this point, and based on our experimental evidence, one argument could be made. In order for the double barbituric acid addition to aromatic aldehydes to occur, a strong electron-withdrawing group attached to the aldehyde's aromatic ring is required. This argument can be validated examining the following facts. In DMSO-d_6 as a reaction media the electron-donating $(CH_3)_2N$ group attached to the aromatic ring is not protonated, therefore only the Knoevenagel condensation product **A1** is detected and isolated. However, in CF_3CO_2H media (pK_a=0.0) the dimethylamino group is protonated, $(CH_3)_2HN^+$, and the substituent becomes electron-withdrawing. The pK_a of anilines (10-12) is considerably higher than the pK_a of trifluoroacetic acid, therefore the aniline should be protonated in TFA. On the other hand, the pK_a for protonated phenols and anisoles is between -6 and -8, and in TFA would exist primarily in the OH and OCH_3 forms.[86]

The ^{1}H-NMR barbituric acid condensation with both 4-methoxy and 4-hydroxybenzaldehyde (**Figure IIe.5**) in trifluoroacetic acid further validates this argument. 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, H_2O-HCl, H_2SO_4, CH_3CO_2H, CF_3CO_2H).[86] This is clearly demonstrated in the ^{1}H-NMR reaction following experiment for the 4-hydroxybenzaldehyde condensation with barbituric acid in trifluoroacetic acid. Only the

condensation product **A4** was detected in the NMR spectra of the reaction mixture (**Figure IIe.5**).

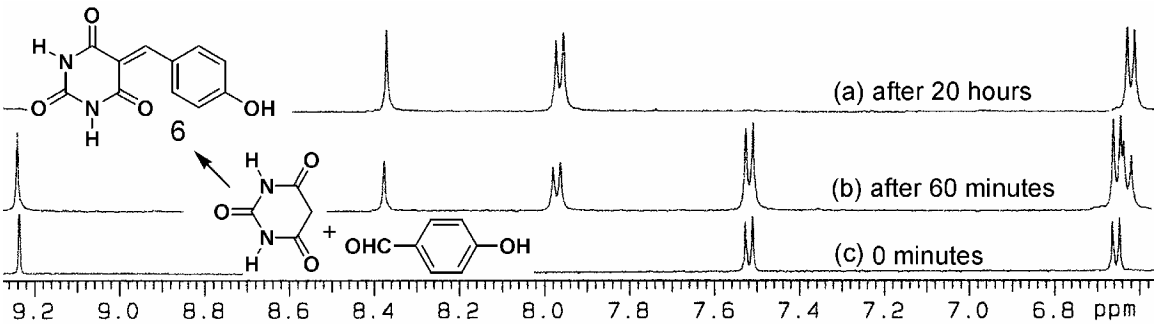


Figure IIe.5: ^{1}H-NMR reaction following of 4-hydroxybenzaldehyde condensation with barbituric acid in CF_3CO_2H yielding **A4**.

We hypothesized that if it was in fact 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 hypothesis was confirmed, and was demonstrated by the H-NMR spectroscopic study following the progression of the reaction for the barbituric acid addition to benzaldehyde in both dimethyl sulfoxide and trifluoroacetic acid as reaction media (**Figure IIe.6**). The same double addition product **E2** was obtained regardless of the nature of the solvent, the difference being only the time required for the reaction completion. For example, the reaction was completed in 40 minutes in trifluoroacetic acid media and in 24 hours in dimethyl sulfoxide media, both at room temperature.

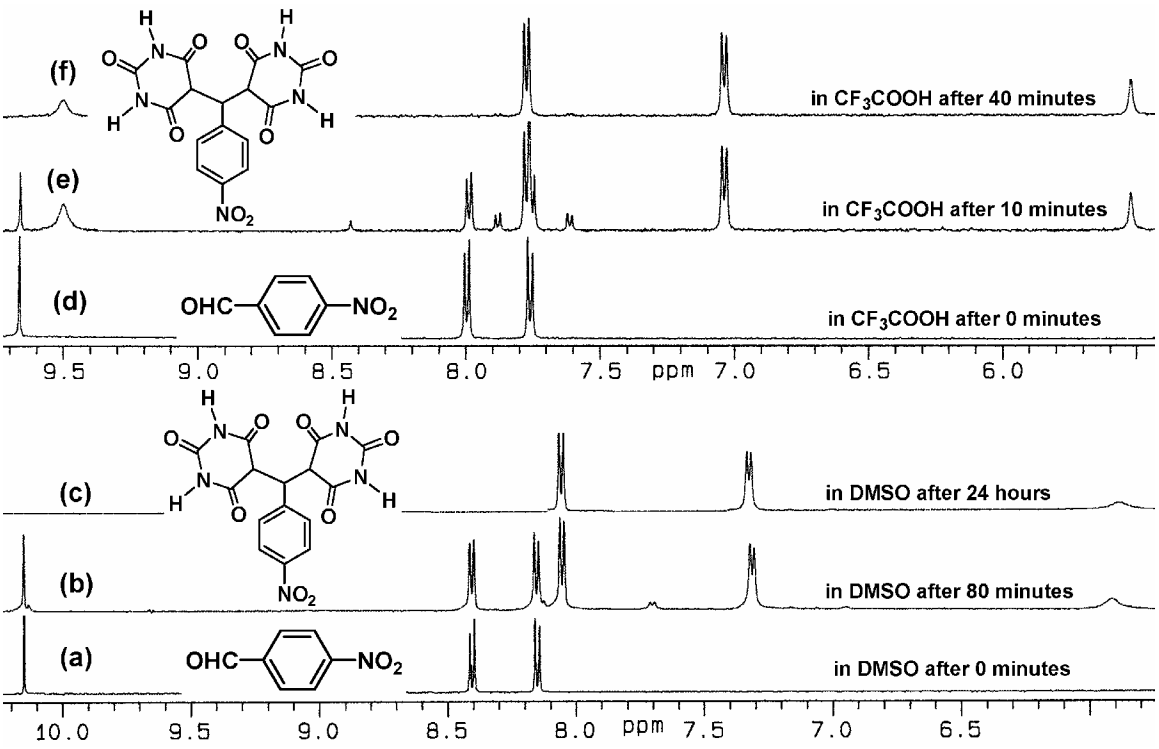


Figure IIe.6: ^{1}H-NMR reaction following in DMSO-d_6-300 MHz Varian Unity and CF_3COOH with electron-deficient aromatic aldehydes to yield **E2**.

Regarding reactivity, nitrogen heterocycles are similar to corresponding nitroaromates.[87] Heterocyclic compounds similar to substituted benzenes have preferences for nucleophilic and electrophilic reactions. In the case of pyridine[87] it is not the free base that is involved in the electrophilic reaction, rather the conjugate acid of pyridine. This is also true if a neutral nucleophile such as barbituric acid, malonic ester, phenylacetonitrile, etc. is added to the heterocyclic carboxaldehyde *N*-oxide.[88]

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 should be relatively short. This was completely

demonstrated in the H-NMR spectra following the reaction between barbituric acid and 4-quinolinecarboxaldehyde **E3** (**Figure IIe.7**). The reaction was complete after one hour at room temperature. It appeared that the second addition of barbituric acid to the Knoevenagel intermediate was a faster reaction than the first addition of barbituric acid to 4-quinolinecarboxaldehyde, we were not able to detect even a trace of the condensation intermediate by NMR spectroscopy.

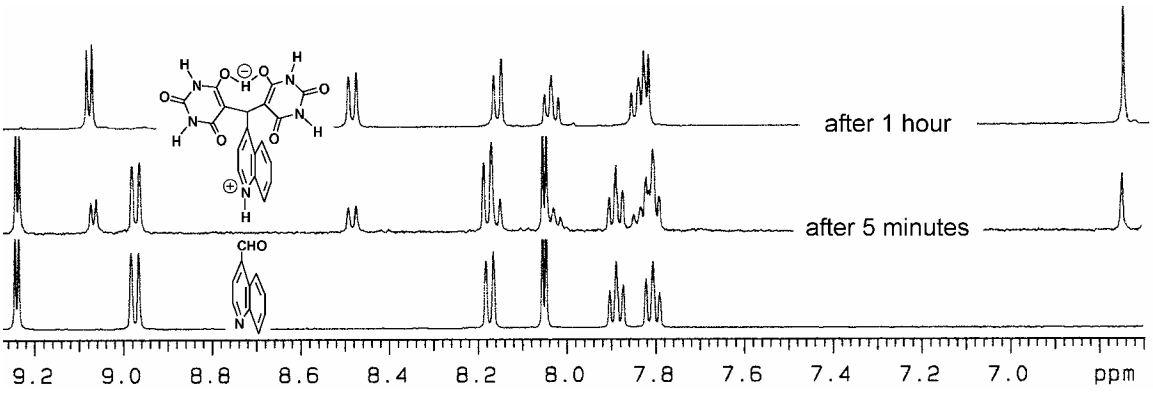


Figure IIe.7: The ^{1}H-NMR (DMSO-d_6 -300 MHz Varian Unity, 500 MHz) reaction following for 4-quinolinecarboxaldehyde condensation with barbituric acid to yield **E3**.

Given the previously described results, it is also logical to assume that larger barbituric acid adducts can be formed if two or more heterocyclic carboxaldehydes are covalently bound together. With respect to biological activity, we had a curiosity to prepare these compounds in order to determine whether the doubles of the structural moieties necessary for activity would have additive effects on the biological activity. Synthetically, this could be a daunting task because increasing the size and the number of the heterocycles makes the new target molecule harder to handle with respect to the formation of various reaction intermediates, their solubility in the course of the reaction, and the solubility of the final compound. These problems are perfectly demonstrated on

the example for the tetra barbituric acid addition to the dipyridinedicarboxaldehyde (**Figure IIe.8**). Although the reaction can occur in any given solvent that can dissolve both barbituric acid and dipyridinedicarboxaldehyde, the solubility of various reaction intermediates as well as tetra-adduct **E4** limits us to using only 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 **E4**, **Figure IIe.8**). 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 IIe.9**) two new aldehyde hydrogen signals around 9.9 ppm and a signal for α-C**H**OH at 6.7 ppm (besides the signals for the starting aldehyde **DPDA)** indicate the formation of **iii**. Signals at 10.15 ppm and 8.2 ppm are assigned to the aldehyde and the vinyl hydrogen of intermediate **iv and v,** respectively. A small singlet at 8.25 ppm belongs to intermediate **vi**, and the singlet at 6.08 ppm belongs to the α-$CH(Ba)_2$ of intermediate **vii,** while the singlet at 6.15 ppm belongs to the same hydrogen (α-$CH(Ba)_2$) of the tetra-adduct **E4** (**Figures IIe.8 and IIe.9**). 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 **iii** and **v** than both the barbituric acid additions. Further spectroscopic study of the mechanism of the tetra-addition of barbituric acid is currently underway using positive electro spray studies and NMR studies.

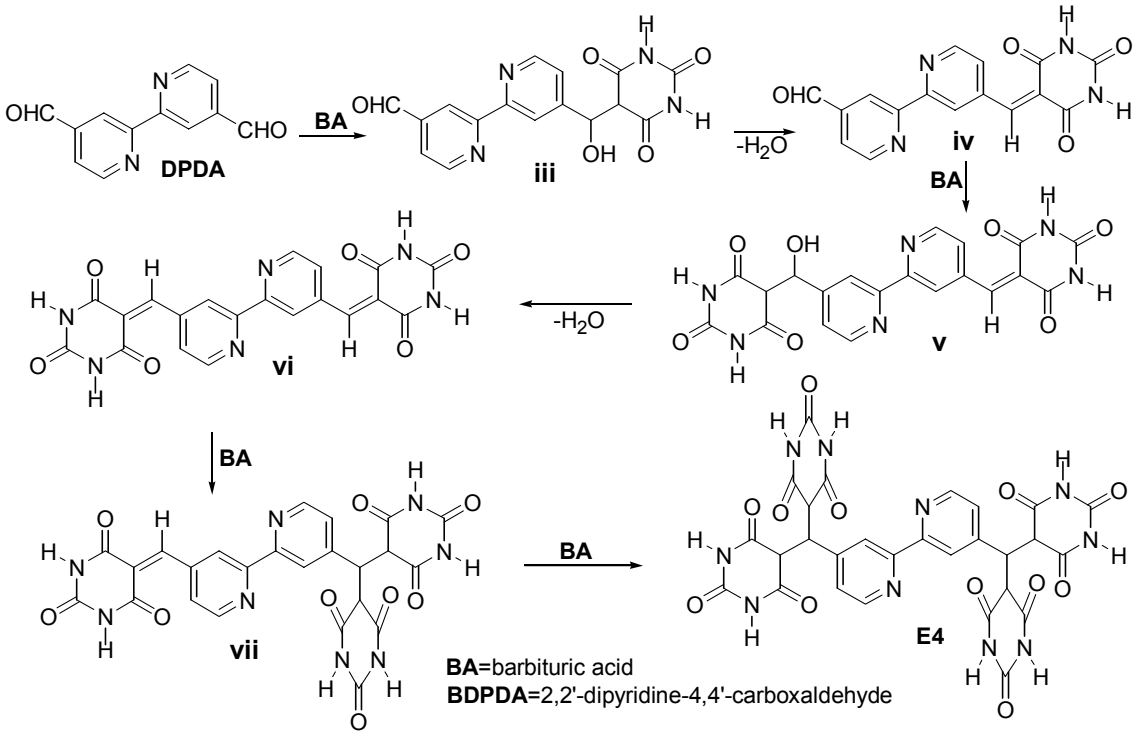


Figure IIe.8: All reactive intermediates that were detected in our NMR following experiments of the barbituric acid addition to 2,2'-dipyridine-4,4'-dicarboxaldehyde.

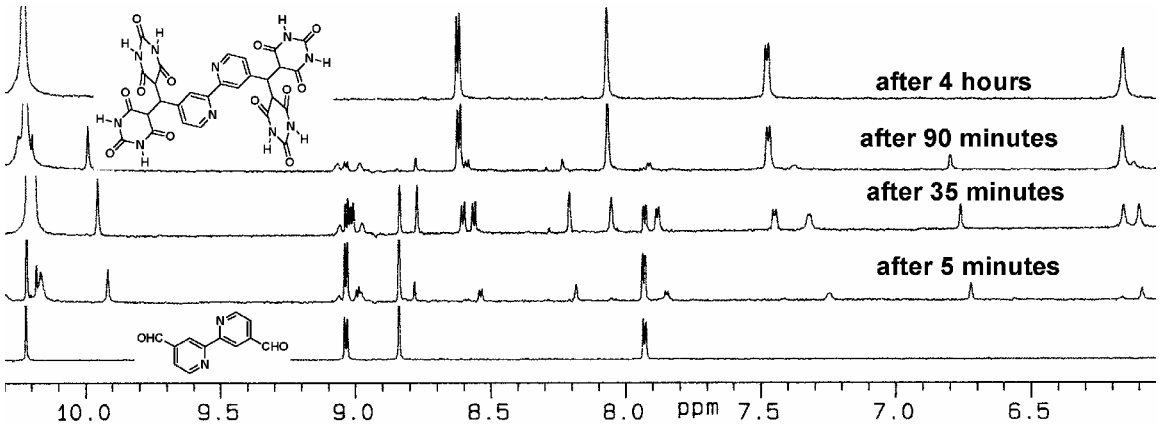


Figure IIe.9: ^{1}H-NMR (500 MHz) following of barbituric acid (10 mM) condensation with 2,2'-bipyridine-4,4'-carboxaldehyde (2.5 mM) in TFA-DMSO (3:1) at room temperature yielding **E4**.

Additionally, 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 **(Figure IIe.10)**. Isolated yields are almost quantitative and in many cases isolation and purification of the product simply involve filtration and washing the precipitate with solvent **(Table IIe.1)**. In these cases, the previously described NMR experiments utilizing both aromatic and heteroaromatic carboxaldehydes in both protic and aprotic solvents provided optimal reaction conditions for the preparation of double barbituric acid addition adducts to aromatic aldehydes. Our preparation procedures developed are applicable to multi-gram as well as multi kilogram scales and considering the simplicity of the preparation and isolation of these compounds, the procedures are directly applicable to the industrial scale preparation with little or no modification. Crystals of **E3** were obtained by slow evaporation of methanol at room temperature. The structure of compound **E3** was confirmed by X-ray structural analysis (**Figure IIe.11).**

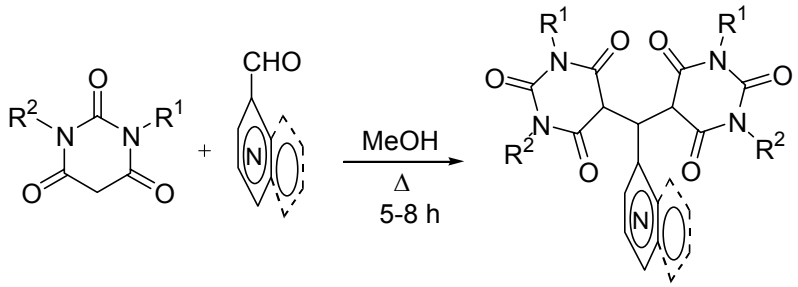


Figure IIe.10: Preparation of heteroaromatic dibarbiturates (General Procedure M).

Table IIe.1: Barbituric acid condensation with aromatic aldehydes

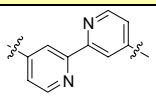
Product	**R^1**	**R^2**	**Aldehyde** CHO-§-	Yield (%)
E5	CH_3	CH_3		**92**
E7	H	H		**97**
E8	CH_3	CH_3		**92**
E9	H	CH_3		**97**
E10	H	C_4H_9		**81**
E11	H	C_6H_5		**93**
E12	H	H		**97**
E13	H	CH_3		**98**
E14	H	C_4H_9		**92**
E15	H	C_6H_5		**92**
E16	CH_3	CH_3		**86**

Table IIe.1 continued…

E17	H	C_6H_5		**93**
E18	CH_3	CH_3		**84**
E19	H	CH_3		**78**
E20	H	C_6H_5		**95**

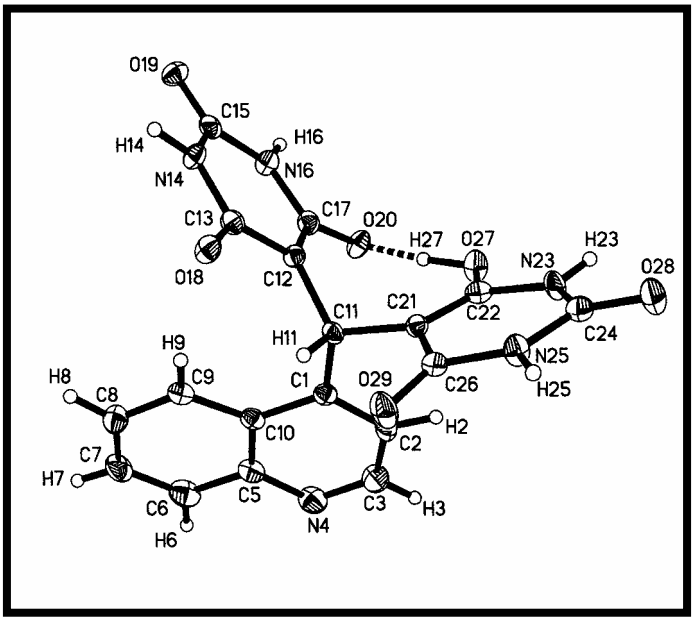


Figure IIe.11: ORTEP drawing of compound **E3** (*courtesy of E. D. Stevens*)**.**

IIf. Unique Molecules: Charge Separated Pyridinium-Barbiturate Zwitterions

IIf.1 Preamble

Pyridinium zwitterions are widely used in organic synthesis, either as nucleophilic agents or as reagents in dipolar cycloaddition reactions. The latter are used to synthesize fused heterocyclic systems that are otherwise very difficult to synthesize. **Figure IIf.1** is an example of the dipolar nature of pyridinium zwitterions and how they can be involved in dipolar cycloaddition reactions.[89-92]

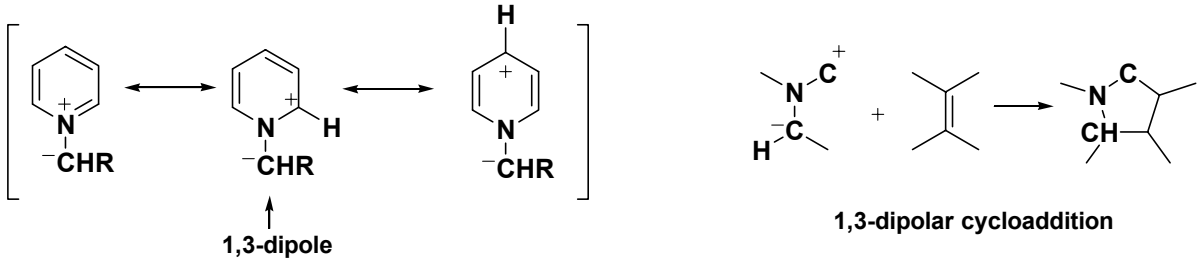


Figure IIf.1: Dipolar nature of pyridinium zwitterions.[91]

Usually, pyridinium zwitterions are compounds that are very reactive toward activated olefins and alkynes, and should be kept at low temperatures and in an inert atmosphere **(Figure IIf.1)**. The majority of pyridinium zwitterions were synthesized by first preparing the pyridinium salt, followed by the elimination of an acid in reaction with a base. However, there are some other routes that are one-step syntheses which utilize the capability of pyridine derivatives to add to reactive double bonds or to trap carbenes **(Figure IIf.2).**[93]

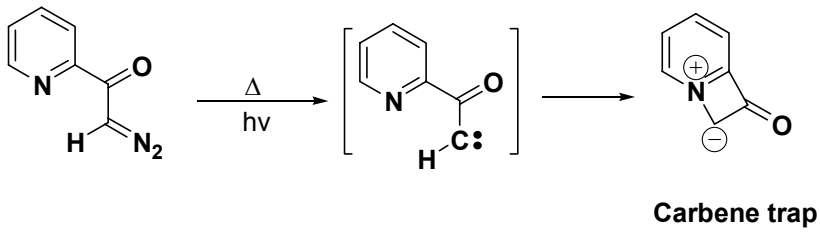


Figure IIf.2: Formation of pyridinium zwitterions.[93b]

Another application is the 1,4-dihydropyridine addition to alkoxycarbene complexes of transition metals, which has been shown to produce pyridinium zwitterions whose negative charge resides on the transition metal **(Figure IIf.3, viii)**. These reactive zwitterions have been shown to be successful in a number of reactions, one of which is selective cyclopropanation **(Figure IIf.3, ix).**[94-96]

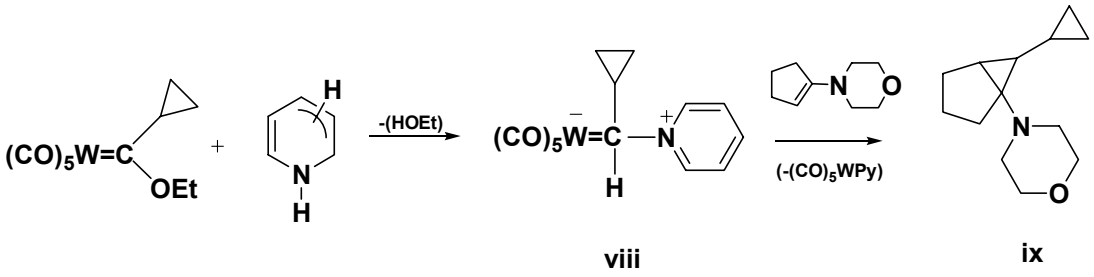


Figure IIf.3: Pyridinium zwitterions used in cyclopropanation reactions.[95]

However, in the majority of cases, the negative charge resides on the carbon attached to the pyridinium nitrogen and is delocalized by the presence of electron-withdrawing substituents.[89-92] For example, pyridinium-cyclopentadienylide **(Figure IIf.4, x)** is probably the most theoretically explored pyridinium zwitterion with aromatic stabilization of a negative charge.[97] Yet, even in this case, the molecule has low stability and little is known about its reactivity.[98-99] To make pyridinium cyclopentadienylide

sufficiently stable for structure determination in order to evaluate its reactivity, the cyclopentadienide moiety must have strong electron-withdrawing groups, as in the case of pyridiniotetrabromocyclopentadienides **(Figure IIf.4, xi).**[100]

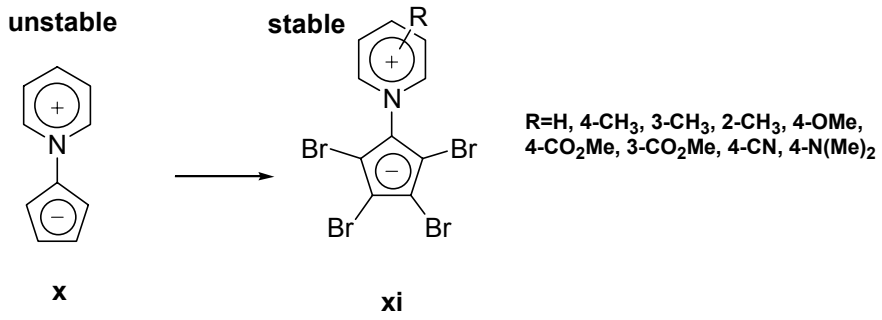


Figure IIf.4: Pyridinium zwitterions with aromatic stabilization of a negative charge

IIf.2 Results and Discussion

In our previous attempts to outline reaction procedures for the double addition of substituted barbituric acid to electron withdrawing aromatic aldehydes described in the previous chapter, we were surprised to find that under comparable reaction conditions, the 2-pyridine and 2-quinolinecarboxaldehydes did not give our desired Michael type adduct. Instead, through these reaction conditions, we obtained a unique compound that we were unable to immediately assign a structure to, based on our spectroscopic data. Later, we characterized the compound through X-Ray structural analysis (**Figure IIf.5**), as a unique, stable pyridinium zwitterion, and therefore set out to design and explore the reaction requirements more thoroughly to form our unique molecule.

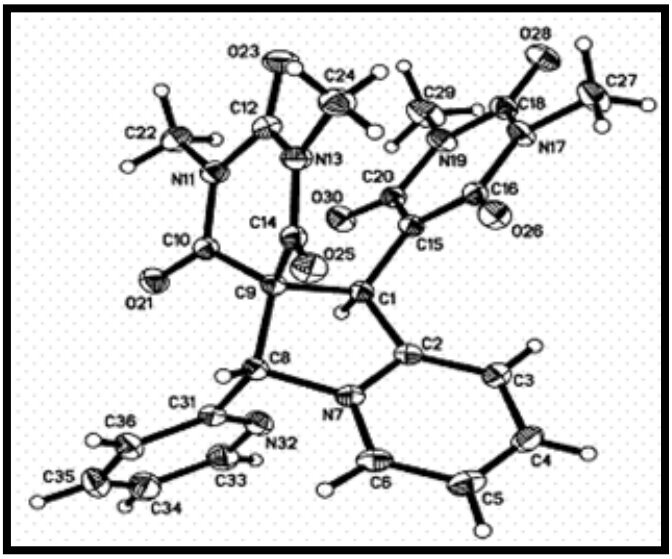
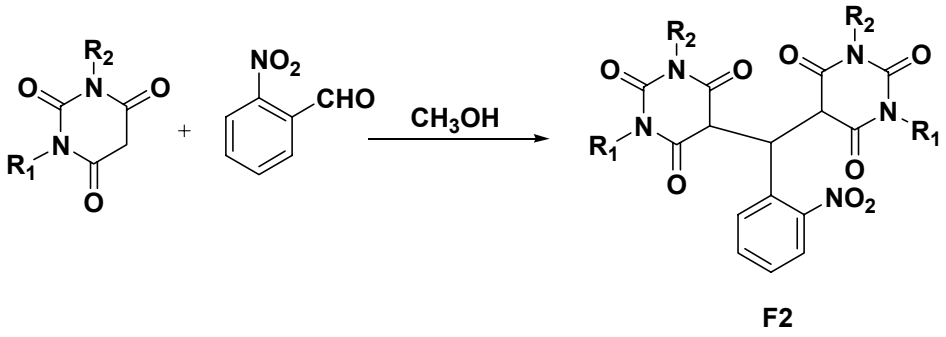


Figure IIf.5: ORTEP drawing of X-ray determined structure of **F1** (*courtesy of E. D. Stevens*).

We subsequently developed an efficient synthetic procedure for the preparation of a unique pyridinium zwitterion (**F1**), synthesized through the controlled condensation between 1,3-dimethyl barbituric acid and 2-pyridinecarbaldehyde, with an aromatic stabilization of the negative charge. In the case of barbituric acids, amide resonance dominates over aromaticity. With a negative charge localized on the barbituric acid ring, it is reasonable to assume that π–π atomic orbital overlap between the atoms in the ring should increase, thereby stabilizing the negative charge, which is indicated by the planarity of one of the barbituric acid rings of **F1**.

Previous literature data suggests that if the reaction between a barbituric acid and an electron-rich aromatic aldehyde is performed, then the Knoevenagel condensation[101-

[102] product **(F4)** must be the major product isolated (**Figure IIf.8**).[29, 84, 103-104] However, this application does not apply to electron poor aldehydes, such as nitrobenzaldehyde, in which there are unexpected products and the double addition product **(**Michael Addition, **F2**) is obtained (**Figure IIf.6**).[105-107]



F2

Figure IIf.6: Typical reaction product of barbituric acids and electron-deficient aromatic aldehydes.

Considering the similarities in the electronic properties of 2-nitrobenzaldehyde and 2-pyridinecarbaldehyde, one would expect that the isolated product of the condensation between 2-pyridinecarbaldehyde and substituted barbituric acids should be of the Michael Type adduct. This is not the case and the isolated product of this condensation is **(F1)** in almost quantitative yield **(Figure IIf.7)**.

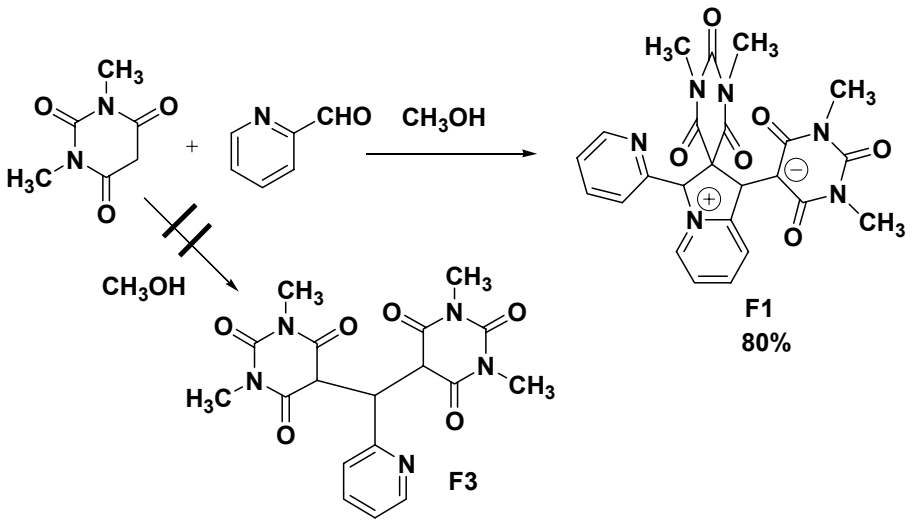


Figure IIf.7: Reaction outcome when 2-pyridinecarboxaldehyde is used as electron-deficient aromatic aldehydes.

To explain the formation of our unique compound, we hypothesized that two intermediates must exist. The first intermediate, and one that we have had previous spectroscopic evidence that lends to its formation during the course of double addition reactions, is the intermediate Knoevenagel product **(F4)**. The second intermediate would be an unstable pyridinium barbiturate zwitterion (**F5) (Figure IIf.8)**, which should undergo rearrangement to produce the more stable compound **F1.**

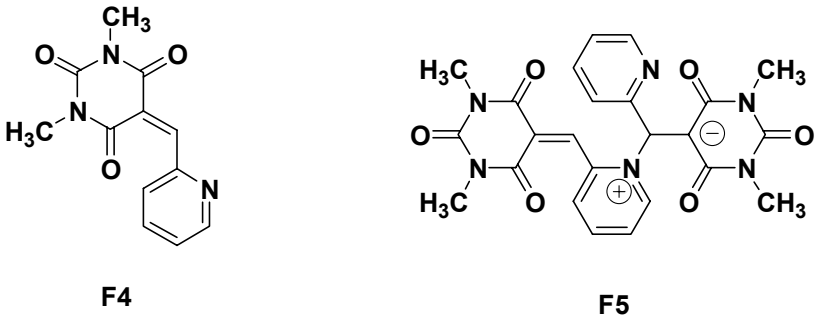


Figure IIf.8: Two proposed reactive intermediates in formation of **F1.**

Our attempt to actually isolate the Knoevenagel condensation product **(F4)** in the reaction between 1,3-dimethyl barbituric acid and 2-pyridinecarbaldehyde was not successful, regardless of the nature of solvent or base and acid used in this reaction. From NMR spectra taken during the reaction, we know that intermediate **(F4)** is formed and almost instantly consumed in nucleophilic addition of the barbituric acid (leading to product **F1**). We hypothesized that when a better nucleophile was not present in the reaction mixture, then the nitrogen of the pyridine moiety of **F4** acted as a nucleophile to another molecule of **F4**, producing the pyridinium zwitterion **F5**. This zwitterion subsequently rearranged into the more stable pyridinium zwitterion **F1**. Both of these zwitterions contain negatively charged barbituric acid rings. Although we do not have direct evidence for the formation of pyridinium zwitterion **F5**, we have indirect experimental information that strongly supports our hypothesis of its existence. For instance, if the reaction is performed in a strong acid, such as sulfuric acid, then the only isolated product is the sulfonate salt of the 2-pyridinium Knoevenagel condensation product. If the reaction is done in acetic acid, then a virtually insoluble polymeric product is obtained. While we were unable to spectroscopically determine the structure of this compound, due to its insolubility in solvents such as DMSO, methanol, water, acetic acid, chloroform, nitromethane, benzene and pyridine, we hypothesized that the insoluble material could be the polymer formed between two molecules of the reactive intermediate **F5.** This assumption was based on the fact that acetic acid should be strong enough to protonate the carbon of the negative barbituric acid ring of **F5,** facilitating the nucleophilic addition of the pyridine-**N** of one molecule of **F5** to the double bond of a second molecule of **F5 (Figure IIf.9).**

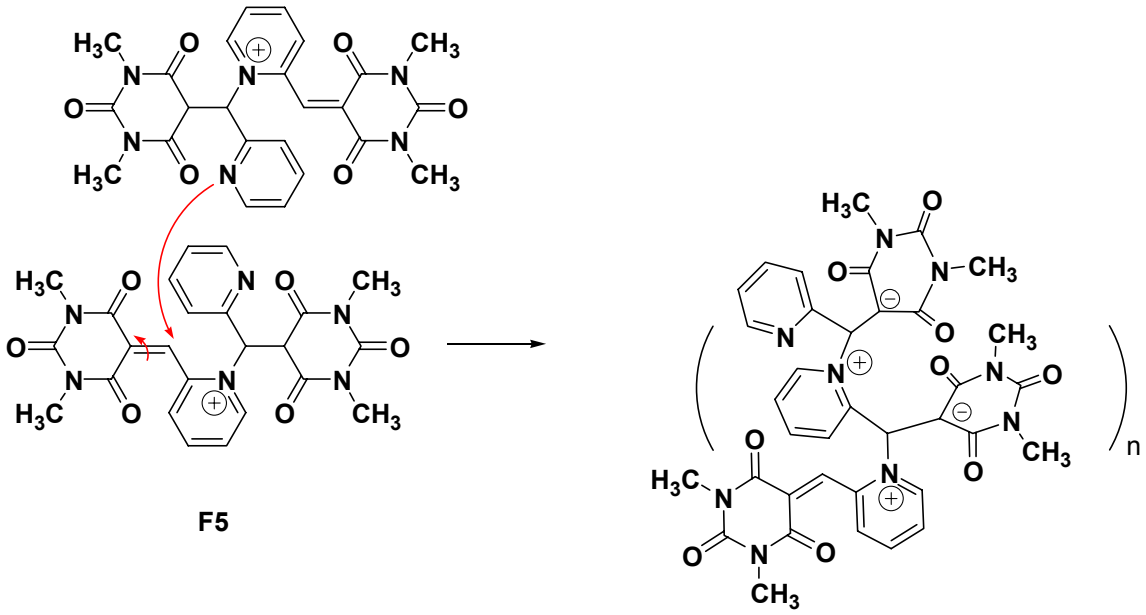


Figure IIf.9: Possible polymeric material of **F5** in acetic acid.

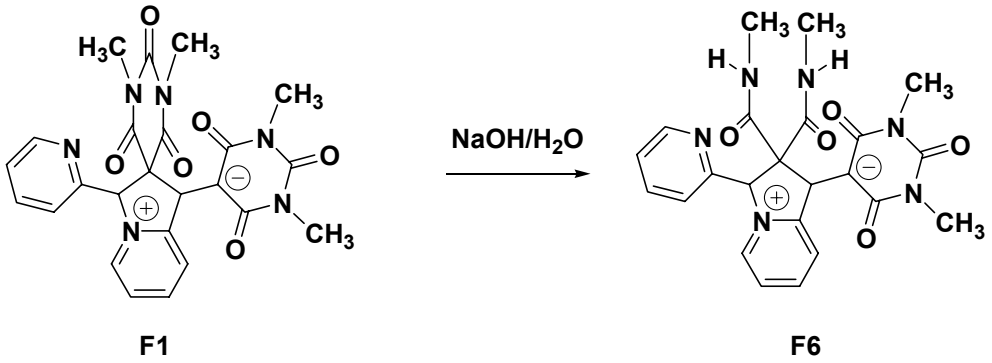
Another indication of the existence of **F5** as a reactive intermediate comes from the fact that we were unable to prepare type **F1** zwitterions if 1-methyl, 1-phenyl, or unsubstituted barbituric acid was used as a starting reagent instead of the disubstituted 1,3-dimethyl barbituric acid in the condensation reaction with 2-pyridinecarbaldehyde. Performing the reaction with these barbiturates in methanol also gave an insoluble material, appearing to be the same as the polymer like material obtained from the previous reaction in acetic acid. We hypothesized that the insoluble material was indeed the polymeric material obtained from reactions of **F5,** catalyzed by the free NH of the barbituric acids used. From this point, we ceased exploration of the characterization of the insoluble material obtained through these reactions, due to solubility problems with further characterization. In the absence of solvents strong enough to either protonate the N of the pyridine ring, resulting in the Knoevenagel condensation product, or protonate

the barbituric acid ring, resulting in the polymer, the zwitterion **F5** would readily rearrange to the more stable isomer, **F1.**

IIf.3 Physical properties of Pyridinium-barbituric acid Zwitterion F1

Pyridinium zwitterion **F1** shows some interesting chemical properties. One would expect that due to the negative charge localized on the barbituric acid ring, zwitterion **F1** would be very sensitive to protic solvents. However, it is stable in water, alcohol, and acetic acid. In fact, the compound is stable in hot acetic acid, which was determined by the lack of formation of decomposition products upon heating. The formation of decomposition products was monitored by (1) spectroscopic characterization by VT ^{1}H-NMR (80º C over 24 hours) and (2) by Thin Layer Chromatography of **F1** before extensive heating and periodic examination of the reaction mixture following several days of heating in acetic acid. In a more extensive, long-term NMR experiment using acetic acid and following the possible decomposition at room temperature over a period of 30 days, the only observable changes in the spectra were proton-deuterium exchange products. This proton exchange in a modest acid such as acetic acid is characteristic of an aromatic ring.[108]

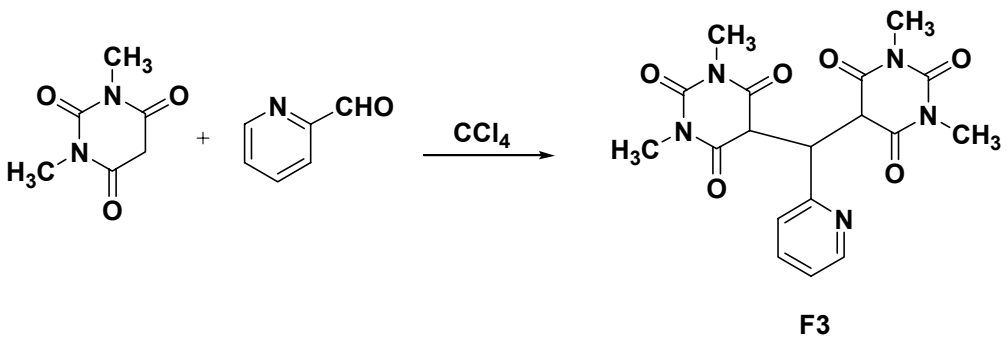
Another surprise comes from the stability of the pyridinium zwitterion skeleton in basic solution. It was expected that in aqueous sodium hydroxide, the five-membered ring of **F1** would open. Instead, the second barbituric acid ring, the ring not part of the pyridinium zwitterion substructure, opens and the decarbonylation product **F6** is isolated (**Figure IIf.10**), again indicating the stability of zwitterion **F1**.



F1 F6

Figure IIf.10: The decarbonylation of **F1.**

This decarbonylation is a typical reaction for highly substituted barbituric acids, the reaction previously developed by Jursic.[109] Given this information, we hypothesized that if the reaction were performed in polar solvents such as DMSO or methanol, the formation of pyridinium zwitterions **F1** and **F6** should be favored, and we were able to confirm this by spectroscopic characterization by NMR of the subsequent products. On the other hand, less polar solvents, such as chloroform or dichloromethane, should inhibit the formation of pyridinium zwitterions **F5**, subsequently inhibiting the formation of the more stable **F1** zwitterion, and the less polar product (**F3, Figure IIf.11**) should be favored. In our NMR experiment using chloroform as the solvent and reaction media, we detected the formation of both **F3** and **F1** in an approximate ratio of 7:3. If even less polar solvents such as carbon tetrachloride were used, then completion of the reaction was prolonged but the ratio of **F3** to **F1** became ~9:1.



F3

Figure IIf.11: Formation of **F3** in non-polar solvents.

What is the source of this unique stability of pyridinium-barbituric acid zwitterion? The unique structure of zwitterion **F1** allows direct comparison of the X-ray structural parameters. Jursic previously postulated that uniformity of the ring bond order is directly related to high stability.[110] This postulate can be supported through X-ray data obtained for zwitterion **F1**. The negative charge that resides mostly on the barbituric acid ring makes that ring more aromatic and adds to the bond order-bond distance uniformity. The barbituric acid ring with the negative charge becomes almost planar. The experimental dihedral angles are almost zero and the dihedral angles for C(16)-N(17)-C(18)-N(19) and C(20)-C(15)-C(16)-N(17) are -0.22 and -3.90º, respectively. Even the carbonyl oxygen and methyl carbon reside close to the plane of the negatively charged barbituric acid. For instance, the dihedral angle for C(27)-N(17)-C(18)-O(28) is -0.89º and the dihedral angle for O(26)-C(16)-N(17)-C(27) are 2.61º. Given this data, it is quite obvious that the second barbituric acid ring is out of the plane. The dihedral angle for C(10)-C(9)-C(14)-N(13) is -40.64º. Comparison of bond distances between two of the barbituric rings further indicates the aromatic character of the ring that bears the negative charge. For instance, bond distances in the nonaromatic barbituric acid ring for C(9)-

C(10), C(10)-N(11), and N(11)-C(12) are 1.5128, 1.3934, and 1.3996 Å, respectively, while for the same kind of bonds in the aromatic barbituric acid moiety these distances for C(15)-C(16), C(16)-N(17), and N(17)-C(18) are 1.4138, 1.4220, and 1.3769 Å. On the other hand, structural changes regarding pyridine and pyridinium rings are not substantial.

IIg. Syntheses of Heteroaromatic, Electron Rich, and Aliphatic Bis-barbiturate Ammonium Salts.

IIg.1 Preamble

In previous chapters, we reported our successful synthesis of pyrilidene and quinolidine bis-barbiturates *via* the Michael-type addition of barbituric acid to intermediate Knoevenagel condensation products.[84] While this methodology proved successful for the synthesis of a wide variety of bis-barbiturates containing heterocyclic or electron poor aromatics, it was equally unsuccessful in producing bis-barbiturates with either electron rich aromatic or aliphatic substituents. During the course of our exploration of barbituric acid double addition of heteroaromatic aldehydes we discovered that it was necessary for the aldehydes to be electron deficient in order for the reaction to occur. Thus, in order to obtain the Michael type adducts rather than the Knoevenagel product with aldehydes such as 4-(dimethylamino)benzaldehyde, it was necessary to do the reaction in highly acidic media, such as TFA. This effectively transformed the electron rich $N(CH_3)_2$ group into the electron deficient $N(CH_3)_2H^+$ group, and the reaction was facilitated.

While we were able to use certain electron rich aromatic aldehydes in reaction with barbituric acids to form the double adducts, as mentioned above, this method was not comprehensive. Many electron rich derivatives, such as aldehydes with OH substitutions, as well as unsubstituted aldehydes were not successfully transformed into the double adduct. Additionally, the dimethylamino derivatives and nitro derivatives were unstable compounds prone to decomposition. Therefore, we began exploring new,

comprehensive methods that would be applicable to all types of aldehydes, inherently necessary for our through exploration of bis-barbiturate adducts.

We did find sporadic literature reports describing the condensations of aromatic electron deficient aldehydes, such as nitrobenzaldehyde, with barbituric acids in pyridine as a reaction media, where the formation of the mono and di pyridinium salts were formed.[111] While this method seemed to produce the corresponding double adduct in relatively high yields (65-95%), the synthesis was again only applicable to electron deficient aromatic aldehydes.

IIg.2 Results and Discussion

Based on our previous studies, we hypothesized that transformation of the electron rich substituent to the electron poor substituents was not the only barrier necessary to overcome to produce our desired products. We hypothesized that during the course of the reaction between barbiturates and aldehydes to form the double addition adduct, it may also be necessary to stabilize the charge formed on the barbituric acid ring, yet still maintain the acidic conditions required to produce the enolate needed (nucleophile) for the second addition of barbituric acid to the intermediate Knoevenagel product. To this end, we began exploring the use of ammonium compounds, such as triethylamine, *N*-methylmorpholine, morpholine, and piperidine, as both a hydrogen acceptor and conjugate acid to form our bis-barbiturates with electron donating and aliphatic aldehydes. We experimentally determined that the best ammonium bases were morpholine, ethanolamine, and piperidine, and when used in a 0.1 molar excess, we were able to generate corresponding bis-barbiturate ammonium salts using electron-donating,

electron-withdrawing, and aliphatic aldehydes in a one-pot synthesis (**Figure IIg.1).** **Table IIg.1** gives a description of the electron-withdrawing aldehydes used to produce the bis-barbiturate ammonium salts.

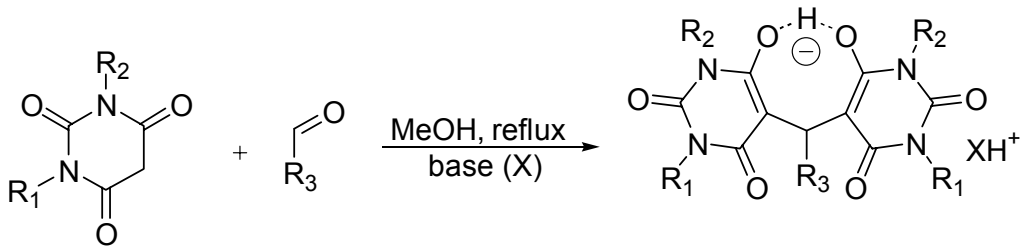


Figure IIg.1: Reaction scheme for the synthesis of bisbarbiturate ammonium salts (General Procedure N).

Table IIg.1: Bis-barbiturate ammonium salts of electron-withdrawing aldehydes

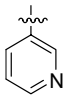
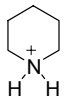
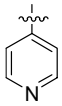
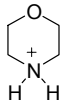
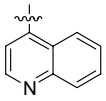
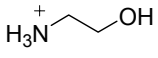
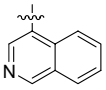
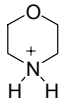
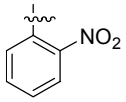
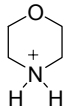
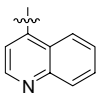
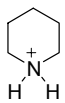
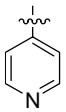
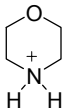
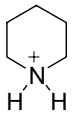
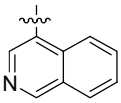
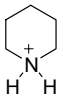
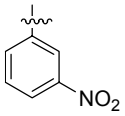
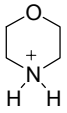
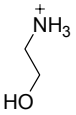
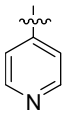
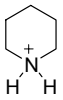
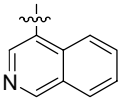
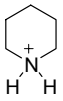
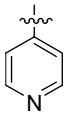
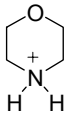
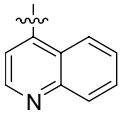
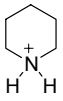
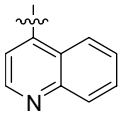
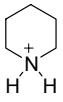
Compound	**R_1**	**R_2**	**R_3**	**XH^+**	Yield (%)
G1	H	H			**93**
G2	H	H			**97**
G3	H	H			**92**
G4	H	H			**82**
G5	H	H			**92**
G6	CH_3	CH_3			**97**

Table IIg.1 continued…

G7	CH_3	CH_3			**93**
G8	CH_3	CH_3			**95**
G9	CH_3	CH_3			**82**
G10	CH_3	CH_3			**84**
G11	H	CH_3			**87**
G12	H	CH_3			**87**
G13	H	CH_3			**69**
G14	H	CH_3			**89**
G15	H	CH_3			**94**
G16	H	Ph			**95**
G17	H	Ph			**89**

Our main objectives in preparing bis-barbiturates having the electron donating substituents centered on the novelty of these types of barbiturates. To the best of our knowledge, there were no experimental reports indicating the existence of these types of compounds. Furthermore, the ammonium salts of these compounds were highly water soluble, making possible biological evaluation of these types of compounds relatively easy. **Table IIg.2** lists a description of the electron-donating aldehydes used, and the bis-barbiturate ammonium salts synthesized as a one-pot synthesis **(Figure IIg.1).** The reaction proceeded to completion and the isolated yields were quantitative, regardless of the electron-donating benzaldehyde used during the course of the reaction. Additionally, substitutions of the benzaldehydes could be in *ortho, meta, or para* positions without altering the outcome of the reaction. *N*-methylmorpholine was used in several of the reaction mixtures as the source of the ammonium counterion, however, in each of these cases, we isolated the Knoevenagel condensation products in quantitative yields and from this point on, the only ammonium compounds used were bases with at least one free NH moiety.

Table IIg.2: Bis-barbiturate ammonium salts of electron-donating aldehydes

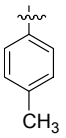
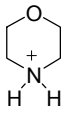
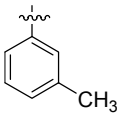
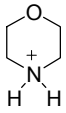
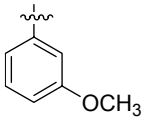
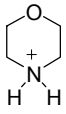
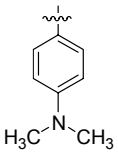
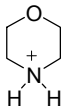
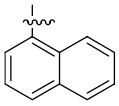
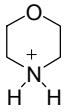
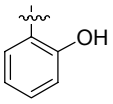
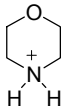
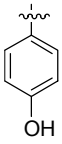
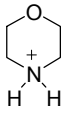
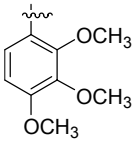
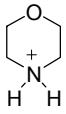
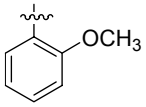
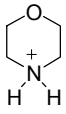
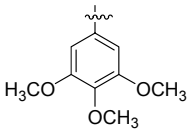
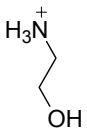
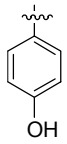
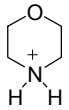
Compound	**R_1**	**R_2**	**R_3**	**XH^+**	Yield(%)
G18	H	H			**95**
G19	H	H			**90**
G20	H	H			**95**
G21	H	H			**96**
G22	H	H			**95**
G23	H	H			**90**
G24	H	H			
G25	H	H			**96**
G26	CH_3	CH_3			**93**

Table IIg.2 contiued…

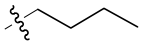
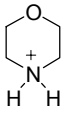
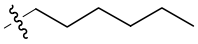
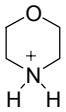
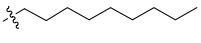
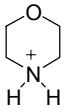
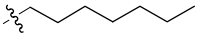
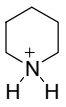
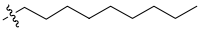
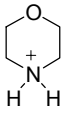
G27	CH_3	CH_3			**93**
G28	CH_3	CH_3			**92**

Considering that the most biologically potent barbituric acid derivatives are usually those with an aliphatic *C-5* moiety, we decided to develop the synthetic procedure for the preparation of aliphatic bisbarbiturate salts. In such cases, we were able to condense simple aliphatic aldehydes, barbituric acids, and amines, and the appropriate ammonium salts are listed in **Table IIg.3.**

While there seemed no apparent restriction on the aliphatic aldehydes used in the course of this reaction, we were unable to isolate pure products of higher aldehydes, such as dodecanal using the method outlined in **Figure IIg.1**. In the reactions between aldehydes containing more than 12 carbons and barbituric acids, the outcomes of the reactions were a viscous oily material that we were unable to re-crystallize. The H-NMR spectra of these products provided evidence of both the unreacted starting material, and the bis barbiturate ammonium salt. Re-crystallization in solvents such as ether, dichloromethane, chloroform, and petroleum ether resulted in the re-precipitation of the oily material, and re-crystallization in solvents such as ethyl acetate, methanol, ethanol, and THF provided the precipitation only of the unreacted barbituric acid. While we did not attempt further methods of purification for these compounds, but expect that separation by column chromatography would provide the pure products of aliphatic aldehydes greater than 12 carbons in reaction with barbituric acids.

To avoid using column chromatography as a method of purification, we attempted to change the reaction conditions to encompass aliphatic aldehydes greater than 12 carbons. Unfortunately, while the aldehydes are soluble in virtually all reaction media attempted, such as THF, ether, ethanol, propanol, and ethyl acetate, the respective barbituric acids were insufficiently soluble to perform these reactions.

Table IIg.3: Bis-barbiturate ammonium salts of aliphatic aldehydes

Compound	**R_1**	**R_2**	**R_3**	**XH^+**	Yield (%)
G29	H	H			**92**
G30	H	H			**75**
G31	H	H			**94**
G32	H	H			**82**
G33	H	Ph			**73**

Because there are different biological properties elicited when a substitution is made on the *C-2* atom of barbituric acids **(Figure IIg.2)**, such as shorter retention times, or changes of potency, we employed the use of thiobarbituric acids to synthesize novel *C-2* substituted bis barbiturates using electron withdrawing, electron donating, and aliphatic aldehydes using the general method outline in **Figure IIg.1.** The products were insoluble

in methanol and immediately precipitated out, regardless of the nature of the aldehydes used **(Table IIg.4)**.

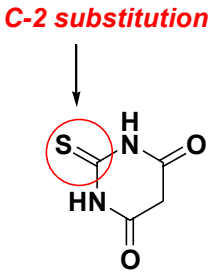
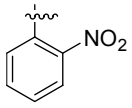
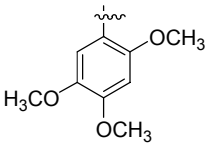
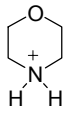
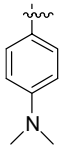
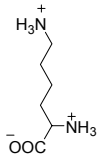


Figure IIg.2: Example of *C-2* substitution of barbituric acids.

Table IIg.4: Thiobisbarbiturate ammonium salts of electron-poor, electron-rich and aliphatic aldehydes.

Compound	**R_1**	**R_2**	**R_3**	**XH^+**	Yield (%)
G34	H	H			**97**
G35	H	H			**91**
G36	H	H			**90**

The H-NMR spectra of bis-barbiturate ammonium salts are very similar to the spectra of the corresponding bis-barbiturates described in Chapter IIe of this manuscript. The singlet for –C**H-** of the bis-barbiturate structure, located between 5.5 and 6.5 ppm**,** is indicative of double barbituric acid addition. In the ammonium salts, this singlet remains

between 5.5 and 6.5 ppm **(Figure IIg.4)**. The signals for the corresponding ammonium base integrate to show a ratio of one molecule of the cation per one molecule of the corresponding bis-barbiturate.

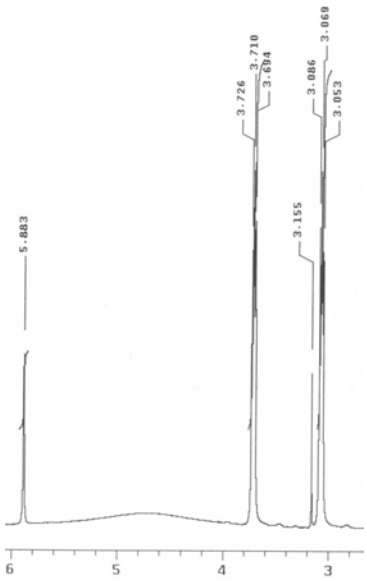


Figure IIg.4: A portion of the typical H-NMR spectra of morpholinium aromatic bisbarbiturates.

Aliphatic bis barbiturates give a triplet (*J*= 8.1 Hz*)* between 4.5 and 5.5 ppm, indicative of the addition of the aliphatic moiety to the barbiturate. To confirm the structure of the bis-barbiturate ammonium salts, compound **G37** was crystallized from DMSO at room temperature **(Figure IIg.5)**.

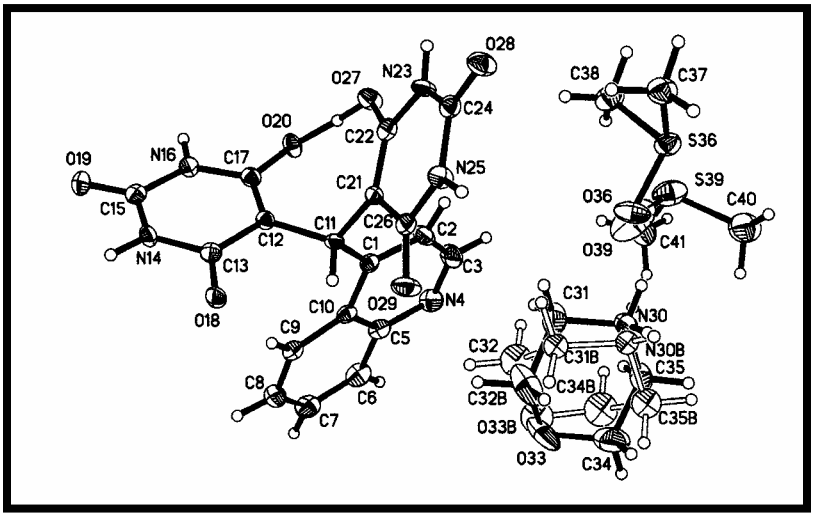


Figure IIg.5: ORTEP drawing of **G37** *(courtesy of E. D. Stevens).*

IIh. Syntheses of Substituted and Unsubstituted 5-benzoylbarbituric acids and Corresponding Phenylhydrazones

IIh.1 Preamble

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.[83, 111-114] Compounds, such as **A-007 (22) (Figure IIh.1),** have been shown to possess these immuno-modulating properties, yet little is known about the mechanism(s) underlying this biological activity. To thoroughly explore the possibility of immune-modulation within aromatic substituted barbiturate Schiff bases, structural variants of the **A-007** molecule, as well as to explore the structural requirements necessary for immune modulating activity, a large variety of both substituted and unsubstituted 5-benzoylbarbiturates were necessary precursors for the synthesis of the targeted phenylhydrozone Schiff bases.

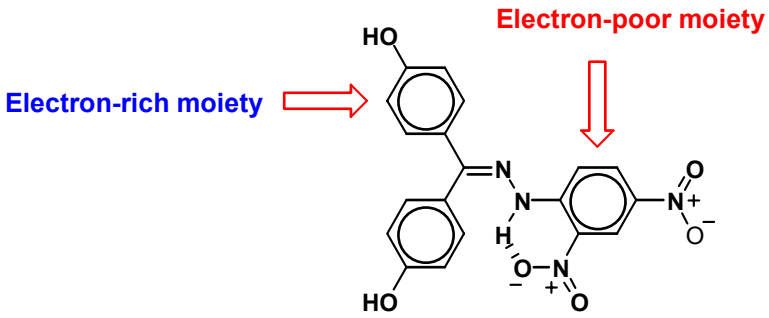


Figure IIh.1: 4,4'-dihydroxybenzophenone-2,4-dinitrophenylhydrazone (**A-007).**

There are literature reports indicating that some substituted and unsubstituted 5-benzoyl barbiturates have been previously synthesized and are used as herbicides and insecticides.[47, 115-116] 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.

IIh.2 Synthesis of benzoyl barbiturates

Through our experimental exploration, we determined that the simplest way to prepare benzoyl substituted barbituric acids was to condense *N*-substituted barbituric acids (R_1, R_2=H, alkyl, or aryl, **Figure IIh.2**) with the corresponding acid chloride.

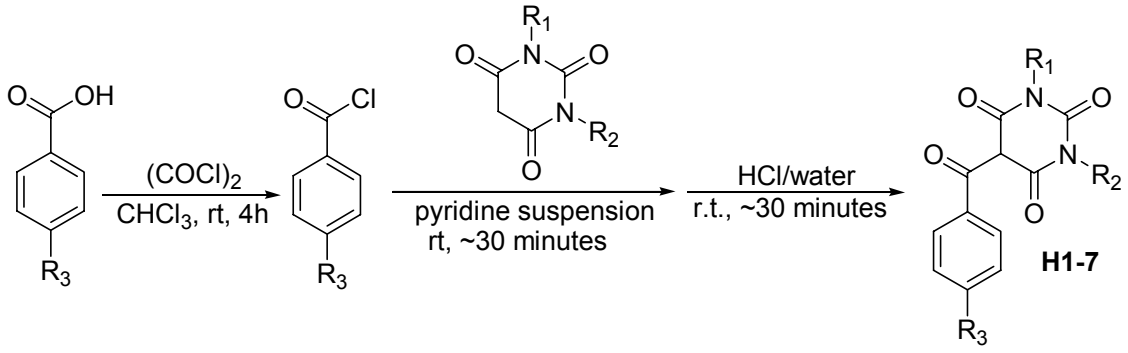


Figure IIh.2: Syntheses of 5-benzoyl and 5-(methoxybenzoyl)barbiturates **H1-7**.

Many of these starting materials are commercially available, however if the desirable starting materials are not available they can be readily prepared.[117] Pyridine seems to be an ideal solvent for this reaction. It was not necessary to fully dissolve the reactants for the reaction to be completed; therefore a relatively small amount of pyridine is sufficient

for the reactant conversion (~25 mL). 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 is not necessary **(Table IIh.1)**.

Table IIh.1: Isolated yields of 5-benzoylbarbiturates.

Product	**R_1**	**R_2**	**R_3**	Yield (%)
H1	H	H	H	**90**
H2	Ph	H	H	**83**
H3	CH_3	H	H	**77**
H4	CH_3	CH_3	H	**84**
H5	C_4H_9	H	H	**97**
H6	H	H	OCH_3	**87**
H7	CH_3	CH_3	OCH_3	**90**

These preparation procedures were not applicable to the preparation of 5-benzoylbarbiturates with strong electron-withdrawing groups, such as nitro groups, and a separate synthetic procedure was developed to produce these derivatives of our Schiff base precursors. The nitro compounds could also be prepared in pyridine as reaction media, but the isolation and separation from both pyridine and the resulting pyridinium chloride was very difficult. Therefore, another synthetic route utilizing *N*-methyl morpholine as a base and dioxane or tetrahydrofuran as the reaction solvent was

developed **(Figure IIh.3)**. In such cases, the desired product was isolated in higher than 90% yield (**Table IIh.2**).

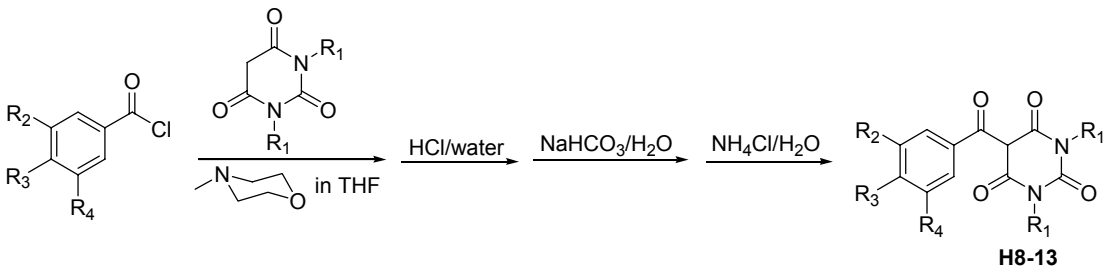


Figure IIh.3: General route for preparation of 5-(nitrobenzoyl)barbiturates **H8-13.**

Table IIh.2: 5-(nitrobenzoyl)barbiturates

Product	R_1	R_2	R_3	R_4	Yield(%)
H8	H	H	H	NO_2	93
H9	CH_3	H	H	NO_2	91
H10	H	H	NO_2	H	93
H11	CH_3	H	NO_2	H	95
H12	H	NO_2	H	NO_2	90
H13	CH_3	NO_2	H	NO_2	93

IIh.2.1 Physical properties

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 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 (**H9**, **Figure IIh.4**). The precipitated product formed by the condensation reaction between 3-nitrobenzoyl chloride and barbituric acid in THF and *N*-methylmorpholine as a base was exclusively in the keto form. If the product is purified by crystallization from large quantities of water, then the enol form was present in crystalline form. It is also obvious that the enol form was the thermally more stable species as demonstrated by NMR following thermal distribution of keto-enol forms in DMSO at 80º C (**Figure IIh.4**).

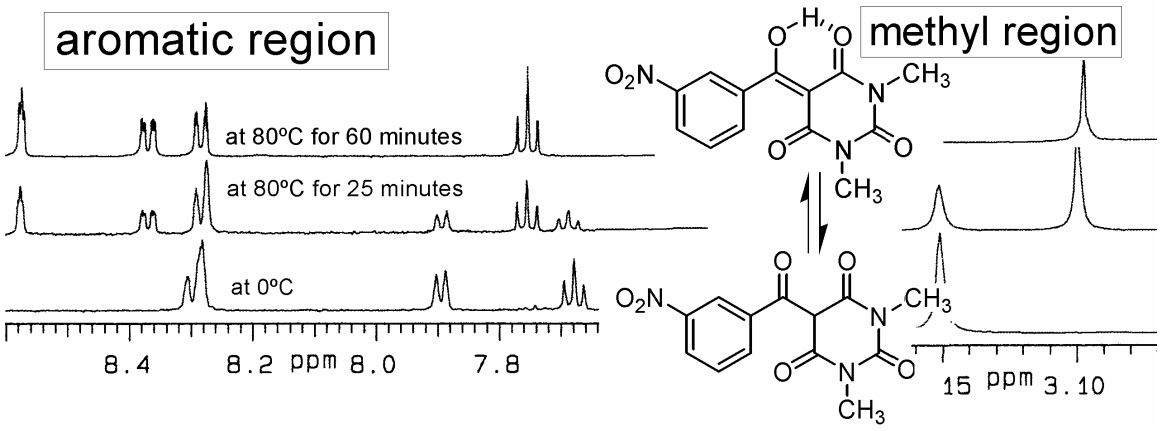


Figure IIh.4: The NMR following of thermal induced transformation of keto form of **H9** into it enol form in DMSO-d_6 at 80º C.

There are couple of very interesting points that can be concluded from the NMR following of the keto-enol equilibrium presented in **Figure IIh.4**. The presence of the enol form of **H9** is determined by the nature of the solvent as well as the temperature. In

solvents that cannot form strong hydrogen bonding with *N, N'*-disubstituted barbiturates, such as **H9,** the keto form is dominant or the only present tautomer. In solvents such as DMSO and water, which can form strong 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 **H9** 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 IIh.5**). The structural orientation of carbonyl group toward the *p*-nitrophenyl moiety is exactly opposite (almost coplanar in its keto-form) and perpendicular in its enol-form, **Figure IIh.5**). There is also 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 the barbituric acid hydrogen was not observed in the NMR spectra of the DMSO-d_6 solution of **H9** due to the H-D exchange.

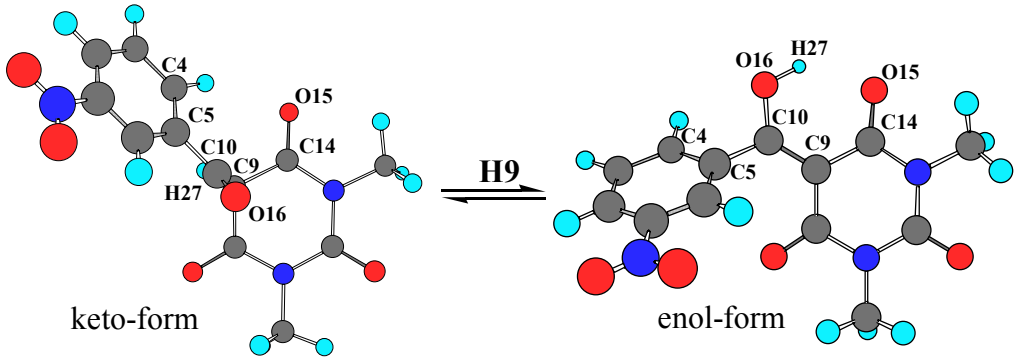


Figure IIh.5: The AM1 semi-empirical computed structures of keto and enol forms of **H9**

NMR spectroscopic studies of **H9** in chloroform is much closer to our AM1 gas-phase computational studies, therefore one can assume that the enol form with intramolecular hydrogen bonding is present. Furthermore, the existence of C9-C10 double bond in the enol-form makes the two methyl barbituric acid groups spectroscopically nonequivalent. In other words, the aromatic portion of the NMR spectra in chloroform at room temperature is very similar to the NMR in DMSO-d_6 at elevated temperatures. The methyl range is different from the previous spectrum (**Figure IIh.4)** because at 80º C in DMSO, due to low rotational barrier, the two methyl groups are equivalent and in chloroform at room temperature they are not (**Figure IIh.6**). The strongest evidence for the enol-form of **H9** 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 carbonyl oxygens of the barbituric acid moiety (**Figure IIh.6**).

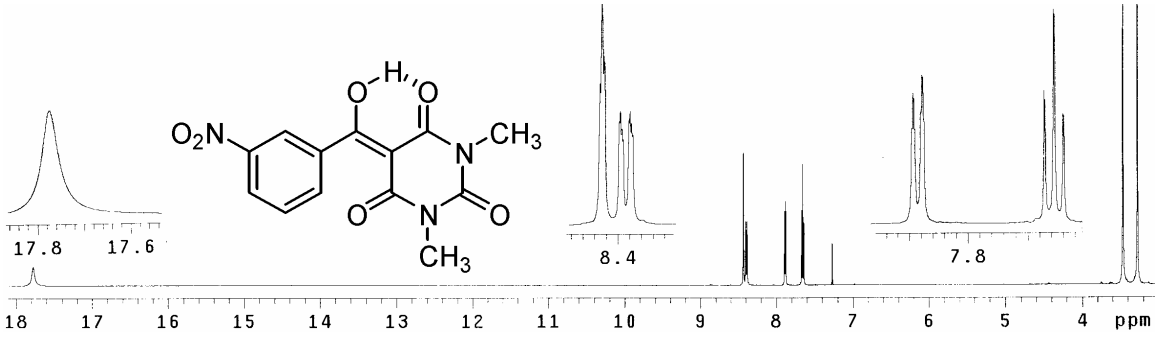


Figure IIh.6: The NMR (500 MHz) spectra of chloroform solution of **H9** at room temperature

IIh.3 Hydroxy-benzoyl barbiturate precursors

None of the discussed procedures applied for the preparation of methyl, methoxy, and nitrobenzoyl barbiturates could be used for the preparation of hydroxybenzoyl barbiturates. Furthermore, our exhaustive literature searches provided no evidence that there is a method of preparation for hydroxybenzoyl barbiturates. Naturally, the hydroxyl group attached to the benzoyl moiety must be protected during the course of the preparation of hydroxybenzoyl barbiturates. Because 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, using various methods of deprotection, during the course of the methoxy group transformation into the unprotected hydroxyl group, the barbituric acid part of the molecule decomposed.[118] After exploring several routes for the preparation of these compounds, we developed a simple and high yield preparation **(Figure IIh.7)**. The preparation starts with acetyloxybenzoic acid, which is converted into the corresponding acid chloride. Then, by following the previously described procedure for the benzoyl chloride condensation with barbituric acid in pyridine, the hydroxyl-protected product was produced. The final step involved hydrolysis of the acetic acid ester protecting group, followed by the isolation of pure product upon acidification (**Table IIh.3**).

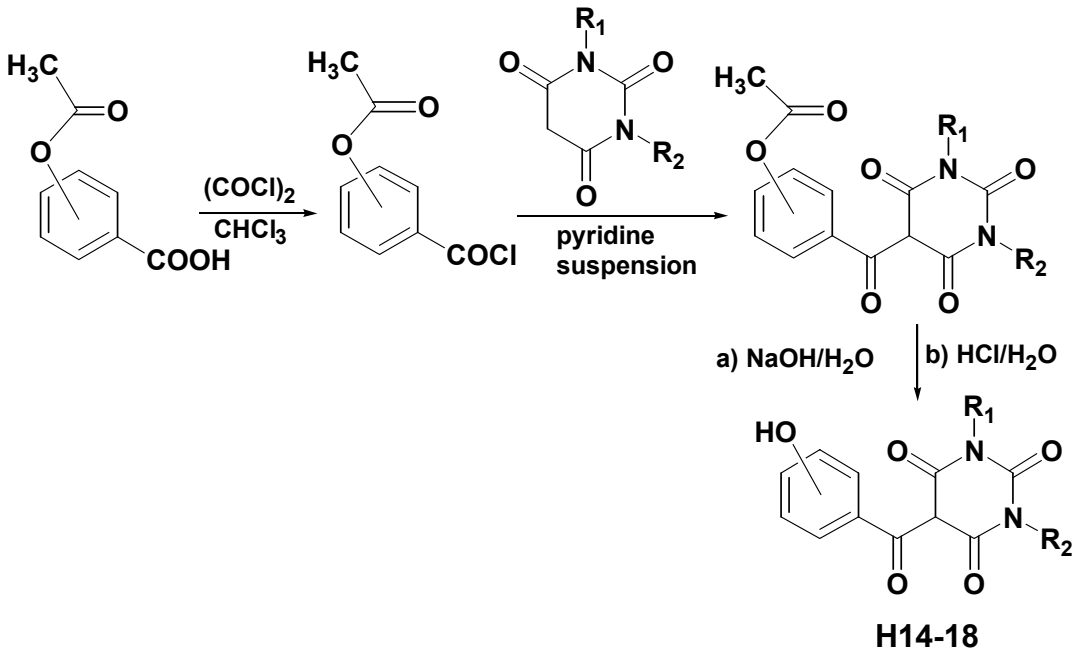


Figure IIh.7: Synthetic partway for preparation hydroxybenzoylbarbiturates **H14-18**

Table IIh.3: Isolated yields of hydroxybenzoylbarbiturates

Compound	**R_1**	**R_2**	**Acid chloride**	Yield(%)
H14	H	H	*m*-$OCOCH_3$	**91**
H15	C_4H_9	H	*p*-$OCOCH_3$	**77**
H16	CH_3	CH_3	*p*-$OCOCH_3$	**85**
H17	H	H	*p*-$OCOCH_3$	**80**
H18	H	Ph	*p*-$OCOCH_3$	**83**

With our 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 herbicides.[47] None of the patented work focused on 5-benzoylbarbituric phenylhydrazones. Our attempt to apply the patented synthetic procedures for the preparation of our phenylhydrazones of benzoylbarbiturates was not successful. From these experiments it was obvious that our benzoylbarbiturates were 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 with the target being to select the optimal reaction conditions for the preparation of these valuable compounds. Wanting to find and optimize appropriate reaction conditions for the preparation of phenylhydrazones of benzoylbarbiturates, we performed several NMR experiments following these types of reactions. A typical ^{1}H-NMR experiment for these compounds was demonstrated by the transformation of *p*-nitrophenylhydrazine and 5-(4-methoxybenzoyl)-1,3-dimethyl pyrimidine-2,4,6-trione (**H7**) into 5-{(4-Methoxyphenyl)-[*N*'-(4-nitrophenyl)hydrazino]methylene}-1,3-dimethyl-pyrimidine-2,4,6-trione **(H25)** (**Figure IIh.8**). The reaction was followed by taking a sample of the reaction mixture (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 **H7** was consumed. It was obvious that there are two major products of the condensation reaction. When sulfuric acid was added, one of the products was transformed into the other. Prolonged refluxing of the reaction mixture

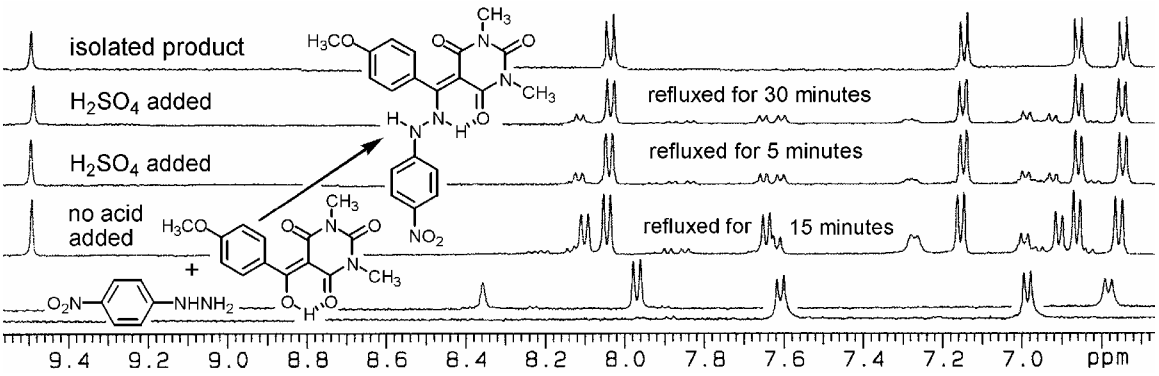


Figure IIh.8: The ^{1}H-NMR (DMSO-*d*$_6$, 500 MHz) reactions following for condensation reaction in 1-propanol without and with sulfuric acid as catalyst to yield **H25**.

does not noticeably change the composition of the product. After cooling down the reaction mixture, a solid precipitate containing only one molecular species, compound **H25** (**Figure IIh.8**) was isolated. Following this synthetic procedure, or by slight modification of this procedure, the phenylhydrazones of benzoylbarbiturates (**Figure IIh.9**) 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**,** specific reaction conditions were developed and are mentioned in the experimental section of this paper. The designed phenylhydrazones were necessary to explore the structural requirements necessary to elicit the immune modulation, as in the case of **A-007 (Table IIh.4).**

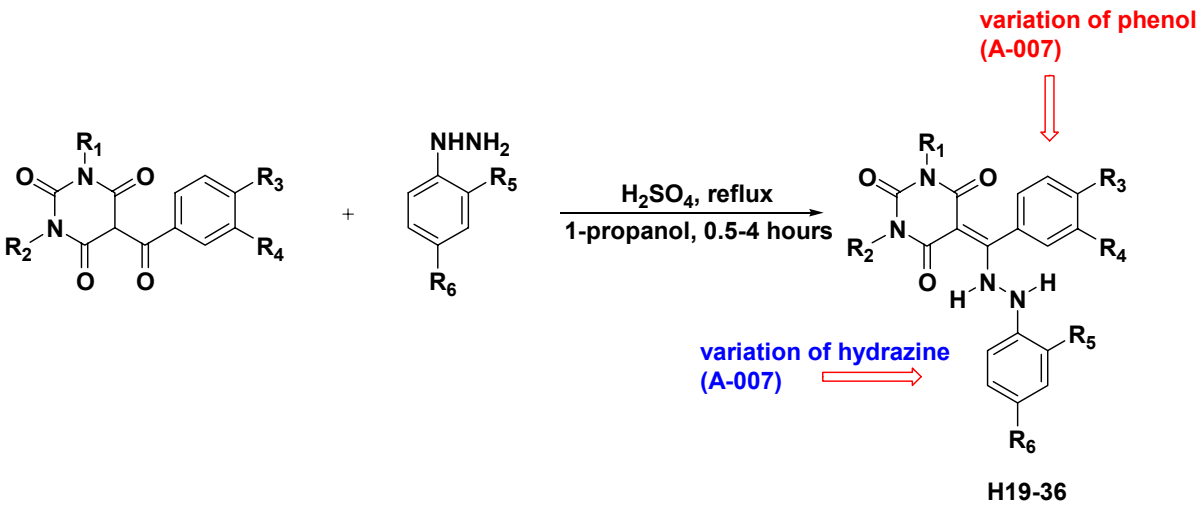


Figure IIh.9: Preparation path for phenylhydrazones of benzoylbarbiturates

Table IIh.4: Phenylhydrazones of benzoylbarbiturates

Product	**R_1**	**R_2**	**R_3**	**R_4**	**R_5**	**R_6**	**Yield(%)**
H19	H	H	H	H	H	NO_2	**73**
H20	H	H	H	H	H	COOH	**79**
H21	CH_3	CH_3	H	H	NO_2	NO_2	**83**
H22	H	Ph	H	H	NO_2	NO_2	**88**
H23	H	H	H	H	NO_2	NO_2	**84**
H24	CH_3	CH_3	H	H	H	COOH	**79**
H25	CH_3	CH_3	OCH_3	H	H	NO_2	**82**
H26	CH_3	CH_3	OCH_3	H	NO_2	NO_2	**81**
H27	H	H	OCH_3	H	NO_2	NO_2	**81**
H28	H	H	H	OH	NO_2	NO_2	**88**
H29	H	CH_3	OH	H	NO_2	NO_2	**88**
H30	H	C_4H_9	OH	H	NO_2	NO_2	**80**
H31	H	H	OH	H	NO_2	NO_2	**91**
H32	H	Ph	OH	H	NO_2	NO_2	**83**
H33	H	CH_3	OH	H	NO_2	NO_2	**84**
H34	CH_3	CH_3	OH	H	NO_2	NO_2	**91**
H35	CH_3	CH_3	NO_2	H	NO_2	NO_2	**89**
H36	H	H	NO_2	H	NO_2	NO_2	**91**

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 solvents where the other form crystallizes from polar aprotic solvents. For instance, phenylhydrazone **H23** crystallizes from the 1-propanol reaction mixture as the hydrazone with a double bond between nitrogen and carbon (**H23-CN**). In pure DMSO solution ^{1}H-NMR shows that the solution actually contains this isomer as a major isomer (**Figure IIh.10**). After the addition of trifluoroacetic acid, the nitrogen of the C=N is protonated and equilibrium is shifted toward the enamine form **H23-CC** (**Figure IIh.10**). In the DMSO-CF_3CO_2H solution after one hour **H23-CC** is the only detectable isomer. Similar behavior was observed with other prepared hydrazones.

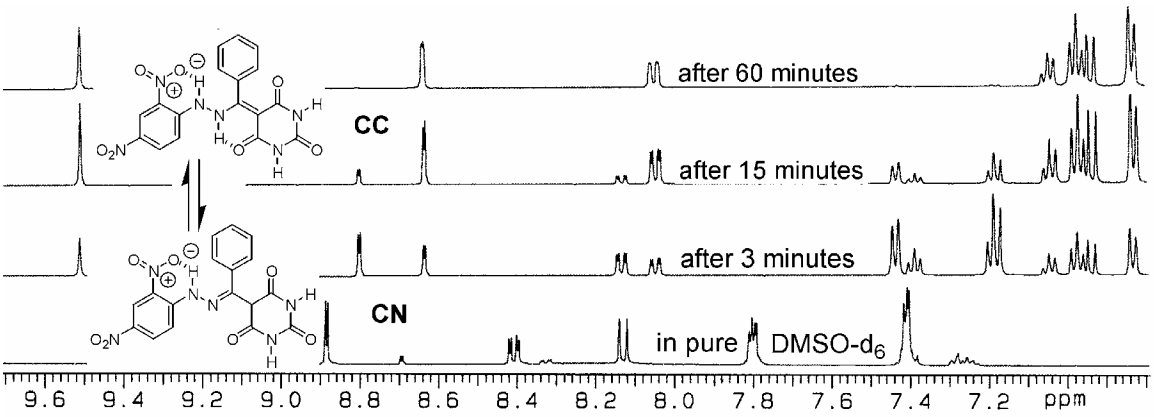


Figure IIh.10: ^{1}H-NMR (500 MHz) isomerization following of **H23-CN** transformation into **H23-CC** in CF_3CO_2H.

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 by increasing the size of the aliphatic or aromatic moieties of 5-benzoylbarbiturates makes these compounds even less water soluble, in order to evaluate the potential 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, therefore preparation of their ammonium salts with secondary amines is 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 (**Figure IIh.11, Table IIh.5**).

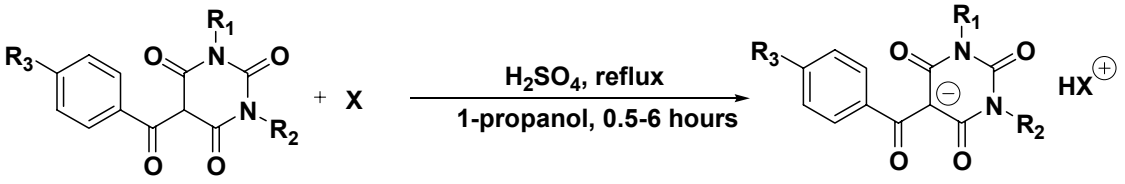


Figure IIh.11: Preparation of substituted ammonium salts of substituted benzoylbarbiturates

Table IIh.5: Ammonium salts of substituted benzoylbarbiturates

Product	**R_1**	**R_2**	**R_3**	**X**	Yield(%)
H37	H	H	H	$HN(CH_2)_5$	**80**
H38	CH_3	H	H	$HN(CH_2)_5$	**95**
H39	H	H	OCH_3	$HN(CH_2)_5$	**88**
H40	CH_3	CH_3	OCH_3	$HN(CH_2)_5$	**93**
H41	H	H	NO_2	$HN(CH_2)_5$	**95**
H42	H	H	NO_2	$HN(CH_2CH_2)_2O$	**90**
H43	H	H	NO_2	$CH_3N(CH_2CH_2)_2O$	**91**
H44	H	H	NO_2	$NH_2CH_2CH_2OH$	**98**
H45	H	H	NO_2	$4\text{-}(CH_3)_2NPy$	**97**
H46	CH_3	CH_3	NO_2	$HN(CH_2)_5$	**92**
H47	CH_3	CH_3	NO_2	$HN(CH_2CH_2)_2O$	**94**
H48	CH_3	CH_3	NO_2	$CH_3N(CH_2CH_2)_2O$	**89**
H49	CH_3	CH_3	NO_2	$NH_2CH_2CH_2OH$	**92**
H50	CH_3	CH_3	NO_2	$4\text{-}(CH_3)_2NPy$	**93**

Similar to benzoylbarbiturates, phenylhydrazones also have low solubility in aqueous media. These compounds are strong carbon acids due to the mobility of hydrogen attached to *C-5* of the barbituric acid moiety of compounds **H19-36**. 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**) **(Figure IIh.12)**.

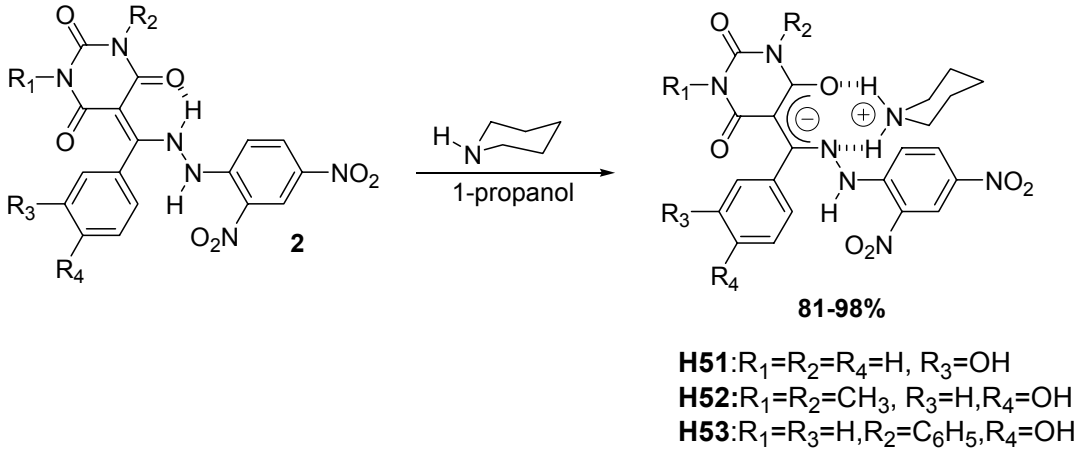


Figure IIh.12: Preparation of piperidinium salts of phenylhydrazones (General Procedure O).

It is very important to emphasize again that both 5-benzoylbarbiturates and their phenylhydrazones can exist in several different tautomeric forms. Therefore, the NMR spectra of the same compound in different solvents can show different ratios of two tautomeric forms, as it was demonstrated in **Figure IIh.13**. To confirm these findings, x-ray structural analysis of **H25** obtained from a 1-propanol solution with a few drops of sulfuric acid was performed (**Figure IIh.14**). According to our NMR spectroscopic studies, hydrazones in acidic polar media should be in an enamine form (**CC**) while in neutral polar media, the Schiff base form (**CN**) should be present, as it was demonstrated on the NMR equilibrium experiment with hydrazone **H25**. Considering this finding, even if hydrazone **H25** is present in its Schiff base **H25-CN** form in neutral solution, in the acidic polar media the enamine isomer **H25-CC** (**Figure IIh.13**) should be a dominate

species. This isomer should also be present in the crystalline state if **H25** is crystallized from 1-propanol with sulfuric acid present.

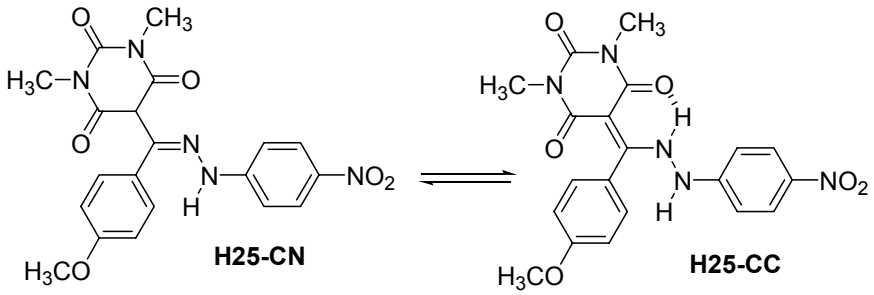


Figure IIh.13: Schiff base **H25-CN** and enamine **H25-CC** tautomeric forms present in solutions.

The x ray structure of **H25** (**Figure IIh.14**) fully confirms our structural assignment based on the NMR spectroscopy. Compound **H25** 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 **H25** are combined through stacking the nitrophenyl and methoxyphenyl moieties of two hydrazones of **H25,** as well as hydrogen bonding between two of these units N9-H-----O66.

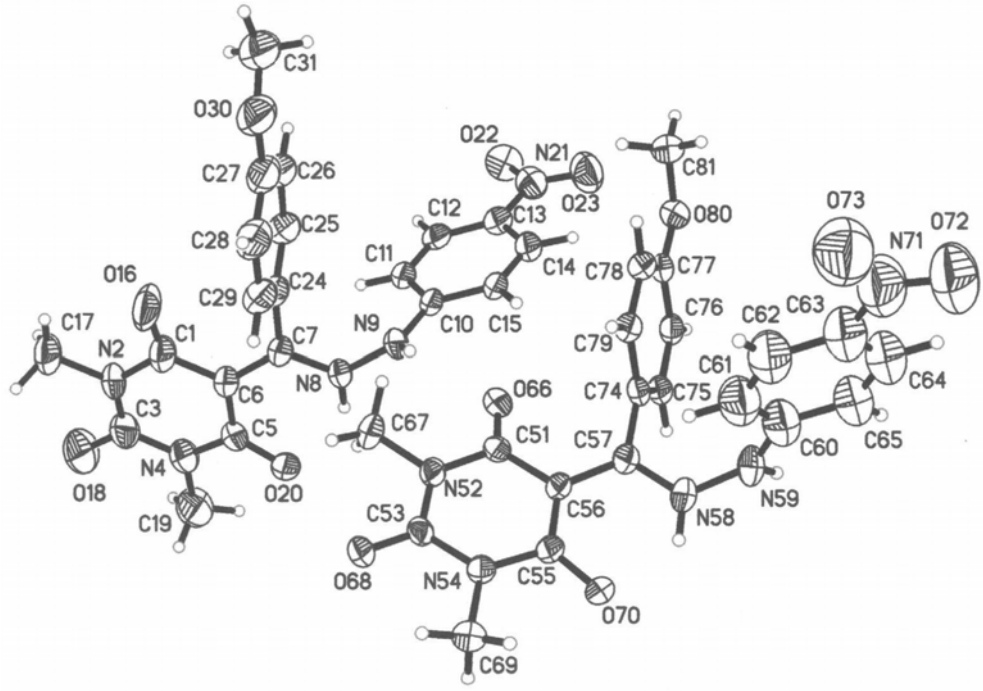


Figure IIh.14: The ORTEP drawing x-ray determined structure of **H25**

The x-ray structure of piperidinium salt **H52** 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 IIh.15**). Hydrogen bonding no longer exists between the nitrogen of the hydrazone moiety and barbituric acid moiety, as in **H25** due to fact that the acidic α-hydrogen of the barbituric acid moiety is removed with piperidene as a base. Negative charge is mostly located on O22 and O26 of the barbituric acid moiety.

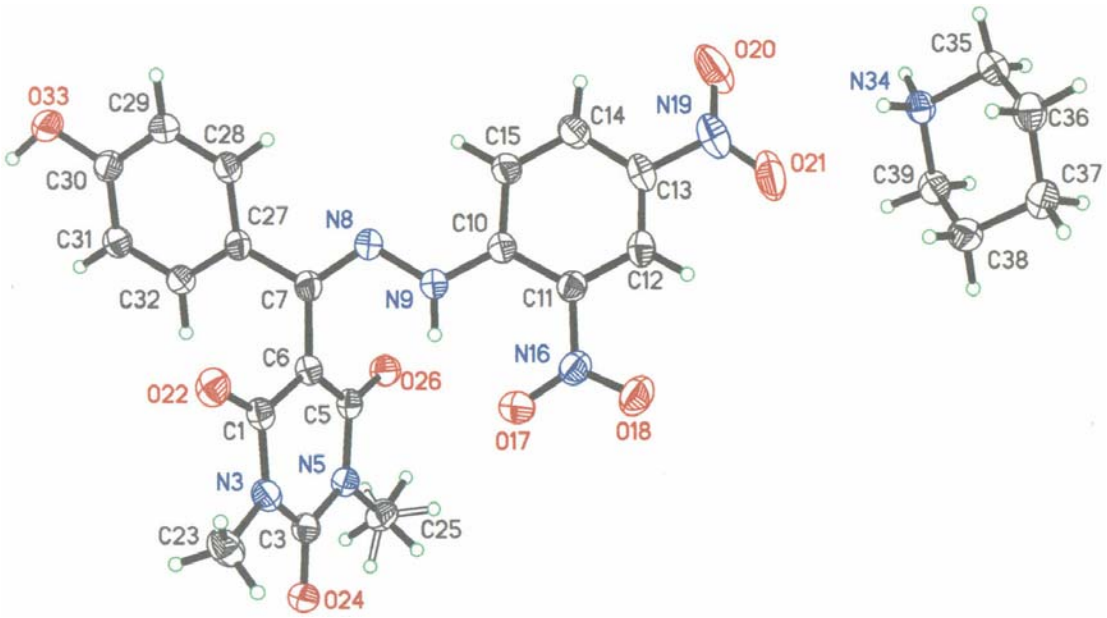


Figure IIh.15: The ORTEP drawing of x-ray determined structure of **H52.**

At this point it is very interesting to compare structural features of **H52** obtained from x-ray experimental data and ones obtained by AM1 semi-empirical modeling of the anion portion of **H52** in the gas phase (**Table IIh.6**). 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 180º, **Table IIh.6**). There is relatively good agreement between experimental and computed structural properties. The biggest discrepancy comes 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 a 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 overestimates the latter one (**Table IIh.6**). 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. 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 **H52** keeps this portion of the molecule in one plane.

Table IIh.6: The X-ray determined and AM1 computed properties for anionic part of **H52** salt

	X-Ray	AM1		X-Ray	AM1
Atoms	Bond distance in Å		Atoms	Bond angles in (º)	
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 (º)	
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

IIi. A Barbituric Acid Initiated Rearrangement Reaction: Formation of 5-5'-(2-pyrilidine)bis barbituric acids

IIi.1 Preamble

While we were able to perform the preparation of a wide variety of 5,5'-(3-pyrilidene) and 5,5'-(4-pyrilidene)bisbarbituric acids and their ammonium salts through the condensation of pyridine carboxaldehydes and the corresponding barbituric acid, the similar condensation between 2-pyridinecarboxaldehyde and 1,3-dimethylbarbituric acid yields a unique pyridinium barbiturate ylide **F1**. Moreover, the desired 5,5'-(2-pyrilidine)bisbarbituric acid analogs were not obtained when either *N,N'*-unsubstituted or N-substituted barbiturates were used as the starting reagents. We were able to obtain the desired bisbarbiturate when dimethylbarbituric acid was used, and the reaction was performed in carbon tetrachloride, but this procedure was not applicable to other barbiturates, nor was it a very practical synthesis for obtaining the desired material in large quantities.

Considering that the 5,5'-(2-pyrilidine)bisbarbiturates could not be prepared by our previously developed methods, we searched for a 2-pyridinecarboxaldehyde synthetic equivalent in order to pursue the preparation of this compound type. In searching the literature, we discovered that in many chemical reactions the phenyl moiety of a molecule can be substituted with pyridine without altering the side chain reaction. We hypothesized that if this is in fact true for benzil (PhCOCOPh), then the corresponding pyridine synthetic equivalent of benzil (PyCOCOPy) could be of use in the preparation of our targeted compounds. There is an abundance of literature reports that indicate that it is possible to transform benzyl benzoates or even benzaldehydes into benzil derivatives.

One example, reported by Zheng *et.al*, demonstrated this with the discovery that *O*-Benzoylbenzaldehyde cyanohydrin was found to form benzil in a base-catalyzed reversible reaction in DMF.[119-120] Examining these reports, we hypothesized that if it is possible to enforce the reverse benzyl reaction of the pyridine synthetic equivalent, then 2,2'-bipyridil should be the logical starting point for this preparation, used as the equivalent of 2-pyridinecarboxaldehyde. It was interesting to note, however, that there was a lack of benzyl-benzylic acid rearrangements in the literature. We believed that this was due to the fact that the base present was too weak to promote the desired rearrangement, but with the addition of a strong base, the desired rearrangement may be possible to enforce.

IIi.2 Results and Discussion

Based on the information provided for the benzil model, the acid catalyzed rearrangement mechanism proposed for the conversion of 2,2'-pyridil into our desired 5,5'-(2-pyrilidene)bisbarbituric acid is presented in **Figure IIi.1**.

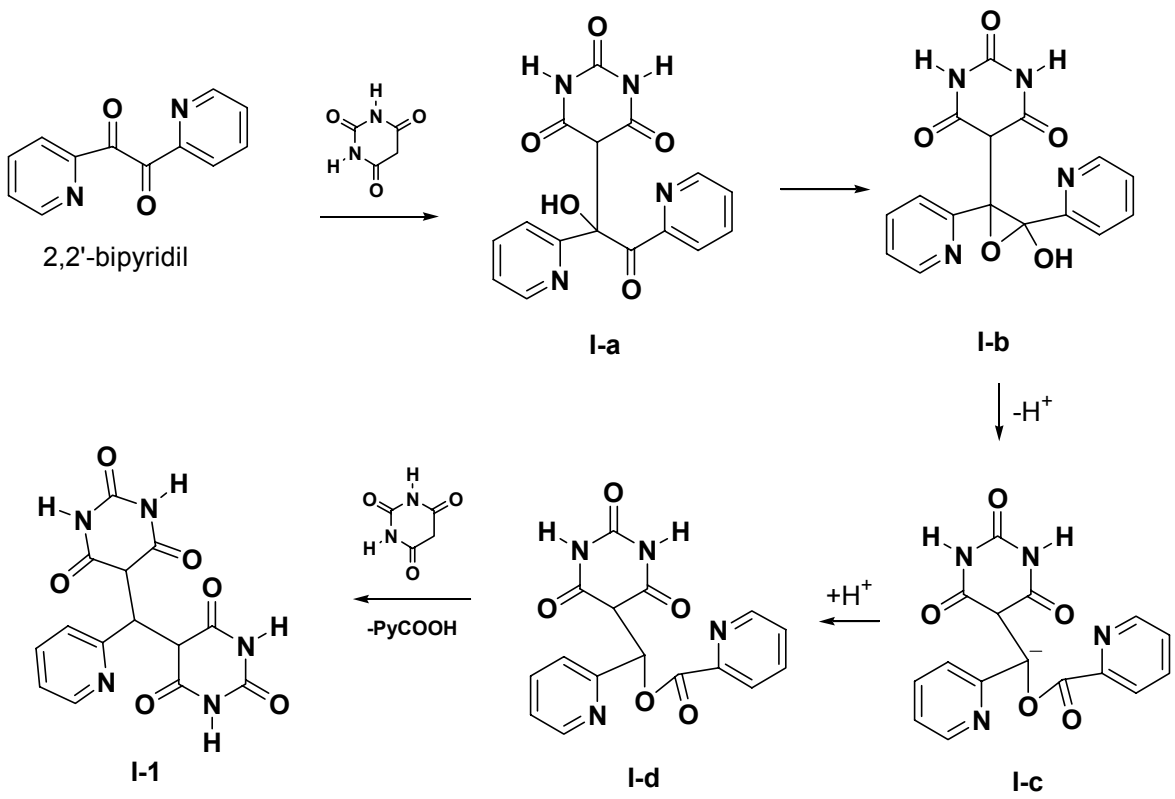


Figure IIi.1: Proposed mechanism for preparation of **I-1**.

It was expected that the most energy demanding transformation would be the rearrangement of keto alcohol **I-a** into ester **I-d**. The third step of the transformation **(I-d to I-1)** would be the nucleophilic substitution by barbituric acid on ester **I-d**. One can envision at least two pathways in the preparation of 5,5'-(2-pyrilidene)bisbarbituric acid; one through the addition of the first barbituric acid, followed by the elimination of picolinic acid and finally the addition of the second barbituric acid; and the other by simple nucleophilic substitution of the picolinic acid moiety of ester **I-d** with barbituric acid. We experimentally determined that depending on the solvent and temperature, both of these reactions can occur. For instance, if the reaction is performed in refluxing methanol, the only product is the product of condensation **I-1** in more than 80% isolated

yield. In our extended time experiment at room temperature, it seemed that the reaction proceeded through either elimination-addition, or the elimination-addition and nucleophilic substitution reactions compete. This determination was based on the fact that from a closed-bottle mixture of 2,2'-pyridil (2mg) and 1,3-dimethylbarbituric acid (5 mg) in 1 mL of methanol, a single crystal was grown after 30 days at room temperature and present in the crystal are both products **F-1** (pyridinium zwitterions) and **I-1** in a ratio of 32:68.

To determine the validity of the mechanism, we followed the reaction through H-NMR spectra recorded at room temperature in various solvents, including methanol, tetrahydrofuran, acetic acid, chloroform, and dimethyl sulfoxide. In DMSO the reaction mixture was solution. In all other solvents a precipitate formed. From this experiment it was obvious that the formation of ester **I-d** was required for a high yield transformation of 2,2'pyridil and barbituric acid into pyrilidene **I-1** and picolinic acid (**Figure IIi.3**). In prolonged DMSO experiments a low field NMR aromatic compound was formed, which was not detected when the preparation of **I-1** was performed in methanol.

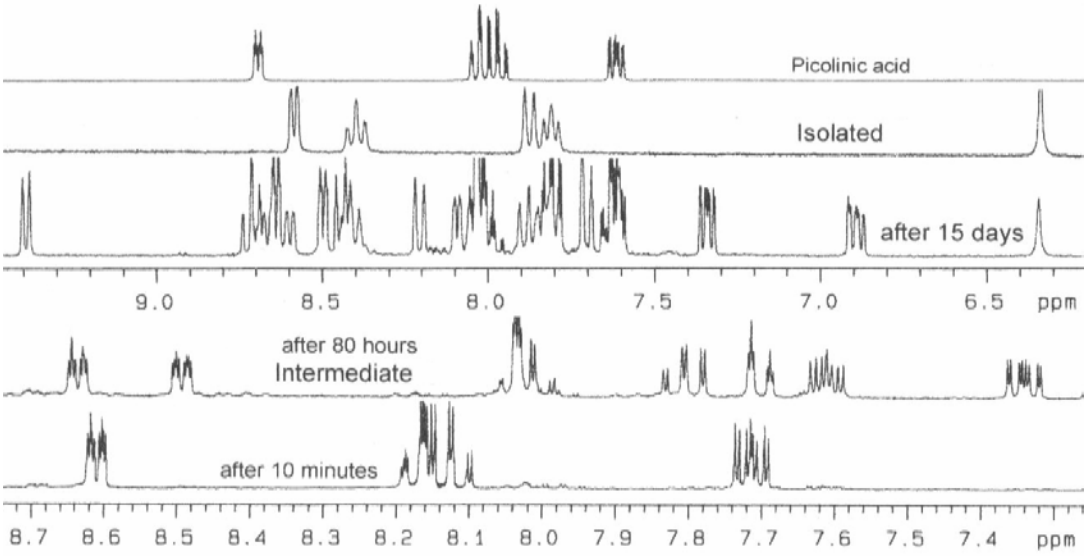


Figure IIi.3: H-NMR (DMSO-d6 -300 MHz Varian Unity) spectra over the course of the reaction time to yield **I-1**.

Finally, to confirm the general applicability of this reaction method in the preparation of a wide variety of 2-pyrilidenes, we used the barbituric acid derivatives 1-phenyl, 1-methyl, 1-butyl, and barbituric acid in itself. In every case, the corresponding **I-1** pyrilidene was isolated in almost quantitative yields. Additionally, we were not able to detect the presence of any other byproducts of the reactions performed through subsequent spectroscopic analysis. Structural properties of **I-1** when R_1 and R_2= CH_3 were determined using x-ray analysis. The single crystal of the **I-1** analog was obtained from slow crystallization in acetic acid, and the structure shows interesting characteristics. In solution, we were unable to determine the location of the 5 and 5' hydrogens. We determined that this was due to the fact that in solution one hydrogen is on the pyridine ring and the other is involved in hydrogen bonding interactions between both barbituric acid rings. In the crystalline state **I-1** has a zwitterionic structure with a

positive charge located on the pyridinium molecule and a negative charge located almost equally on both barbituric acid rings (**Figure IIi.4**). The plane with the pyridinium ring is almost perpendicular to the plane that separates the two barbituric acid rings. The C(1)-C(4) bond distance is 1.365 Å in comparison with the C(1)-C(2) distance of 1.4275 Å, and the C(1)-C(7) distance of 1.5201 Å, indicating a strong double bond character of the first two bonds, and delocalization of the negative charge. All atoms in the ring and the ones attached to the ring are basically in the ring plane, indicating aromaticity.

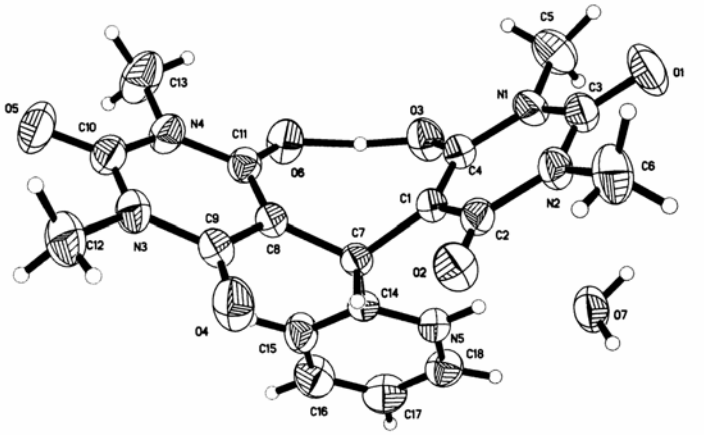


Figure IIi.4: ORTEP drawing of X-ray determined structure of **I-1** *(courtesy of E. D. Stevens and K. L. Martin)***.**

BIOLOGICAL EVALUATIONS OF NOVEL BARBITURATES

IIIa. Introduction

In order to gather preliminary information on the concept that **A-007** and analogs of **A-007** may be binding to a CD45+ surface receptor, or other CD surface receptors, and upgrading dendritic cells and /or T- lymphocytes, we have successfully synthesized and tested a number of phenylhydrazones, all structural analogs of our lead compound, **A-007.** To date, the synthesized compounds were tested *in vitro* on various cell lines to determine if they have the ability to bind to (or up-regulate) surface CD receptors, with cytotoxicity or apoptosis. Structural changes made to **A-007** include changes to the a) bis-diphenyl methane and b) the phenylhydrazone moieties.

IIIb. Biology Methods

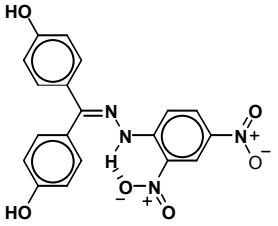
The T-leukemia cell line, HH (CRL-2105), available from ATCC, Manassas, VA ,having the receptors, CD45+, CD3+, CD4+ and CD11C+, all dendritic cell surface CD receptors, was used to screen **A-007** and analogs for up-regulation of CD surface receptor expression, loss of agglutination properties and cell death (**Tables III.1-III.5**). Multicolor immunofluorescence staining and analysis were performed by standard procedures.[20b] Primary and secondary antibodies were conjugated to biotin, fluorescin isothiocyanate (FITC), phyco-erythrin (PE), peridinin-chlorophyl protein or allo-phycocyanin. Antibodies and conjugates for CD3, CD4, CD8, CD11C, CD19, and CD30, were obtained from Becton-Dickinson; CD45 was obtained from PharMingen.

Cells were analyzed using a FACSscan flow cytometer (Becton-Dickinson). HH T-lymphocytic leukemia cells were cultured in RPMI 1640 media (BioCell) supplemented with activated 10% fetal calf serum, 10 mcg/mL streptomycin and 100 U/mL penicillin (Sigma) in a CO_2 incubator at 36º C. All analogs were prepared in DMSO and stored in a 1:15 ratio of DMSO/RPMI1640 media. CD marker assays and standard cytotoxicity/apoptosis studies were conducted in Corning Cell Wells™. Assys involved 10^5 HH-cells incubated with the analogs for 24 hours, cells were removed, washed with RPMI media and analyzed by a BD fluorescent-activated cell sorter. Agglutination was documented using scanning density assays.[20c] Cytotoxicity analysis was conducted using the MTT assay. [20c] Apoptosis was followed with - Annexin V – FITC and fluorescein Fragel DNA kits (Oncogene, Inc, San Diego, CA) and DNA fragmentation/cell death analyzed with a FACScanner.

IIIc. Results and Discussion

Table III.1 reviews toxicity and binding intensity values for the **A-007** molecule. **A-007** prevented HH cells from agglutination, resulting in well-differentiated cells with up-regulation of CD45+ and CD11C+ binding affinities. Apoptosis, or programmed cell death, occurred 12-24 hours post **A-007** exposure, as determined by the DNA fragments detected. The up-regulation of CD receptors varied depending on the structural analogs tested, and are indicated in the data provided in the tables. All biological evaluations were performed by Dr. Lee Roy Morgan and Dekk-Tec, Inc.

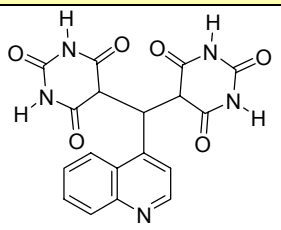
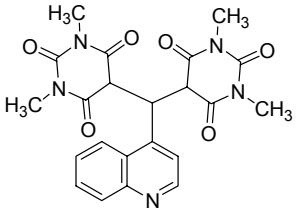
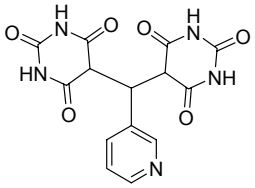
Table III.1: Toxicity and binding intensity values for the **A-007,** our lead compound*.

Compound	**Structure**	**Cytotoxicity IC_{50} μg/mL)**	**Binding Intensity @ 5 μg/mL for CD4+**	**Binding Intensity @ 5 μg/mL CD11C+**	**Binding Intensity @ 5 μg/mL CD45+**
A-007		**3.2**	**[a]NC**	**30%**	**100%**

[a]*Vs* HH leukemia cells. *All *in vitro* evaluations were performed by Lee Roy Morgan through Dekk-Tec, Inc.

Subsequent modification of the bis-diphenyl and the phenylhydrazone moieties, such as replacement of this structural motif with the corresponding bis-barbiturate moiety resulted in loss of activity. The compounds of this type tested and the results obtained are indicated in **Table III.2.**

Table III.2: Anticancer and up-regulation for quinoline and pyridine bis-barbituric acid analogs.[a,]*

Compound	Structure	Cytotoxicity IC_{50} μg/mL)	Binding Intensity @ 5 μg/mL CD4+	Binding Intensity @ 5 μg/mL CD11C+	Binding Intensity @ 5 μg/mL CD45+
E3		**>10**	**[b]NC**	**NC**	**↑25%**
E18		**>10**	**[c]NA**	**NA**	**NA**
E7		**>10**	**NA**	**NA**	**NA**

[a]*Vs* HH leukemia cells; [b]NC – no change in CD; [c]NA – not available. *All *in vitro* evaluations were performed by Lee Roy Morgan through Dekk-Tec, Inc.

The replacements of **A-007**'s bis-diphenyl rings with a barbituric acid moiety with retention of nitrophenylhydrazone moiety resulted in some retention of activity, but no surface CD up-regulation was noted. The compounds belonging to this class of analogs tested are presented in

the following table (**Table III.3**). These analogs utilized the 5-formyl and acetyl barbiturate analogs as well as some benzoyl analogs.

Table III.3: Anticancer and up-regulation for formyl and acetylbarbituric phenylhydrazone analogs.[a,*]

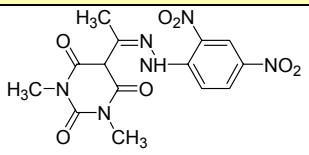
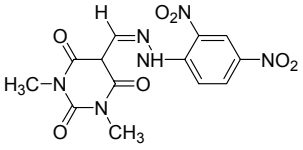
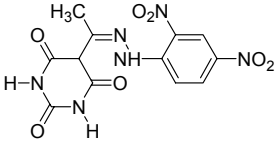
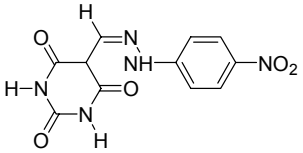
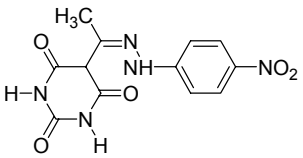
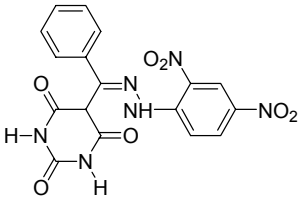
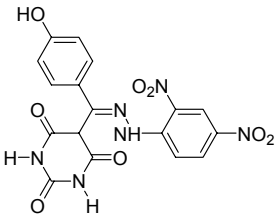
Compound	**Structure**	**Cytotoxicity IC_{50} µg/mL)**	**Binding Intensity @ 5 µg/mL CD4+**	**Binding Intensity @ 5 µg/mL CD11C+**	**Binding Intensity @ 5 µg/mL CD45+**
D25		**>10**	**[b]NA**	**NC**	**NA**
		**>8**	**NA**	**NA**	**NA**
D21		**3.5**	**[c]NC**	**NC**	**NC**
D14		**>6**	**NC**	**NC**	**NC**
D20		**>10**	**NC**	**NC**	**NC**

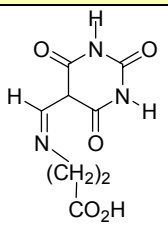
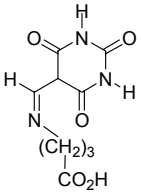
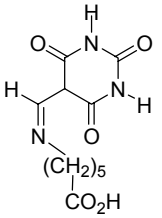
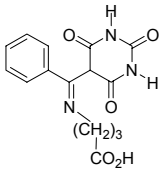
Table III.3 continued…

H23		**>10**	**NC**	**NC**	**NC**
H28		**>10**	**NC**	**NC**	**NC**

[a]*Vs* HH leukemia cells; [b]NC – no change in CD; [c]NA – not available. *All *in vitro* evaluations were performed by Lee Roy Morgan through Dekk-Tec, Inc.

Further modifications that consisted of the elimination of the phenylhydrazone moiety (**Table III.4)** provided at least one analog with equivalent properties to **A-007**. **Table III.4** reviews Schiff base analogs of barbituric acids that have been prepared and screened. Analog **D8** is a very encouraging lead that also has slight (~25%) binding with CD45+. Similarly, effects on cell agglutination, but with less apoptosis (25% *vs* 100% for **A-007**) were noted.

Table III.4: Anticancer and up-regulation for formylbarbituric acid Schiff base analogs.[a,]*

Compound	Structure	Cytotoxicity IC_{50} µg/mL)	Binding Intensity @ 5 µg/mL CD4+	Binding Intensity @ 5 µg/mL CD11C+	Binding Intensity @ 5 µg/mL CD45+
D13		**>12**	**[b]NC**	**NC**	**NC**
D8		**3.5**	**NC**	**NC**	**↑25%**
D9		**>10**	**NC**	**NC**	**NC**
		**>10**	**NC**	**NC**	**NC**

[a]*Vs* HH leukemia cells; [b]NC – no change in CD. *All *in vitro* evaluations were performed by Lee Roy Morgan through Dekk-Tec, Inc.

To date, no analog with improved immune modulating activity over **A-007,** which includes apoptosis without direct cytotoxicity, has been identified. In designing these potential cell surface modulators, the new products cannot be cytotoxic to the point of the therapeutic index being surpassed.[121, 122] Based on our initial screenings of these compounds, the biological properties for some of the described simple analogs appeared to be associated with modulation which resulted in programmed cell death. This is in contrast to previously described analogs containing fused ring systems, such as anthracenes, xanthenes, thioxanthenes, fluorenes and phthalazenes. In these cases, only intracellular changes occurred with immediate cancer cell death, as well as toxicity to normal tissues.[121] **A-007**'s –NH moiety could be involved in intramolecular –H---O= bonding, which would cause it to have little reactivity with any cell surface receptors.[18] As a result, **A-007** and its active analogs may be initiating the CD4+/8+ T-cell cascade *via* up-regulation of the CD45+ receptor at the level of antigen presenting cells (APC).[16-17] The potential use of the immune modulating properties of these compounds in malignant, as well as infectious disease processes, is encouraging.

It appears that in order for the CD45+ up-regulation to occur, several structural features must be present within the phenylhydrazones molecule. At least one NO_2 moiety, or an isostere of this moiety, such as a pyridine ring, appears necessary for up-regulation. In the absence of these groups, compounds containing the COOH moiety, also elicit CD45+ up-regulation, lending to the fact that at least one strong electron-deficient moiety is necessary for activity.

CONCLUSIONS

Through the synthetic explorations described in the previous chapters, we have made available a new class of compounds containing the barbituric acid moiety as a functional moiety that could potentially elicit histone deacetylase inhibition, immune modulation, apoptotic effects on various cancer cell lines. Our hypothesis that barbituric acids could replace the hydroxamic acid moieties of potent HDACI's is currently being investigated. While the *in vitro* biological evaluations are still underway for a large number of these derivatives, we have successfully synthesized several novel barbituric acid derivatives that do act as CD45+ up-regulators, or as compounds with a therapeutic index within the range of several other potent drugs, such as **A-007,** which are currently undergoing clinical trials.

Through the course of our synthetic preparations, several new and interesting molecular systems were designed, studied, and explained. These systems include the 5,5'-barbituric acid initiated rearrangement reactions, as well as the preparation of the novel pyridinium-barbituric acid zwitterions. Spectroscopic studies evaluating the physical properties, as well as reaction mechanisms were performed to enable us to outline synthetic procedures that could be performed in the multi-gram quantities, or that could be easily adapted to industrial applications should our target molecules show promise after subsequent *in vitro* evaluation.

Our target molecules were identified as either histone deacetylase inhibitors, modeled after the successful HDACIs SAHA and PCHA, or as immune modulators,

modeled after the potent drug **A-007.** All targets containing the barbiturate moiety were successfully synthesized. While not all tested compounds proved active, valuable research was performed surrounding the synthesis of these analogs, enabling future scientists to find other potential uses for either the compounds designed or the reactions performed.

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EXPERIMENTALS

All solvents and starting materials in this synthesis were obtained from Aldrich and used without further purification. Thin-layer chromatography was performed using plastic-based 0.25 mm thick silica gel 60 F-254 plates (E. Merc, Inc.). All ^{1}H and ^{13}C NMR are recorded in DMSO-d_6 on a Gemini 2000 Varian instrument with the chemical shift of the solvent at 2.49 and 36.0 ppm as referenced in hydrogen and carbon NMR spectra. All DMSO-d_6 samples were clear solutions. The CF_3COOH samples contained a few drops of DMSO-d_6 as an internal reference and part of barbituric acid was not in the solution. All 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. The ES-MS parameters (i.e., pressure, temperature, and voltage on the needle, etc.) were kept constant in each series of solutions. A flow rate of 10 μL/min was applied using 100 μL of sample solution. Elemental analyses were performed by Atlantic Microlab, Inc. X-ray structure determination was performed on a Bruker SMART 1KCCD automated diffractometer.

General Procedure A:

Synthesis of 5-(4-Dimethylamino-benzylidene)-pyrimidine-2,4,6-trione (A1)

A mixture of barbituric acid (12.8 g; 0.1 mol) and 4-(dimethylamino)benzaldehyde (14.9 g; 0.1 mol) in methanol (500 mL) were stirred at room temperature. After a few minutes the solution became a suspension, and the color of solid went from yellow to dark purple. The suspension was allowed to stir at room temperature overnight. The solid product was separated by filtration and washed with cold methanol (3×50 mL). The isolated yield was 35.4 g (98%). An analytical sample after drying in vacuum had m.p. 277º C with decomposition; lit. m.p. 275º C with decomposition. IR (KBr) 3095-3080, 1700, 1640, 1500, cm^{-1}. ^{1}H-NMR (DMSO-d_6-400 MHz Varian Unity) δ 11.04 (s, 1H, NH), 10.91 (s, 1H, NH), 8.42 (d, *J*= 12.4 Hz, 2H, Ar), 8.13 (s, 1H, CH), 6.78 (d, *J*= 12.4 Hz, 2H, Ar), 3.11 (s, 6H, $N(CH_3)_2$). ^{13}C-NMR (DMSO-d_6-400 MHz Varian Unity) δ 161.2, 159.2, 152.0, 150.7, 146.8, 135.6, 116.5, 107.7, 106.0, and 38.0 ppm. MS (CI^+-NH_3) 259 (5%, M^+) 215 (100%), 172 (96%), 166 (11%), 144 (7%), 128 (18%), 101 (15%). *Anal.* Calcd. For $C_{13}H_{13}N_3O_3$: C, 60.23: H, 5.05; N, 16.21. Found: C, 60.11; H, 5.13; N, 16.08.

Synthesis of 5-(3-Phenyl-allylidene)-pyrimidine-2,4,6-trione (A2)

A mixture of barbituric acid (1.28 g; 0.01 mol) and *trans*-cinnamaldehyde (1.32 g; 0.01 mol) in methanol (100 mL) were stirred at room temperature. After a few minutes the solution became a suspension, and the color of solid went from white to yellow. The suspension was allowed to stir at room temperature overnight. The solid product was separated by filtration and washed with cold methanol (3×20 mL). The isolated yield

was 2.30 g (95%). An analytical sample after drying in vacuum had m.p. 260º C with decomposition. ^{1}H-NMR (DMSO-d_6-400 MHz Varian Unity) δ 11.27 (s, 1H, NH), 11.20 (s, 1H, NH), 8.42 (m, 1H, CH), 7.99 (d, *J*= 11.4, 1H, CH), 7.65 (m, 3H), 7.45 (m, 3H) ppm. ^{13}C-NMR (DMSO-d_6-400 MHz Varian Unity) δ 159.6, 159.4, 150.1, 149.1, 146.8, 131.8, 127.6, 125.7, 125.0, 120.7, and 112.2 ppm. MS (ESI^-) in methanol: 241 (50%, M-1), 273 (100%, M+MeOH).

Synthesis of 5-[3-(4-Dimethylamino-phenyl)-allylidene]-pyrimidine-2,4,6-trione (A3)

A mixture of barbituric acid (1.28 g; 0.01 mol) and 4-amino-*trans*-cinnamaldehyde (1.75 g; 0.01 mol) in methanol (100 mL) were stirred at room temperature. After a few minutes the solution became a suspension, and the color of solid went from yellow to dark purple. The suspension was allowed to stir at room temperature overnight. The solid product was separated by filtration and washed with cold methanol (3×20 mL). The isolated yield was 2.82 g (99%). An analytical sample after drying in vacuum had m.p. 250º C. ^{1}H-NMR (DMSO-d_6-400 MHz Varian Unity) δ 11.01 (s, 1H, NH), 10.95 (s, 1H, NH), 8.19 (m, 1H, CH), 7.94 (d, *J*= 16.8 Hz, 1H, CH), 7.59 (d, *J*= 19.6 Hz, 1H, CH), 7.51 (d, *J*= 11.6 Hz, 2H, Ar), 6.76 (d, *J*= 12.0, 2H, Ar), 3.02 (s, 6H, $N(CH_3)_2$). ^{13}C-NMR (DMSO-d_6-400 MHz Varian Unity) δ 161.2, 159.7, 152.3, 150.9, 146.6, 131.1, 126.8, 125.5, 125.0, 119.9, and 112.1 ppm.

Synthesis of 5-(4-Hydroxy-benzylidene)-pyrimidine-2,4,6-trione (A4)

A mixture of barbituric acid (1.28 g; 0.01 mol) and 4-hydroxybenzaldehyde (1.22 g; 0.01 mol) in methanol (100 mL) were stirred at room temperature. After a few minutes the solution became a suspension, and the color of solid went from white to yellow. The suspension was allowed to stir at room temperature overnight. The solid product was separated by filtration and washed with cold methanol (3×20 mL). The isolated yield was 2.20 g (95%). An analytical sample after drying in vacuum had m.p. 280º C with decomposition. ^{1}H-NMR (DMSO-d_6-400 MHz Varian Unity) δ 11.24 (s, 1H, NH), 11.11 (s, 1H, NH), 10.81 (s, 1H, OH), 8.31 (d, J= 8.8 Hz, 2H, Ar), 8.19 (s, 1H, CH), 6.86 (d, J= 8.8 Hz, 2H, Ar). ^{13}C-NMR (DMSO-d_6-400 MHz Varian Unity) δ 164.6, 163.4, 162.7, 155.9, 150.7, 138.7, 124.2, 115.9, and 114.6 ppm. MS (ESI$^-$) in methanol: 231 (100%, M-1), 263 (45%, M+MeOH).

General Method B:

Synthesis of 5-Furan-2-ylmethylene-pyrimidine-2,4,6-trione (A5)

A mixture of barbituric acid (1.28 g; 0.01 mol) and 2-furaldehyde (0.96 g; 0.01 mol) in methanol (150 mL) was stirred at room temperature for 5 days. Methanol was evaporated at room temperature under reduced pressure. The solid residue was slurred in cold water (100 mL), stirred for 2 hours and then the solid residue was separated by filtration. The crystalline product was washed with cold water (3×50 mL) and then slurred in ether After the second filtration, crystalline material was washed with ether (3×20 mL) and dried in the air, resulting in a pure yellow crystalline product (1.67 g; 81%). An analytical sample after drying in vacuum had a m.p. 264º C with

decomposition. The reported literature melting point is 260º C with decomposition. IR (KBr) 3520-3480, 1730, 1690, 1645, 1615-1590, 1560-1530 cm^{-1}. ^{1}H-NMR (DMSO-d_6 - 400 MHz Varian Unity) δ 11.35 (s, 1H, NH), 11.26 (s, 1H, NH), 8.45 (d, *J*= 3.6 Hz, 1H, Ar), 8.24 (s, 1H, CH), 8.01 (s, 1H, Ar), 6.90 (d, *J*= 2.4 Hz, 1H, Ar) ppm. ^{13}C-NMR (DMSO-d_6 -400 MHz Varian Unity) δ 159.8, 158.6, 147.7, 133.4, 123.0, 111.8, and 109.3 ppm. *Anal.* Calcd. . For $C_9H_6N_2O_4$: C, 52.44; H, 2.93; N, 13.59. Found: C, 52.36; H, 3.07; N, 13.40.

Synthesis of 5-Benzylidene-pyrimidine-2,4,6-trione (A6)

A mixture of barbituric acid (1.28 g; 0.01 mol) and benzaldehyde (1.06 g; 0.01 mol) in methanol (150 mL) was stirred at room temperature for 5 days. Methanol was evaporated at room temperature under reduced pressure. The solid residue was slurred in cold water (100 mL), stirred for 2 hours and then the solid residue was separated by filtration. The crystalline product was washed with cold water (3×50 mL) and then slurred in ether After the second filtration, crystalline material was washed with ether (3×20 mL) and dried in the air, resulting in a pure yellow crystalline product (1.84 g; 85%). An analytical sample after drying in vacuum had m.p. 250º C with decomposition. The reported literature melting point is 250º C with decomposition. ^{1}H-NMR (DMSO-d_6 -400 MHz Varian Unity) δ 11.39 (s, 1H, NH), 11.23 (s, 1H, NH), 8.27 (s, 1H, CH), 8.06 (d, *J*= 6.6 Hz, 2H, Ar), 7.52 (t, *J*= 4.8 Hz, 1H, Ar), 7.45 (t, *J*= 8.2, 2H, Ar). ^{13}C-NMR (DMSO-d_6 -400 MHz Varian Unity) δ 159.9, 158.1, 151.2, 146.7, 129.6, 129.2, 124.6, and 115.6 ppm. MS (ESI^-) in methanol 172 (10%), 215 (75%, M-1), 247 (100%, M+MeOH).

Synthesis of 5-Naphthalen-2-ylmethylene-pyrimidine-2,4,6-trione (A7)

A mixture of barbituric acid (1.28 g; 0.01 mol) and naphthaldehyde (1.56 g; 0.01 mol) in methanol (100 mL) were stirred at room temperature. After a few minutes the solution became a suspension, and the color of solid went from white to yellow. The suspension was allowed to stir at room temperature overnight. The solid product was separated by filtration and washed with cold methanol (3×20 mL). The isolated yield was 2.20 g (**83%**). An analytical sample after drying in vacuum had m.p. 250º C with decomposition. ^{1}H-NMR (DMSO-d_6-400 MHz Varian Unity) δ 11.46 (s, 1H, NH), 11.17 (s, 1H, NH), 8.78 (s, 1H, CH), 8.01 (m, 2H, Ar), 7.84 (m, 2H, Ar), 7.56 (m, 3H, Ar) ppm. ^{13}C-NMR (DMSO-d_6-400 MHz Varian Unity) δ 163.4, 161.5, 152.1, 150.8, 133.1, 131.5, 131.1, 129.2, 128.8, 127.5, 126.8, 125.4, 124.8, and 122.4 ppm. MS (ESI$^-$) in methanol 265 (M-1), 297 (100%, M+MeOH)

Synthesis of 5-(2,4-Dihydroxy-benzylidene)-pyrimidine-2,4,6-trione (A8)

A mixture of barbituric acid (1.28 g; 0.01 mol) and 2,4-dihydroxybenzaldehyde (1.38 g; 0.01 mol) in methanol (150 mL) was stirred at room temperature for 36 h. Methanol was evaporated at room temperature under reduced pressure. The solid residue was slurred in cold water (100 mL), stirred for 2 hours and then the solid residue was separated by filtration. The crystalline product was washed with cold water (3×50 mL) and then slurred in ether After the second filtration, crystalline material was washed with ether (3×20 mL) and dried in the air, resulting in a pure yellow crystalline product (2.11 g, 85%). An analytical sample after drying in vacuum had a m.p. 264º C with decomposition. ^{1}H-NMR (DMSO-d_6-400 MHz Varian Unity) δ 11.10 (s, 1H, NH),

10.96 (s, 1H, NH), 10.80 (broad s, 2H, OH), 8.75 (s, 1H, CH), 8.71 (d, *J*= 9.2 Hz, 1H, Ar), 6.38 (d, *J*= 2.0 Hz, 1H, Ar), 6.30 (d, *J*= 11.6 Hz, 1H, Ar) ppm. ^{13}C-NMR (DMSO-d_6-400 MHz Varian Unity) δ 162.1, 161.1, 159.8, 159.1, 146.8, 146.3, 132.7, 108.8, 107.9, 104.5, and 97.9 ppm. MS (ESI^-) in methanol: 247 (M-1).

Synthesis of 5-(1H-Indol-2-ylmethylene)-pyrimidine-2,4,6-trione (A9)

A mixture of barbituric acid (1.28 g; 0.01 mol) and 2-indolecarboxaldehyde (1.45 g; 0.01 mol) in methanol (150 mL) was stirred at room temperature for 36 h. Methanol was evaporated at room temperature under reduced pressure. The solid residue was slurred in cold water (100 mL), stirred for 2 hours and then the solid residue was separated by filtration. The crystalline product was washed with cold water (3×50 mL) and then slurred in ether. After the second filtration, crystalline material was washed with ether (3×20 mL) and dried in the air, resulting in a pure yellow crystalline product of 2.44 g, (96%) yield. An analytical sample after drying in vacuum had a m.p. 260º C with decomposition. ^{1}H-NMR (DMSO-d_6-400 MHz Varian Unity) δ 12.71 (s, 1H, NH), 11.10 (s, 1H, NH), 11.02 (s, 1H, NH), 9.48 (s, 1H, CH), 8.69 (s, 1H, Ar), 7.85 (d of d, J_1= 4.0 Hz, J_2= 8.0 Hz, 1H, Ar), 7.56 (d of d, J_1= 4.0 Hz, J_2= 8.0 Hz, 1H, Ar), 7.29 (d of d, J_1= 8.4 Hz, J_2= 2.4 Hz, 2H, Ar). ^{13}C-NMR (DMSO-d_6-400 MHz Varian Unity) δ 161.0, 159.7, 146.9, 140.2, 136.2, 132.9, 125.6, 120.1, 119.1, 114.1, 109.6, 107.9, and 105.1 ppm. MS (CI^+) 256 (100%, M^+), 145 (10%), 130 (40%), 118 (45%), 79 (5%).

Synthesis of 5-(2-Hydroxy-benzylidene)-pyrimidine-2,4,6-trione (A10)

A mixture of barbituric acid (1.28 g; 0.01 mol) and 2-hydroxybenzaldehyde (1.22 g; 0.01 mol) in methanol (150 mL) was stirred at room temperature for 36 h. Methanol was evaporated at room temperature under reduced pressure. The solid residue was slurred in cold water (100 mL), stirred for 2 hours and then the solid residue was separated by filtration. The crystalline product was washed with cold water (3×50 mL) and then slurred in ether. After the second filtration, crystalline material was washed with ether (3×20 mL) and dried in the air, resulting in a pure yellow crystalline product of 1.85 g, (80%) yield. An analytical sample after drying in vacuum had a m.p. 230º C with decomposition. ^{1}H-NMR (DMSO-d_6-400 MHz Varian Unity) δ 11.29 (s, 1H, NH), 11.12 (s, 1H, NH), 10.61 (s, 1H, OH), 8.60 (s, 1H, CH), 8.14 (d, *J*= 10.4 Hz, 1H, Ar), 7.35 (t, *J*= 10 Hz, 1H, Ar), 6.91 (d, *J*= 11.2 Hz, 1H, Ar), 6.80 (t, *J*= 10 Hz, 1H, Ar) ppm. ^{13}C-NMR (DMSO-d_6-400 MHz Varian Unity) δ 160.2, 158.2, 155.4, 146.8, 131.1, 129.2, 116.3, 114.7, 113.6, and 111.9 ppm. MS (ESI$^-$) in methanol: 231 (M-1).

General Procedure C:

1,3-Dimethyl-5-(2,4,6-trimethoxy-benzylidene)-pyrimidine-2,4,6-trione (A11)

A mixture of 1,3-dimethylbarbituric acid (1.56 g; 0.01 mol) and 2,4,6-trimethyoxybenzaldehyde (1.98 g; 0.01 mol) in methanol (150 mL) with 2 drops sulfuric acid was stirred at room temperature for 12 h. Methanol was evaporated at room temperature under reduced pressure. The solid residue was slurred in cold water (100 mL), stirred for 2 hours and then the solid residue was separated by filtration. The crystalline product was washed with cold water (3×50 mL) and then slurred in ether (20

mL). After the second filtration, crystalline material was washed with ether (3×10 mL) and dried in the air, resulting in a pure crystalline product of 2.72 g (81%) yield. An analytical sample after drying in vacuum had a m.p. 200º C with decomposition. ^{1}H-NMR (DMSO-d_6-500 MHz Varian Unity) δ 8.71 (s, 1H, CH), 8.45 (s, 1H, Ar), 6.65 (s, 1H, Ar), 3.90 (s, 6H, OCH_3), 3.71 (s, 3H, OCH_3), 3.16 (s, 3H, CH_3), 3.14 (s, 3H, CH_3) ppm. ^{13}C-NMR (DMSO-d_6-500 MHz Varian Unity) δ 159.4, 157.4, 154.7, 152.9, 147.6, 146.0, 138.0, 112.3, 109.7, 109.2, 92.6, 53.2, 52.6, 52.3, 25.0, and 24.5 ppm.

Synthesis of 1,3-Dimethyl-5-(2,3,4-trimethoxy-benzylidene)-pyrimidine-2,4,6-trione (A12)

A mixture of 1,3-dimethylbarbituric acid (1.56 g; 0.01 mol) and 2,3,4-trimethyoxybenzaldehyde (1.98 g; 0.01 mol) in methanol (150 mL) with 2 drops sulfuric acid was stirred at room temperature for 12 h. Methanol was evaporated at room temperature under reduced pressure. The solid residue was slurred in cold water (100 mL), stirred for 2 hours and then the solid residue was separated by filtration. The crystalline product was washed with cold water (3×50 mL) and then slurred in ether (20 mL). After the second filtration, crystalline material was washed with ether (3×10 mL) and dried in the air, resulting in a pure orange crystalline product of 2.65 g (79%) yield. An analytical sample after drying in vacuum had m.p. 200º C with decomposition. ^{1}H-NMR (DMSO-d_6-500 MHz Varian Unity) δ 8.52 (s, 1H, CH), 8.22 (d, J= 8.5 Hz, 1H, Ar), 6.89 (d, J= 9.5 Hz, 1H, Ar), 3.89 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 3.19 (s, 3H, CH_3), 3.16 (s, 3H, CH_3) ppm. ^{13}C-NMR (DMSO-d_6-500 MHz

Varian Unity) δ 158.9, 156.9, 154.6, 151.5, 147.5, 146.7, 137.1, 125.6, 115.4, 112.6, 103.5, 58.4, 56.9, 52.7, 25.0, and 24.4 ppm.

Synthesis of 5-(4-Hydroxy-benzylidene)-1,3-dimethyl-pyrimidine-2,4,6-trione (A13)

A mixture of 1,3-dimethylbarbituric acid (1.56 g; 0.01 mol) and 4-hydroxybenzaldehyde (1.22 g; 0.01 mol) in methanol (150 mL) with 2 drops sulfuric acid was stirred at room temperature for 12 h. Methanol was evaporated at room temperature under reduced pressure. The solid residue was slurred in cold water (100 mL), stirred for 2 hours and then the solid residue was separated by filtration. The crystalline product was washed with cold water (3×50 mL) and then slurred in ether (20 mL). After the second filtration, crystalline material was washed with ether (3×10 mL) and dried in the air, resulting in a pure orange crystalline product of 2.08 g (80%) yield. An analytical sample after drying in vacuum had m.p. 180º C with decomposition. ^{1}H-NMR (DMSO-d_6-500 MHz Varian Unity) δ 10.80 (s, 1H, OH), 8.26 (d, J= 8.5 Hz, 2H, Ar), 8.22 (s, 1H, CH), 6.85 (d, J= 10 Hz, 2H, Ar), 3.18 (s, 3H, CH3), 3.16 (s, 3H, CH_3) ppm. ^{13}C-NMR (DMSO-d_6-500 MHz Varian Unity) δ 163.8, 163.3, 161.4, 157.0, 151.7, 138.9, 124.4, 116.1, 114.4, 29.2, and 28.6 ppm. MS (ESI^-) in methanol: 259 (M-1).

Synthesis of 5-(2,4-Dihydroxy-benzylidene)-1,3-dimethyl-pyrimidine-2,4,6-trione (A14)

A mixture of 1,3-dimethylbarbituric acid (1.56 g; 0.01 mol) and 2,4-dihydroxybenzaldehyde (1.38 g; 0.01 mol) in methanol (150 mL) with 2 drops sulfuric acid was stirred at room temperature for 12 h. Methanol was evaporated at room temperature under reduced pressure. The solid residue was slurred in cold water (100

mL), stirred for 2 hours and then the solid residue was separated by filtration. The crystalline product was washed with cold water (3×50 mL) and then slurred in ether (20 mL). Material was washed with ether (3×10 mL) and dried in the air, resulting in a pure orange crystalline product of 2.18 g (79%) yield. An analytical sample after drying in vacuum had m.p. 220º C with decomposition. ^{1}H-NMR (DMSO-d_6-500 MHz Varian Unity) δ 10.80 (s, 1H, OH), 10.68 (s, 1H, OH), 8.78 (s, 1H, CH), 8.63 (d, *J*= 11 Hz, 1H, Ar), 6.37 (s, 1H, Ar), 6.28 (d, *J*= 11.5 Hz, 1H, Ar), 3.14 (s, 3H, CH_3), 3.11 (s, 3H, CH_3) ppm. ^{13}C-NMR (DMSO-d_6-500 MHz Varian Unity) δ 162.3, 160.1, 159.7, 157.5, 147.7, 147.3, 132.6, 109.0, 107.5, 104.5, 97.9, 25.0, and 24.4 ppm. MS (CI^{+}-NH_3) 277 (70%, M+1), 261 (75%), 139 (30%), 96 (95%), 79 (100%).

Synthesis of 1,3-Dimethyl-5-(3-phenyl-allylidene)-pyrimidine-2,4,6-trione (A15)

A mixture of 1,3-dimethylbarbituric acid (1.56 g; 0.01 mol) and *trans*-cinnamaldehyde (1.32 g; 0.01 mol) in methanol (150 mL) with 2 drops sulfuric acid was stirred at room temperature for 12 h. Methanol was evaporated at room temperature under reduced pressure. The solid residue was slurred in cold water (100 mL), stirred for 2 hours and then the solid residue was separated by filtration. The crystalline product was washed with cold water (3×50 mL) and then slurred in ether (20 mL). After the second filtration, crystalline material was washed with ether (3×10 mL) and dried in the air, resulting in a pure orange crystalline product of 2.20 g (81%) yield. An analytical sample after drying in vacuum had m.p. 200º C with decomposition. ^{1}H-NMR (DMSO-d_6-500 MHz Varian Unity) δ 8.44 (m, 1H, CH), 8.06 (d, *J*= 15.6, 1H, CH), 7.73 (d, *J*= 20.8 Hz, 1H, CH), 7.66 (m, 2H, Ar), 7.46 (t, *J*= 3.8 Hz, 3H, Ar), 3.18 (s, 6H, CH_3) ppm.

^{13}C-NMR (DMSO-d_6-500 MHz Varian Unity) δ 158.1, 157.8, 150.8, 149.4, 147.5, 131.6, 127.6, 125.6, 125.0, 120.7, 111.8, 24.7, and 24.2 ppm.

General Procedure D: Preparation of mono C-alkylated barbituric acids with aliphatic aldehydes and ketones

Synthesis of 5-isopropyl-1-phenylbarbituric acid (B1)

A suspension of 1-phenylbarbituric acid (2.04 g, 10.0 mmol) and 5% Pt-C with 50% water (0.200 g) in acetone (30 mL) and acetic acid (100 mL) was hydrogenated under hydrogen pressure of 50 psi for ~20 hours. The catalyst was separated by filtration, the filtrate was evaporated to an oily residue and benzene (3×50 mL) was added successively and evaporated to eliminate residue of acetic acid to give racemic 5-isopropyl-1-phenylbarituric acid (2.35 g, 96%). Product decomposes at temperatures above 200º C. ^{1}H-NMR (DMSO-d_6-500 MHz Varian Unity): δ 11.58 (1H, s, NH), 7.43 (3H, m) 7.22 (2H, d, J= 8.1 Hz), 3.41 (1H, d, J= 3.9 Hz) 2.48 (1H, m), 1.08 (6H, d, J= 5.7 Hz) ppm. ^{13}C-NMR (DMSO-d_6-500 MHz Varian Unity): δ 165.6, 165.4, 147.3, 131.2, 125.2, 125.2, 125.1, 124.7, 124.6, 51.3, 28.8, 16.0, and 15.9 ppm. MS (EI): *m/z* 69 (40%, $CH_3CH{=}CHCO^+$), 77 (5%, Ph) 83 (40%) 91, 119 (80%, $PhN{=}C{=}O^+$), 176 (25%, $PhNHCOCH_2CONH_2^+$), 204 (100%, M-$C(CH_3)_2^+$), 231 (20%, M-CH_3^+), 246 (20%, M^+). *Anal.* Calcd. for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.21; H, 5.92; N, 11.14.

Synthesis of 5-Isopropyl-1,3-dimethyl-pyrimidine-2,4,6-trione (B2)

A suspension of 1,3-dimethylbarbituric acid(1.56 g, 10.0 mmol), 2 drops sulfuric acid and 5% Pt-C with 50% water (0.2 g) in acetone (30 mL) and acetic acid (100 mL) was hydrogenated under hydrogen pressure of 50 psi for ~20 hours. The catalyst was separated by filtration, the filtrate was evaporated to an oily residue and benzene (3×50 mL) was added successively and evaporated to eliminate residue of acetic acid to give 1.92 g (97%) of racemic 5-isopropyl-1,3-dimethylbarituric acid. m.p. 157.2-159.1º C. ^{1}H-NMR (DMSO-d_6-500 MHz Varian Unity): δ 3.42 (1H, d, J= 3.3 Hz), 3.144 (6H, s), 0.976 (6H, d, J= 6.9 Hz) ppm. ^{13}C-NMR (DMSO-d_6-500 MHz Varian Unity): δ 164.9, 148.3, 51.1, 29.0, 24.2, and 15.8 ppm.

Synthesis of 5-Cyclohexyl-pyrimidine-2,4,6-trione (B3)

A suspension of barbituric acid (1.28 g, 10 mmol), cyclohexanone (1.55 mL, 1.47 g, 15 mmol) and 5% Pt-C with 50% water (0.2 g) in methanol (100 mL) was hydrogenated under hydrogen pressure of 50 psi for ~20 hours. The catalyst was separated by filtration, the filtrate volume was reduced to 1/10 the original volume, and diluted with water (100 mL) to precipitate the product. The precipitate was separated by filtration and dried on the air to afford 2.00 g (95%) 5-Cyclohexyl-pyrimidine-2,4,6-trione. Product decomposes at temperatures above 150º C. ^{1}H-NMR (DMSO-d_6-500 MHz Varian Unity): δ 11.19(2H, s, NH), 3.11(1H, d, J= 3.6 Hz, CH), 2.11(1H, m), 1.67(6H, m), 1.23(4H, m) ppm. ^{13}C-NMR (DMSO-d_6-500 MHz Varian Unity): δ 166.7, 147.6, 50.5, 50.4, 38.0, 25.9, 22.4, 21.9 ppm. MS (CI^{+}-NH_3) 129 (100%, ba $^{+}$), 211 (55%, M^{+}).

Synthesis of 5-Heptyl-pyrimidine-2,4,6-trione (B4)

A suspension of barbituric acid (1.28 g, 10 mmol), heptaldehyde (2.10 mL, 1.71 g, 15 mmol) and 5% Pt-C with 50% water (0.2 g) in methanol (100 mL) was hydrogenated under hydrogen pressure of 50 psi for ~20 hours. The catalyst was separated by filtration, the filtrate volume was reduced to 1/10 the original volume, and diluted with water (100 mL) to precipitate product. The precipitate was removed by filtration and dried on the air to afford 2.19 g (97%) pure product. Product decomposes at temperatures above 160º C. ^{1}H-NMR (DMSO-d_6-500 MHz Varian Unity): δ 11.18 (2H, s, NH), 3.49 (1H, t, *J*= 5.1 Hz, CH), 1.85 (2H, m), 1.20 (10H, m), 0.83 (3H. t. *J*= 6.8 Hz) ppm. ^{13}C-NMR (DMSO-d_6-500 MHz Varian Unity): δ 167.0, 147.3, 44.3, 27.6, 25.3, 24.8, 24.4, 22.2, 18.5, and 10.4 ppm. MS (CI^{+}-NH_3) 129 (100%, ba), 227 (75%, M^{+}).

General Procedure E:

Preparation of C-5 monobenzylated barbituric acids with aromatic aldehydes:

Synthesis of 5-benzylbarbituric acid (B5)

Barbituric acid (1.28 g, 10 mmol), and benzaldehyde (1.06 g, 10 mmol) were refluxed in methanol (100 mL) for 30 minutes. The reaction suspension was cooled to room temperature and 5% Pd-C with 50% water (0.1 g) was added, together with benzene (50 mL) and hydrogenated at 30 psi for 4 hours. The catalyst was separated by filtration and the solvent was evaporated to a solid residue. The solid residue was re-dissolved in methanol (10 mL) and diluted with water (300 mL). The white precipitate was separated by filtration and dried in the air to give 1.85 g (85%) pure product. m.p. > 200º C with

decomp. ^{1}H-NMR (DMSO-d_6-500 MHz Varian Unity): δ 11.16 (2H, s, NH), 7.22 (5H, broad m, Ar), 3.88 (2H, s, CH_2). ^{13}C-NMR (DMSO-d_6-500 MHz Varian Unity): δ 170.6, 151.1, 137.9, 129.4, 128.9, 127.3, 49.9, and 39.3 ppm. MS (CI^+-NH_3) 91 (100%, $CH_2C_6H_5^+$), 218 (70%, M).

Synthesis of 5-naphthalen-2-ylmethylbarbituric acid (B6)

Barbituric acid (1.28 g, 10 mmol), and 2-naphthaldehyde (1.56 g, 10 mmol) were refluxed in methanol (100 mL) for 30 minutes. The reaction suspension was cooled to room temperature and 5% Pd-C with 50% water (0.1 g) was added, together with benzene (50 mL) and hydrogenated at 30 psi for 4 hours. The catalyst was separated by filtration and the solvent was evaporated to a solid residue. The solid residue was re-dissolved in methanol (10 mL) and diluted with water (300 mL). The white precipitate was separated by filtration and dried in the air to give 2.40 g (90%) 5-naphthalen-2-ylmethylbarbituric acid. m.p. > 200º C with decomp. ^{1}H-NMR (DMSO-d_6-500 MHz Varian Unity): δ 11.15 (2H, s, NH), 8.13 (1H, d, *J*= 6.6 Hz), 7.89 (1H, d, *J*= 6.6 Hz), 7.71 (1H, d, *J*= 8.7 Hz), 7.51 (2H, m), 7.41 (1H, t, *J*= 7.5 Hz), 7.25 (1H, d, *J*= 6.6 Hz), 3.95 (1H, t, *J*= 6.6 Hz), 3.66 (2H, d, *J*= 6.6 Hz) ppm. ^{13}C-NMR ((DMSO-d_6-500 MHz Varian Unity): δ 166.0, 146.6, 130.2, 129.2, 127.4, 124.4, 122.9, 122.5, 44.8, and 25.9 ppm. MS (CI^+-NH_3) *m/z* 91 ($C_7H_7^+$), 115 (12%, $C_8H_9^+$), 128 (17%, ba^+), 129 (16%, $C_{10}H_9^+$), 141 (100%, $C_{11}H_{10}^+$), 169 (7%, $C_{11}H_{10}CO^+$), 268 (45%, M^+), 269 (10%, M++1). *Anal.* Calcd. for $C_{16}H_{12}N_2O_3$: C, 67.16; H, 4.51; N, 10.44. Found: C, 67.01; H, 4.82; N, 10.08.

Synthesis of 5-(3-Phenyl-propyl)-pyrimidine-2,4,6-trione (B7)

Barbituric acid (1.28 g, 10 mmol), and *trans*-cinnamaldehyde (1.32 g, 10 mmol) were refluxed in methanol (100 mL) for 30 minutes. The reaction suspension was cooled to room temperature and 5% Pd-C with 50% water (0.100 g) was added, together with benzene (50 mL) and hydrogenated at 30 psi for 4 hours. The catalyst was separated by filtration and the solvent was evaporated to a solid residue. The solid residue was re-dissolved in methanol (10 mL) and diluted with water (300 mL). The formed precipitate was separated by filtration and dried in the air to give 2.26 g (92%). ^{1}H-NMR (DMSO-d_6 -300 MHz Varian Unity): δ 11.17 (2H, s, NH), 7.25 (2H, m), 7.16 (3H, m), 3.53 (1H, t, J= 5.1 Hz), 2.53 (2H, m), 1.87 (2H, m), 1.54 (2H, m) ppm. ^{13}C-NMR (DMSO-d_6 -300 MHz Varian Unity): δ 166.7, 147.2, 137.9, 124.6, 124.6, 122.1, 44.2, 36.8, 24.3, and 24.1 ppm.

5-[3-(4-Dimethylamino-phenyl)-propyl]-pyrimidine-2,4,6-trione (B8)

Barbituric acid (1.28 g, 10 mmol), and 4-dimethylaminocinnamaldehyde (1.75 g, 10 mmol) were refluxed in methanol (100 mL) for 30 minutes. The reaction suspension was cooled to room temperature and 5% Pd-C with 50% water (0.100 g) was added, together with benzene (50 mL) and hydrogenated at 30 psi for 4 hours. The catalyst was separated by filtration and the solvent was evaporated to a solid residue. The solid residue was re-dissolved in methanol (10 mL) and diluted with water (300 mL). The white precipitate was separated by filtration and dried in the air to give 2.57 g (89%) pure product. ^{1}H-NMR (DMSO-d_6 -300 MHz Varian Unity): δ 6.960 (2H, d, J= 7.8 Hz), 6.628 (2H, d, J= 8.7 Hz), 3.157 (2H, s), 2.816 (6H, s), 2.402 (2H, m), 1.484 (2H, m). ^{13}C-NMR (DMSO-

d_6-300 MHz Varian Unity): δ 164.2, 147.7, 145.4, 125.6, 119.9, 108.0, 45.0, 36.1, 24.4, and 21.3 ppm.

Synthesis of 5-(4-Dimethylamino-benzyl)-1,3-dimethyl-pyrimidine-2,4,6-trione (B10)

1,3-dimethylbarbituric acid (1.56 g, 10 mmol), and 4-dimethylaminobenzaldehyde (1.49 g, 10 mmol) were refluxed in methanol with 2 drops sulfuric acid (100 mL) for 30 minutes. The reaction suspension was cooled to room temperature and 5% Pd-C with 50% water (0.100 g) was added, together with benzene (50 mL) and hydrogenated at 30 psi for 4 hours. The catalyst was separated by filtration and the solvent was evaporated to a solid residue. The solid residue was re-dissolved in methanol (10 mL) and diluted with water (300 mL). The precipitate was separated by filtration and dried in the air to give 2.80 g (97%) product. ^{1}H-NMR (DMSO-d_6-300 MHz Varian Unity): δ 6.80 (2H, d, J= 7.8 Hz), 6.56 (2H, d, J= 8.7 Hz), 3.86 (1H, broad t), 3.16 (2H, broad d), 2.99 (6H, s), 2.80 (6H, s). ^{13}C-NMR (DMSO-d_6-300 MHz Varian Unity): δ 164.9, 147.6, 145.7, 125.5, 119.8, 108.5, 47.1, 36.8, 32.0, and 24.2 ppm.

Synthesis of 1,3-Dimethyl-5-(3-phenyl-propyl)-pyrimidine-2,4,6-trione (B11)

1,3-dimethylbarbituric acid (1.56 g, 10 mmol), and *trans*-cinnamaldehyde (1.32 g, 10 mmol) were refluxed in methanol (100 mL) for 30 minutes. The reaction suspension was cooled to room temperature and 5% Pd-C with 50% water (0.100 g) was added, together with benzene (50 mL) and hydrogenated at 30 psi for 4 hours. The catalyst was separated by filtration and the solvent was evaporated to a solid residue. The solid residue was re-dissolved in methanol (10 mL) and diluted with water (300 mL). The formed precipitate

was separated by filtration and dried in the air to give 2.49 g (91%). ^{1}H-NMR (DMSO-d_6 -300 MHz Varian Unity): δ 7.24 (2H, t, *J*= 7.4 Hz), 7.16 (3H, m), 3.71 (1H, t, *J*= 5.4 Hz), 3.10 (6H, s), 2.54 (2H, m), 1.95 (2H, m), 1.57 (2H, m). ^{13}C-NMR (DMSO-d_6 -300 MHz Varian Unity): δ 166.6, 164.6, 147.6, 137.4, 124.1, 121.6, 44.3, 30.8, 24.5, 24.0, 23.8 ppm. MS (CI^{+}-NH_3) 156 (45%, dmba), 170 (80%, $C_7H_9^{+}$), 274 (20%, M^{+}).

5-[3-(4-Dimethylamino-phenyl)-propyl]-1,3-dimethylpyrimidine-2,4,6-trione (B12)

1,3-dimethylbarbituric acid (1.56 g, 10 mmol), and 4-(dimethylamino)cinnamaldehyde (1.75 g, 10 mmol) were refluxed in methanol with 2 drops sulfuric acid (100 mL) for 30 minutes. The reaction suspension was cooled to room temperature and 5% Pd-C with 50% water (0.100 g) was added, together with benzene (50 mL) and hydrogenated at 30 psi for 4 hours. The catalyst was separated by filtration and the solvent was evaporated to a solid residue. The solid residue was re-dissolved in methanol (10 mL) and diluted with water (300 mL). The white precipitate was separated by filtration and dried in the air to give 2.99 g (94%) pure product. ^{1}H-NMR (DMSO-d_6 -300 MHz Varian Unity): δ 6.960 (2H, d, *J*= 7.8 Hz), 6.628 (2H, d, *J*= 8.7 Hz), 3.157 (2H, s), 2.816 (6H, s), 2.787 (6H, s), 2.402 (2H, m), 1.484 (2H, m). ^{13}C-NMR (DMSO-d_6 -300 MHz Varian Unity): δ 164.2, 147.7, 145.4, 125.6, 119.9, 108.0, 45.0, 36.1, 24.4, 24.1, and 21.3 ppm.

Synthesis of 5-(1H-Indol-3-ylmethyl)-1,3-dimethyl-pyrimidine-2,4,6-trione (B13)

1,3-dimethylbarbituric acid (1.56 g, 10 mmol), and indole-3-carboxaldehyde (1.45 g, 10 mmol) were refluxed in methanol (100 mL) for 30 minutes. The reaction suspension was cooled to room temperature and 5% Pd-C with 50% water (0.100 g) was added, together

with benzene (50 mL) and hydrogenated at 30 psi for 4 hours. The catalyst was separated by filtration and the solvent was evaporated to a solid residue. The solid residue was re-dissolved in methanol (10 mL) and diluted with water (300 mL). The formed precipitate was separated by filtration and dried in the air to give 2.70 g (95%). ^{1}H-NMR (DMSO-d_6 -300 MHz Varian Unity): δ 10.87 (1H, s, NH), 7.32 (1H, t, *J*= 6.0 Hz), 7.28 (1H, s), 7.03 (1H, t, *J*= 5.6 Hz), 6.95 (2H, m), 3.89 (1H, t, *J*= 3.5 Hz), 3.43 (2H, d, *J*= 3.6 Hz), 2.87 (6H, s). ^{13}C-NMR (DMSO-d_6 -300 MHz Varian Unity): δ 165.5, 147.6, 132.2, 123.0, 120.0, 117.4, 114.7, 114.5, 107.8, 104.9, 46.8, 24.2, and 23.6 ppm.

Synthesis of 5-(4-Hydroxy-benzyl)-1,3-dimethylpyrimidine-2,4,6-trione (B14)

1,3-dimethylbarbituric acid (1.56 g, 10 mmol), and 4-hydroxybenzaldehyde (1.22 g, 10 mmol) were refluxed in methanol (100 mL) for 30 minutes. The reaction suspension was cooled to room temperature and 5% Pd-C with 50% water (0.100 g) was added, together with benzene (50 mL) and hydrogenated at 30 psi for 4 hours. The catalyst was separated by filtration and the solvent was evaporated to a solid residue. The solid residue was re-dissolved in methanol (10 mL) and diluted with water (300 mL). The formed precipitate was separated by filtration and dried in the air to give 2.38 g (91%) product. ^{1}H-NMR (DMSO-d_6 -300 MHz Varian Unity): δ 9.26 (1H, s, OH), 6.78 (2H, d, *J*= 8.4 Hz), 6.58 (2H, d, *J*= 8.4 Hz), 3.84 (2H, s), 2.97 (6H, s). ^{13}C-NMR (DMSO-d_6 -300 MHz Varian Unity): δ 165.0, 152.7, 147.6, 126.0, 122.6, 111.5, 47.1, 32.2, 24.2 ppm.

Synthesis of 5-(4-Hydroxy-benzyl)-pyrimidine-2,4,6-trione (B15)

Barbituric acid (1.28 g, 10 mmol), and 4-hydroxybenzaldehyde (1.22 g, 10 mmol) were refluxed in methanol (100 mL) for 30 minutes. The reaction suspension was cooled to room temperature and 5% Pd-C with 50% water (0.100 g) was added, together with benzene (50 mL) and hydrogenated at 30 psi for 4 hours. The catalyst was separated by filtration and the solvent was evaporated to a solid residue. The solid residue was re-dissolved in methanol (10 mL) and diluted with water (300 mL). The formed precipitate was separated by filtration and dried in the air to give 2.2 g (94%) product. ^{1}H-NMR (DMSO-d_6-300 MHz Varian Unity): δ 6.85 (2H, d, J= 8.1 Hz), 6.62 (2H, d, J= 8.1 Hz), 3.73 (1H, broad t), 3.15 (2H, d, J= 3.9 Hz). ^{13}C-NMR (CF_3COOH- DMSO-d_6-300 MHz Varian Unity): δ 169.6, (162.2, 161.7, 161.1, 160.5-belonging to TFA), 152.4, 134.7, 120.6, 116.8, 113.1, 109.3, and 38.2 ppm.

Synthesis of 5-(2-Hydroxy-benzyl)-pyrimidine-2,4,6-trione (B16)

Barbituric acid (1.28 g, 10 mmol), and 2-hydroxybenzaldehyde (1.22 g, 10 mmol) were refluxed in methanol (100 mL) for 10 minutes. The reaction suspension was cooled to room temperature and 5% Pd-C with 50% water (0.100 g) was added, together with benzene (50 mL) and hydrogenated at 30 psi for 4 hours. The catalyst was separated by filtration and the solvent was evaporated to a solid residue. The solid residue was re-dissolved in methanol (10 mL) and diluted with water (300 mL). The white precipitate was separated by filtration and dried in the air to give 1.75 g (75%) of 5-(2-Hydroxy-benzyl)-pyrimidine-2,4,6-trione. ^{1}H-NMR (DMSO-d_6-300 MHz Varian Unity): δ 11.11 (2H, s, NH), 9.41 (1H, broad s, OH), 6.97 (1H, t, J= 7.4 Hz), 6.88 (1H, d, J= 7.5 Hz),

6.71 (1H, d, *J*= 7.8 Hz), 6.64 (1H, t, *J*= 7.4 Hz), 3.78 (1H, t, *J*= 5.4 Hz), 3.14 (2H, d, *J*= 5.4 Hz). ^{13}C-NMR (DMSO-d_6-300 MHz Varian Unity): δ 166.6, 151.7, 147.5, 126.5, 123.9, 120.1, 115.1, 111.2, 84.0, 44.3, 25.3 ppm.

General Procedure F: Preparation of C-5 dibenzylated barbituric acids:

Preparation of 5,5-di(benzyl)barbituric acid (B17)

A mixture of barbituric acid (0.64 g, 5.0 mmol) and benzaldehyde (1.59 g, 15 mmol) in methanol (100 mL) was refluxed for 15 minutes. The reaction mixture changed from a suspension (low solubility of barbituric acid) to a clear solution, and then again to a new suspension. Into this suspension, 5% Pd-C with 50% water (0.150 g) was added and the suspension was hydrogenated at 30 psi at room temperature overnight (14h). The catalyst was separated by filtration and the methanol volume was evaporated to a reduced volume (10 mL). Water was added (100 mL) and the resulting solid precipitate was separated by filtration and washed with carbon tetrachloride (3×50 mL), and dried on the air to give 5,5-di(benzyl)barbituric acid (1.31 g, 86%). The product decomposed at temperatures above 200º C**.** ^{1}H-NMR (DMSO-d_6-300 MHz Varian Unity): δ 11.21 (2H, s, NH), 7.24 (6H, m), 7.03 (4H, d, *J*= 5.7 Hz), 3.27 (4H, s). ^{13}C-NMR (DMSO-d_6-300 MHz Varian Unity): δ 167.9, 144.8, 131.0, 125.2, 124.4, 123.3, 54.9, 39.7 ppm. MS (CI^{+}-NH_3) *m/z* 309 (100%, M+1).

Preparation of 5,5-di(4-dimethyl-aminobenzyl)barbituric acid (B18)

A mixture of barbituric acid (0.64 g, 5.0 mmol) and 4-dimethylaminobenzaldehyde (2.44 g, 15 mmol) in methanol (100 mL) was refluxed for 15 minutes. The reaction mixture

changed from a suspension (low solubility of barbituric acid) to a clear solution, and then again to a new suspension. Into this suspension, 5% Pd-C with 50% water (0.150 g) was added and the suspension was hydrogenated at 30 psi at room temperature overnight (14h). The catalyst was separated by filtration and the methanol volume was evaporated to a reduced volume (10 mL). Water was added (100 mL) and the resulting solid precipitate was separated by filtration and washed with carbon tetrachloride (3 x 50 mL), and dried on the air to give 5,5-di(4-dimethyl-aminobenzyl)barbituric acid (1.87 g, 95%). The product decomposed at temperatures above 230º C. ^{1}H-NMR (DMSO-d_6-300 MHz Varian Unity): δ 11.09 (2H, s, NH), 6.84 (4H, d, J= 8.7 Hz), 6.57 (4H, d, J= 8.7 Hz), 3.10 (4H, s), 2.81 (12H, s,). ^{13}C-NMR (DMSO-d_6-300 MHz Varian Unity): δ 169.1, 145.8, 145.7, 126.3, 118.7, 108.6, 56.1, 39.6, 36.5 ppm. MS (EI): *m/z* 134 (100%, $N(CH_3)_2C_6H_4CH_2^+$), 261 (12%, M-($N(CH_3)_2C_6H_4CH_2^+$), 394 (48%, M^+). *Anal.* Calcd. for $C_{22}H_{26}N_4O_3$: C, 66.99; H, 6.64; N, 14.20. Found: C, 66.55; H, 6.85; N, 13.97.

General Procedure G: Preparation of C-5-non-symmetric double alkylated barbituric acids:

Synthesis of 5-(4-dimethylanimobenzyl)-5-(3-phenylpropyl)barbituric acid (B19). A suspension of barbituric acid (0.64 g, 5.0 mmol) and cinnamaldehyde (0.66 g, 5.0 mmol) in methanol (100 mL) was heated at 80º C for 2 hours. The reaction suspension was cooled to room temperature and 4-dimethylaminobenzaldehyde (0.75 g, 5 mmol) and 5% Pt-C (0.5 g) with 67% water content was added. The suspension was hydrogenated at 70 psi at room temperature for 4 hours. The catalyst was separated by filtration, and the filtrate concentrated to a volume of 10 mL. The concentrated solution was diluted with

water (200 mL), and the resulting white precipitate was separated by filtration and dried on the air to afford 1.55 g (79%) of pure product. m.p.>250º C with decomp. ^{1}H-NMR (DMSO-d_6-300 MHz Varian Unity): δ 7.24 (2H, t, *J*= 5.7 Hz), 7.20 (1H, t, *J*= 5.4 Hz), 7.11 (2H, d, *J*= 5.7 Hz), 6.77 (2H, d, *J*= 5.7 Hz), 6.5 4(2H, d, *J*= 5.7 Hz), 2.98 (2H, s), 2.79 (6H, s), 2.51 (2H, t, *J*= 5.4 Hz), 1.91 (2H, m), 1.35(2H, m). ^{13}C-NMR (DMSO-d_6-300 MHz Varian Unity): δ 169.6, 146.2, 146.2, 137.9, 126.5, 125.1, 125.0, 122.7, 118.8, 108.8, 54.0, 40.4, 34.3, 31.5, 23.2 ppm. *Anal.* Calcd. for $C_{22}H_{25}N_3O_3$: C, 66.64; H, 6.64; N, 11.07. Found: C, 66.32; H, 6.88; N, 10.83.

General Procedure H:

Synthesis of 5-(cyclohexylmethyl)barbituric acid (C1). Into a methanol (100 mL) suspension of barbituric acid (0.940 g, 7.35 mmol) and 4-methoxybenzaldehyde (1.00 g, 7.35 mmol), concentrated hydrochloric acid (100 mL) and 5% Pt-C with 50% water (1.30 g) were added. The resulting suspension was shaken under hydrogen pressure (70 psi) for 5 hours. The catalyst was separated by filtration and the filtrate was concentrated to 50 mL and diluted with water (100 mL). The formed white precipitate was separated by filtration and purified by crystallization from methanol, yielding 1.47 g (89%). Product decomposes at temperatures above 170º C. ^{1}H-NMR (DMSO-d_6-300 MHz Varian Unity): δ 11.13 (2H, s, NH), 3.15 (1H, t, *J*= 8.7 Hz), 1.75 (2H, t, *J*= 6.0 Hz), 1.61 (4H, m), 1.20 (1H, m), 1.10 (4H, m), 0.834 (2H, m). ^{13}C-NMR (DMSO-d_6-300 MHz Varian Unity): δ 167.2, 147.3, 42.3, 31.6, 31.2, 28.9, 22.3, 22.1 ppm.

Preparation of 5-(cyclohexylmethyl)-1-methylbarbituric acid (C2)

Into a methanol (100 mL) suspension of 1-methylbarbituric acid (1.16 g, 8.20 mmol) and 4-hydroxybenzaldehyde (1.00 g, 8.20 mmol), concentrated hydrochloric acid (100 mL) and 5% Pt-C with 50% water (1.30 g) were added. The resulting suspension was shaken under hydrogen pressure (70 psi) for 5 hours. The catalyst was separated by filtration and the filtrate was concentrated to 50 mL and diluted with water (100 mL). The formed white precipitate was separated by filtration and purified by crystallization from methanol, yielding 1.64 g (84%) pure product. Product decomposes at temperatures above 170º C. ^{1}H-NMR (DMSO-d_6-300 MHz Varian Unity): δ 11.31 (1H, s, NH), 3.54 (1H, t, J= 6.0 Hz), 3.04 (3H, s), 1.76 (2H, t, J= 6.3 Hz), 1.60 (5H, m), 1.09 (2H, m), 0.83 (4H, m). ^{13}C-NMR (DMSO-d_6-300 MHz Varian Unity): δ 168.4, 167.6, 146.7, 71.5, 43.1, 30.1, 28.8, 24.1, 22.2, 22.1 ppm.

Preparation of 5-(cyclohexylmethyl)-1-phenylbarbituric acid (C3). Into a methanol (100 mL) suspension of 1-phenylbarbituric acid (1.50 g, 7.35 mmol) and 4-methoxybenzaldehyde (1.00 g, 7.35 mmol), concentrated hydrochloric acid (100 mL) and 5% Pt-C with 50% water (1.00 g) were added. The resulting suspension was shaken under hydrogen pressure (70 psi) for 5 hours. The catalyst was separated by filtration and the filtrate was concentrated to 50 mL and diluted with water (100 mL). The formed white precipitate was separated by filtration and purified by crystallization from methanol, yielding 2.05 g (93%). Product decomposes at temperatures above 200º C. ^{1}H-NMR (DMSO-d_6-300 MHz Varian Unity): δ 11.70 (1H, s, NH), 7.41 (3H, m), 7.19 (2H, broad singlet), 3.73 (1H, t, J= 6.7 Hz), 1.85 (2H, t, J= 6.7 Hz), 1.63 (5H, m), 1.12 (4H,

m), 0.855 (2H, m). ^{13}C-NMR (DMSO-d_6-300 MHz Varian Unity): δ 167.5, 167.0, 145.8, 130.7, 124.9, 124.7, 124.4, 71.5, 42.6, 29.6, 28.3, 26.6, 21.6 ppm.

Synthesis of 5-(cyclohexylmethyl)-1,3-dimethylbarbituric acid (C4). **MW 252.31**

Into a methanol (100 mL) suspension of 1,3-dimethylbarbituric acid (1.27 g, 8.20 mmol) and 4-hydroxybenzaldehyde (1.00 g, 8.20 mmol), concentrated hydrochloric acid (100 mL) and 5% Pt-C with 50% water (1.30 g, 2 molar percent) were added. The resulting suspension was shaken under hydrogen pressure (70 psi) for 5 hours. The catalyst was separated by filtration and the filtrate was concentrated to 50 mL and diluted with water (100 mL). The formed white precipitate was separated by filtration and purified by crystallization from methanol, yielding 1.82 g (88%) pure product. Product decomposes at temperatures above 150º C. ^{1}H-NMR (DMSO-d_6-300 MHz Varian Unity): δ 3.66 (1H, t, J= 6.0 Hz), 3.10 (6H, s), 1.79 (2H, t, J= 6.6 Hz), 1.63 (4H, m), 1.45 (1H, m), 1.12 (4H, m), 0.83 (2H, m). ^{13}C-NMR (DMSO-d_6-300 MHz Varian Unity): δ 165.4, 148.1, 42.8, 32.7, 31.1, 28.8, 24.5, 22.4, 22.0 ppm. MS (EI): *m/z* 83 (93%, $C_6H_{11}^+$), 97 (30%, $C_6H_{11}CH_3^+$), 157 (100%, dmba + 1), 169 (80%, M-$C_6H_{11}^+$), 252 (15%, M^+). *Anal.* Calcd. for $C_{13}H_{20}N_2O_3$: C, 61.88; H, 7.99; N, 11.10. Found: C, 61.63; H, 5.11; N, 11.02. Crystals were obtained by crystallization from methanol by allowing slow solvent evaporation. *Crystal data:* M_r = 252.31, monoclinic space group $P2_1$, a = 24.369(3), b = 6.3025(8), c = 18.301(2) Å, β + 11.449(2)º, V = 2616.0(6) Å^3, Z = 8, $\rho_{Calcd.}$ 1.281 Mgm^{-3}, F_{000} = 1088, wavelength (λ) = 0.71073 Å, absorption coefficient (μ) = 0.091 mm^{-1}.

Method I: Preparation procedure for formylation of barbituric acid with chloroform. The Reimer-Tiemann Reaction.

Preparation of 5-formyl-1,3-dimethylbarbituric acid (D1)

Into a 50% ethanol (400 mL) solution of potassium hydroxide (84.0 g, 1.50 mol), the chloroform solution of 1,3-dimethylbarbituric acid (33.6 g, 0.20 mol) was added. The rreaction is exothermic, and is controlled by an ice-water bath. A yellow precipitate forms almost immediately. The reaction mixture was stirred at room temperature for an additional 3 hours, then cooled in ice water (5º C). The solid was separated by filtration and slurred in water (100 mL), and the pH was adjusted to ~3 by adding concentrated hydrochloric acid. After cooling at 5º C for 1 hour, the solid was again separated by filtration, washed with acetone (3×20 mL) and dried at 110º C for 0.5 hours, resulting in isolation of pure product. If necessary, further purification can be performed using a small amount of water-ethanol mixture. The yield of isolated product was 27.6 g (75%). Product decomposes at temperatures above 200º C. ^{1}H-NMR (DMSO-d_6-D_2O; 5:1-500 MHz Varian Unity): δ 9.63 (1H, s), 3.04 (6H, s). ^{13}C-NMR (DMSO-d_6- D_2O; 5:1-500 MHz Varian Unity): δ 188.2, 148.5, 147.2, 97.0, 24.0 ppm. MS (EI): *m/z* 156 (39%, M-CO)$^+$, 169 (28%, M-CH_3)$^+$, 184 (20%, M^+). *Anal.* Calcd. for $C_7H_8N_2O_4$ (MW 184.15): C, 45.66; H, 4.38, N, 15.21. Found: C, 45.34; H, 4.65; N, 15.02.

Synthesis of 5-formylbarbituric acid (D2)

Into a 50% ethanol (400 mL) solution of potassium hydroxide (84.0 g, 1.50 mol), the chloroform solution of barbituric acid (25.6 g, 0.20 mol) was added. The reaction is exothermic, and is controlled by an ice-water bath. A yellow precipitate forms almost

immediately. The reaction mixture was stirred at room temperature for an additional 3 hours, then cooled in ice water (5º C). The solid was separated by filtration and slurred in water (100 mL), and the pH was adjusted to ~3 by adding concentrated hydrochloric acid. After cooling at 5º C for 1 hour, the solid was again separated by filtration, washed with acetone (3×20 mL) and dried at 110º C for 0.5 hours, resulting in isolation of pure product. If necessary, further purification can be performed using a small amount of water-ethanol mixture. The yield of isolated product was 14.0 g (45%). Product decomposes at temperatures above 250º C. ^{1}H-NMR (D_2O:DMSO-d_6 (2:1) 500 MHz Varian Unity): δ 9.78 (2H, s, N**H**), 8.59 (1H, s, **H**CO). ^{13}C-NMR (D_2O:DMSO-d_6 (2:1) 500 MHz Varian Unity): δ 185.3, 150.6, 145.3, and 95.6 ppm.

Synthesis of 5-formyl-1-phenylbarbituric acid (D3)

Into a 50% ethanol (400 mL) solution of potassium hydroxide (84.0 g, 1.50 mol), the chloroform solution of barbituric acid (40.8 g, 0.20 mol) was added. The reaction is exothermic, and is controlled by an ice-water bath. A yellow precipitate forms almost immediately. The reaction mixture was stirred at room temperature for an additional 3 hours, then cooled in ice water (5º C). The solid was separated by filtration and slurred in water (100 mL), and the pH was adjusted to ~3 by adding concentrated hydrochloric acid. After cooling at 5º C for 1 hour, the solid was again separated by filtration, washed with acetone (3×20 mL) and dried at 110º C for 0.5 hours, resulting in isolation of pure product. If necessary, further purification can be performed using a small amount of water-ethanol mixture. The yield of isolated product was 31.1 g (67%). Product decomposes at temperatures above 200º C. ^{1}H-NMR (D_2O:DMSO-d_6 (2:1) 500 MHz

Varian Unity): δ 11.38 (1H, s, NH), 7.41 (5H, broad m, Ph), 3.70 (1H, s, CH). ^{13}C-NMR (D_2O:DMSO-d_6 (2:1) 500 MHz Varian Unity): δ 163.3, 163.0, 148.2, 145.3, 131.2, 125.5, 125.4, 125.2, and 124.7 ppm.

Method J: Preparation for acetylbarbiturates.

Preparation of 5-acetylbarbituric acid (D4)

A mixture of barbituric acid (12.8 g, 0.10 mol) and acetic anhydride (300 mL) with a few drops of concentrated sulfuric acid was refluxed for 1 hour. In the beginning the reaction is a suspension, but quickly becomes solution. The reaction mixture was concentrated to ½ the original volume and cooled at 5º C, in an ice water bath. The formed solid was separated by filtration, washed with hot water (3×25 mL), then acetone (3×25 mL), and dried at 80º C for 30 minutes, yielding 16.1 g product (95%). Product decomposes at temperatures above 250º C.^{1}H-NMR (DMSO-d_6-300 MHz Varian Unity): δ 11.76 (1H, s, N**H**), 11.03 (1H, s, N**H**), 2.56 (3H, s, **H$_3$**C). ^{13}C-NMR (DMSO-d_6-300 MHz Varian Unity): δ 191.3, 168.1, 158.7, 145.5, 91.9, and 20.3 ppm. MS (ESI$^+$) in methanol with 0.1% acetic acid. 215.2 (M+2Na) and 251.1 (M+Na+HOAc).

Synthesis of 5-acetyl-1-phenylbarbituric acid (D5)

A mixture of 1-phenylbarbituric acid (20.4 g, 0.10 mol) and acetic anhydride (300 mL) with a few drops of concentrated sulfuric acid was refluxed for 1 hour. In the beginning the reaction is a suspension, but quickly becomes solution. The reaction mixture was concentrated to ½ the original volume and cooled at 5º C in an ice water bath. The formed solid was separated by filtration, washed with hot water (3×25 mL), then acetone

(3×25 mL), and dried at 80º C for 30 minutes, yielding 16.0 g (65%) pure product. Product decomposes at temperatures above 200º C. ^{1}H-NMR (DMSO-d_6-300 MHz Varian Unity): δ 11.48 (1H, s, NH), 7.39 (5H, broad m, phenyl ring), 3.71 (1H, s, CH), 2.58 (3H, s, CH_3). ^{13}C-NMR (DMSO-d_6-300 MHz Varian Unity): δ 163.1, 163.0, 147.9, 145.5, 131.4, 125.5, 125.3, 125.2, 124.7, 20.5 ppm.

Synthesis of 5-acetyl-1,3-dimethylbarbituric acid (D6)

A mixture of 1,3-dimethylbarbituric acid (15.6 g, 0.10 mol) and acetic anhydride (300 mL) with a few drops of concentrated sulfuric acid was refluxed for 1 hour. In the beginning the reaction is a suspension, but quickly becomes solution. The reaction mixture was concentrated to ½ the original volume and cooled at 5º C in an ice water bath. The formed solid was separated by filtration, washed with hot water (3×25 mL), then acetone (3×25 mL), and dried at 80º C for 30 minutes, yielding 18.2 g product (92%). Product decomposes at temperatures above 190º C. ^{1}H-NMR (DMSO-d_6-300 MHz Varian Unity): δ 3.13 (6H, s, dmba-CH_3), 2.58 (3H, s, CH_3). ^{13}C-NMR (DMSO-d_6 -300 MHz Varian Unity): δ 191.0, 165.4, 146.3, 92.2, 24.0, 20.5 ppm.

Method K: Preparation for Schiff bases with ω-aminoalkanoic acids.

Preparation of 6-[1,3-dimethyl-2,4,6-trioxo-hexahydro-pyrimidin-5-ylmethylene)-amino]-hexanoic acid (D7)

A mixture of 5-formyl-1,3-dimethylbarbituric acid (0.92 g, 5.0 mmol) and 6-aminohexanoic acid (0.655 g, 5.0 mmol) in methanol (200 mL) was refluxed for 5 hours. Methanol was evaporated to a solid residue and the solid residue was re-dissolved in a

small amount of hot methanol (50 mL). The solution was left at room temperature to slowly evaporate to 1/5 the original volume. The formed white needles were separated by filtration, washed with cold methanol (3×5 mL), and dried at 60º C for 30 minutes to afford 1.3 g (87%) product. ^{1}H-NMR (DMSO-d_6 - D_2O (3:1) 500 MHz Varian Unity): δ 8.08 (1H, s). 3.41 (2H, d, *J*= 6.7 Hz), 3.08 (6H, d, *J*= 0.6 Hz), 2.18 (2H, t, *J*= 7.2 Hz), 1.48 (4H, m), 1.21 (2H, m). ^{13}C-NMR (DMSO-d_6 - D_2O (3:1) 500 MHz Varian Unity): δ 173.0, 161.3, 160.4, 156.6, 149.4, 86.7, 47.1, 30.9, 26.7, 25.0, 24.4, 22.5, 21.3. MS (ESI^+) in methanol with 0.1% acetic acid: 320.1 and 320.3 (M+Na), 617 and 618.1 (2M+Na).

Synthesis of 4-[(2,4,6-Trioxo-hexahydro-pyrimidin-5-ylmethylene)-amino]-butyric acid (D8)

A mixture of 5-formylbarbituric acid (0.85 g, 5.0 mmol) and 4-aminobutanoic acid (0.515 g, 5.0 mmol) in methanol (200 mL) was refluxed for 5 hours. Methanol was evaporated to a solid residue and the solid residue was re-dissolved in a small amount of hot methanol (50 mL). The solution was left at room temperature to slowly evaporate to 1/5 the original volume. The formed white needles were separated by filtration, washed with cold methanol (3×5 mL), and dried at 60º C for 30 minutes to afford 1.14 g (95%) product. **C=C isomer recorded.** ^{1}H-NMR (DMSO-d_6:D_2O (5:1) 500 MHz Varian Unity): δ 8.83 (1H, s), 4.25 (2H, t, *J*= 5.3 Hz), 3.04 (2H, t, *J*= 5.5 Hz), 2.58 (2H, m). ^{13}C-NMR (DMSO-d_6:D_2O (5:1) 500 MHz Varian Unity): δ 171.0, 162.4, 160.5, 155.2, 147.5, 85.9, 45.7, 27.8, and 22.3 ppm.

Synthesis of 6-[(2,4,6-Trioxo-hexahydro-pyrimidin-5-ylmethylene)-amino]-hexanoic acid (D9)

A mixture of 5-formylbarbituric acid (0.85 g, 5.0 mmol) and 6-aminohexanoic acid (0.655 g, 5.0 mmol) in methanol (200 mL) was refluxed for 5 hours. Methanol was evaporated to a solid residue and the solid residue was re-dissolved in a small amount of hot methanol (50 mL). The solution was left at room temperature to slowly evaporate to 1/5 the original volume. The formed white needles were separated by filtration, washed with cold methanol (3×5 mL), and dried at 60º C for 30 minutes to afford 1.22 g (91%) product. **C=C isomer recorded.** ^{1}H-NMR (DMSO-d_6:D_2O (5:1) 300 MHz Varian Unity): δ 8.09 (1H, s), 3.43 (2H, t, *J*= 6.9 Hz), 2.10 (2H, t, *J*= 7.2 Hz), 1.51 (4H, m), 1.26 (2H, m) ppm. ^{13}C-NMR (DMSO-d_6:D_2O (5:1) 300 MHz Varian Unity): δ 171.7, 162.4, 160.4, 155.1, 147.4, 85.7, 46.0, 31.1, 26.2, 22.0, 20.9 ppm.

Synthesis of 4-[(2,4,6-Trioxo-1-phenyl-hexahydro-pyrimidin-5-ylmethylene)-amino]-butyric acid (D10)

A mixture of 5-formyl-1-phenylbarbituric acid (1.16 g, 5.0 mmol) and 4-aminobutanoic acid (0.515 g, 5.0 mmol) in methanol (200 mL) was refluxed for 5 hours. Methanol was evaporated to a solid residue and the solid residue was re-dissolved in a small amount of hot methanol (50 mL). The solution was left at room temperature to slowly evaporate to 1/5 the original volume. The formed yellow needles were separated by filtration, washed with cold methanol (3×5 mL), and dried at 60º C for 30 minutes to afford 1.27 g (80%) product. **C=C isomer recorded.** ^{1}H-NMR (DMSO-d_6:D_2O (5:1) 300 MHz Varian Unity): δ 8.10 (1H, d, *J*= 7.0 Hz), 7.38 (3H, m), 7.19 (2H, m), 3.48 (2H, m), 2.15 (2H,

m), 1.742 (2H, m). ^{13}C-NMR (DMSO-d_6:D_2O (5:1) 300 MHz Varian Unity): δ 170.6, 161.2, 159.3, 155.4, 147.3, 131.6, 125.9, 125.0, 124.4, 86.1, 45.7, 27.4, 22.1 ppm.

Synthesis of 4-[1-(2,4,6-Trioxo-hexahydro-pyrimidin-5-yl)-ethylideneamino]-butyric acid. (D11)

A mixture of 5-acetylbarbituric acid (0.85 g, 5.0 mmol) and 4-aminobutyric acid (0.515 g, 5.0 mmol) in methanol (200 mL) was refluxed for 5 hours. Methanol was evaporated to a solid residue and the solid residue was re-dissolved in a small amount of hot methanol (50 mL). The solution was left at room temperature to slowly evaporate to 1/5 the original volume. The formed white needles were separated by filtration, washed with cold methanol (3×5 mL), and dried at 60º C for 30 minutes to afford 1.13 g (89%) product. **C=C isomer recorded.** ^{1}H-NMR (D2O:DMSO-d_6 5:1-500 mHz): δ 3.06 (2H, t, J= 7.5 Hz), 2.53 (3H, s, CH_3), 2.51 (2H, t, J= 7.0 Hz), 1.98 (2H, m).

Synthesis of 6-[1-(2,4,6-Trioxo-hexahydro-pyrimidin-5-yl)-ethylideneamino]-hexanoic acid (D12)

A mixture of 5-acetylbarbituric acid (0.85 g, 5.0 mmol) and 6-aminohexanoic acid (0.65 g, 5.0 mmol) in methanol (200 mL) was refluxed for 5 hours. Methanol was evaporated to a solid residue and the solid residue was re-dissolved in a small amount of hot methanol (50 mL). The solution was left at room temperature to slowly evaporate to 1/5 the original volume. The formed white needles were separated by filtration, washed with cold methanol (3×5 mL), and dried at 60º C for 30 minutes to afford 1.23 g (87%)

product. ^{13}C-NMR (TFA:DMSO-d_6 5:1 500 mHz): δ 200.7, 181.4, 163.3, (161.3, 160.8, 160.2, 159.6 for TFA), 150.8, 94.5, 40.9, 32.5, 26.1, 24.5, 23.3, 22.9 ppm.

Synthesis of 3-[1-(2,4,6-Trioxo-hexahydro-pyrimidin-5-yl)-ethylideneamino]-propanoic acid. (D13)

A mixture of 5-acetylbarbituric acid (0.85 g, 5.0 mmol) and 3-aminopropanoic acid (0.44 g, 5.0 mmol) in methanol (200 mL) was refluxed for 5 hours. Methanol was evaporated to a solid residue and the solid residue was re-dissolved in a small amount of hot methanol (50 mL). The solution was left at room temperature to slowly evaporate to 1/5 the original volume. The formed white needles were separated by filtration, washed with cold methanol (3×5 mL), and dried at 60º C for 30 minutes to afford 1.17 g (90%) product. **C=C isomer recorded.** ^{1}H-NMR (D2O:DMSO-d_6 5:1 500 mHz): δ 2.98 (2H, t, J= 7.5 Hz), 2.65 (2H, t, J= 7.5 Hz), 2.30 (3H. s).

Method L: Preparation procedure for nitrophenylhydrazones of formylated barbituric acids.

Synthesis of 5-[(4-nitrophenyl)hydrazonomethyl]-pyrimidine-2,4,6-trione (D14)

A methanol (200 mL) suspension of 5-formylbarituric acid (1.56 g, 10 mmol) and 4-nitrophenylhydrazine (1.53 g, 10 mmol) was refluxed overnight. After cooling to room temperature, the solid was separated by filtration, slurred in hot water, washed with methanol and recrystallized from acetic acid (500 mL) to give 2.3 g (80%) of pure compound. ^{1}H-NMR (DMSO-d_6- 300 MHz Varian Unity): δ 11.22 (1H, broad singlet), 10.84 (1H, s), 10.74 (1H, s), 9.85 (1H, s), 8.12 (2H, d, J= 9.0 Hz), 7.98 (1H, s), 6.81 (2H,

d, *J*= 9.0 Hz). ^{13}C-NMR (DMSO-d_6- 300 MHz Varian Unity): δ 155.4, 150.0, 147.1, 136.0, 122.1, 108.227, 108.227, 87.0 ppm. *Anal.* Calcd. for $C_{11}H_9N_5O_5$ (MW 291.2): C, 45.37; H, 3.11; N, 24.05. Found: C, 45.04; H, 3.38; N, 23.88.

Synthesis of 5-[(2,4-Dinitro-phenyl)-hydrazonomethyl]-pyrimidine-2,4,6-trione (D15)

A methanol (200 mL) suspension of 5-formylbarituric acid (1.56 g, 10 mmol) and 2,4-dinitrophenylhydrazine (1.98 g, 10 mmol) was refluxed overnight. After cooling to room temperature, the solid was separated by filtration, slurred in hot water, washed with methanol and recrystallized from acetic acid (500 mL) to give 2.96 g (88%) of pure compound. **C=N isomer recorded.** ^{1}H-NMR (TFA:DMSO-d_6 (5:1)-300 MHz Varian-Unity): δ 10.92 (1H, s, NH), 10.87 (2H, s, NH), 8.88 (1H, d, *J*= 2.7 Hz), 8.40 (1H, d of d, J_1=9.3 Hz, J_2=2.7 Hz), 8.11 (1H, s), 7.24 (1H, d, *J*= 9.6 Hz) ppm. ^{13}C-NMR (TFA:DMSO-d_6 (5:1)-300 MHz Varian-Unity): δ 160.8, 155.6, 147.2, 143.8, 134.1, 126.7, 126.4, 119.1, 112.6, 87.8 ppm.

Synthesis of 5-[(4-Nitro-phenyl)-hydrazonomethyl]-1-phenyl-pyrimidine-2,4,6-trione (D16)

A methanol (200 mL) suspension of 5-formyl-1-phenylbarituric acid (2.32 g, 10 mmol) and 4-nitrophenylhydrazine (1.53 g, 10 mmol) was refluxed overnight. After cooling to room temperature, the solid was separated by filtration, slurred in hot water, washed with methanol and recrystallized from acetic acid (500 mL) to give 3.37 g (92%) of pure compound. **C=C isomer recorded.** ^{1}H-NMR (DMSO-d_6 -300 MHz Varian-Unity): δ 11.24 (2H, broad singlet, NH), 11.13 (1H, s, NH), 9.93 (1H, s), 8.13 (2H, d, *J*= 8.4 Hz),

7.42 (3H, m), 7.24 (2H, m), 6.82 (2H, d, *J*= 7.5 Hz) ppm. ^{13}C-NMR (DMSO-d_6-300 MHz Varian-Unity): δ 161.1, 159.8, 155.5, 147.9, 147.1, 136.5, 132.2, 125.7, 125.4, 124.0, 122.2, 108.0, 86.6 ppm.

Synthesis of 4-[N'-(2,4,6-Trioxo-1-phenyl-hexahydro-pyrimidin-5-ylmethylene)-hydrazino]-benzoic acid (D17)

A methanol (200 mL) suspension of 5-formyl-1-phenylbarituric acid (2.32 g, 10 mmol) and 4-hydrazinobenzoic acid (1.52 g, 10 mmol) was refluxed overnight. After cooling to room temperature, the solid was separated by filtration, slurred in hot water, washed with methanol and recrystallized from acetic acid (500 mL) to give 3.40 g (93%) of pure compound. **C=C isomer recorded.** ^{1}H-NMR (DMSO-d_6-300 MHz Varian-Unity): δ 11.40 (2H, broad s, NH), 11.09 (1H, s, NH), 9.37 (1H, s), 8.07 (2H, m), 7.80 (2H, d, *J*= 8.7 Hz), 7.41 (3H, m), 6.78 (2H, d, *J*= 8.1 Hz) ppm. ^{13}C-NMR (DMSO-d_6-300 MHz Varian-Unity): δ 164.5, 162.0, 159.9, 155.3, 147.7, 147.2, 132.1, 127.8, 125.5, 125.4, 124.8, 118.0, 108.9, and 86.1 ppm.

Synthesis of 1,3-Dimethyl-5-[(4-nitro-phenyl)-hydrazonomethyl]-pyrimidine-2,4,6-trione (D18)

A methanol (200 mL) suspension of 5-formyl-1,3-dimethylbarituric acid (1.84 g, 10 mmol) and 4-nitrophenylhydrazine (1.53 g, 10 mmol) was refluxed overnight. After cooling to room temperature, the solid was separated by filtration, slurred in hot water, washed with methanol and recrystallized from acetic acid (500 mL) to give 3.03 g (95%) of pure compound. **C=C isomer recorded.** ^{1}H-NMR (DMSO-d_6-300 MHz Varian-

Unity): δ 11.40 (1H, s, NH), 11.30 (1H, s, NH), 9.95 (1H, s), 8.13 (2H, d, *J*= 7.8 Hz), 6.82 (2H, d, *J*= 7.2 Hz), 3.18 (3H, s), 3.153 (3H, s) ppm. ^{13}C-NMR (DMSO-d_6-300 MHz Varian-Unity): δ 159.4, 158.1, 156.0, 149.8, 147.8, 136.1, 122.0, 108.1, 87.0, 23.8, 23.2 ppm.

Synthesis of 4-[N'-(1,3-Dimethyl-2,4,6-trioxo-hexahydro-pyrimidin-5-ylmethylene)-hydrazino]-benzoic acid (D19)

A methanol (200 mL) suspension of 5-formyl-1,3-dimethylbarituric acid (1.84 g, 10 mmol) and 4-hydrazinobenzoic acid (1.52 g, 10 mmol) was refluxed overnight. After cooling to room temperature, the solid was separated by filtration, slurred in hot water, washed with methanol and recrystallized from acetic acid (500 mL) to give 2.89 g (91%) of pure compound. **C=C isomer recorded.** ^{1}H-NMR (DMSO-d_6-300 MHz Varian-Unity): δ 11.27 (1H, s, NH), 11.24 (1H, s, NH), 9.36 (1H, s), 7.79 (2H, d, *J*= 8.4 Hz), 6.74 (2H, d, *J*= 8.7 Hz), 3.14 (3H, s), 3.11 (3H, s) ppm. ^{13}C-NMR (DMSO-d_6-300 MHz Varian-Unity): δ 163.6, 159.6, 158.4, 156.5, 148.1, 148.0, 127.5, 118.6, 108.4, 86.6, 24.0, 23.4 ppm.

Synthesis of 5-{1-[(4-Nitro-phenyl)-hydrazono]-ethyl}-pyrimidine-2,4,6-trione (D20)

A methanol (200 mL) suspension of 5-acetylbarbituric acid (1.70 g, 10.0 mmol) and 4-nitrophenylhydrazine (1.53 g, 10.0 mmol) was refluxed overnight. After cooling to room temperature, the solid was separated by filtration, slurred in hot water (~15 mL) and washed with methanol (3×20 mL), yielding 2.23 g (73%). **(C=C isomer recorded).** ^{1}H-NMR (DMSO-d_6- 300 MHz Varian Unity): δ 13.22 (1H, s, NH), 10.73 (2H, s, NH), 9.66

(1H, s, NH), 8.13 (2H, d, *J*= 9.0 Hz), 6.83 (2H, d, *J*= 9.0 Hz), 2.61 (3H, s, CH_3). ^{13}C-NMR (DMSO-d_6- 300 MHz Varian Unity): δ 171.5, 162.0, 148.8, 146.0, 136.0, 122.4, 107.7, 85.6, 12.1.

Synthesis of 5-{1-[(2,4-dinitrophenyl)-hydrazono]-ethyl}-pyrimidine-2,4,6-trione (D21)

A methanol (200 mL) suspension of 5-acetylbarbituric acid (1.70 g, 10.0 mmol) and 2,4-dinitrophenylhydrazine (1.98 g, 10.0 mmol) was refluxed overnight. After cooling to room temperature, the solid was separated by filtration, slurred in hot water (~15 mL) and washed with methanol (3×20 mL) to give 3.01 g (86%) of pure compound. **(C=C isomer recorded).** ^{1}H-NMR (DMSO-d_6- 300 MHz Varian Unity): δ 13.18 (1H, s, NH), 10.92 (1H, s, NH), 10.64 (1H, s, NH), 10.546 (1H, s, NH), 8.86 (1H, d, *J*= 2.4 Hz), 8.34 (1H, d of d, J_1=9.4 Hz, J_2=2.4 Hz), 7.17 (1H, d, *J*= 9.6 Hz), 2.59 (3H, s, CH_3).

Synthesis of 5-{1-[(4-Nitro-phenyl)-hydrazono]-ethyl}-1-phenyl-pyrimidine-2,4,6-trione (D22)

A methanol (200 mL) suspension of 5-acetyl-1-phenylbarbituric acid (2.46 g, 10.0 mmol) and 4-nitrophenylhydrazine (1.53 g, 10.0 mmol) was refluxed overnight. After cooling to room temperature, the solid was separated by filtration, slurred in hot water (~15 mL) and washed with methanol (3×25 mL), yielding 3.20 g, (84%) pure product. **(C=C isomer recorded).** ^{1}H-NMR (DMSO-d_6- 300 MHz Varian Unity): δ 13.19 (1H, s, NH), 11.13 (1H, s, NH), 9.72 (1H, s, NH), 8.14 (2H, d, *J*= 9.3 Hz), 7.41 (3H, m), 7.24 (2H, d, *J*= 7.2 Hz), 6.84 (2H, d, *J*= 9.3 Hz), 2.62 (3H, s, CH_3). ^{13}C-NMR (DMSO-d_6- 300 MHz Varian

Unity): δ 171.8, 148.7, 146.0, 136.0, 125.7, 125.3, 125.1, 125.0, 124.6, 124.2, 122.4, 107.8, 85.9, and 12.5 ppm.

Synthesis of 5-{1-[(2,4-Dinitro-phenyl)-hydrazono]-ethyl}-1-phenyl-pyrimidine-2,4,6-trione (D23)

A methanol (200 mL) suspension of 5-acetyl-1-phenylbarbituric acid (2.46 g, 10.0 mmol) and 2,4-dinitrophenylhydrazine (1.98 g, 10.0 mmol) was refluxed overnight. After cooling to room temperature, the solid was separated by filtration, slurred in hot water (~15 mL) and washed with methanol (3×20 mL), yielding 3.45 g, (81%) pure product. **(C=C isomer recorded).** ^{1}H-NMR (DMSO-d_6- 300 MHz Varian Unity): δ 13.10 (1H, s, NH), 11.12 (1H, s, NH), 10.60 (1H, s, NH), 8.87 (1H, d, J= 2.7 Hz), 8.37 (1H, d of d, J_1= 9.3 Hz, J_2= 2.4 Hz), 7.42 (3H, m), 7.24 (3H, m), 2.61 (3H, s CH_3).

Synthesis of 1,3-Dimethyl-5-{1-[(4-nitro-phenyl)-hydrazono]-ethyl}-pyrimidine-2,4,6-trione. (D24)

A methanol (200 mL) suspension of 5-acetyl-1,3-dimethylbarbituric acid (1.98 g, 10.0 mmol) and 4-nitrophenylhydrazine (1.53 g, 10.0 mmol) was refluxed overnight. After cooling to room temperature, the solid was separated by filtration, slurred in hot water (5 mL) and washed with methanol (3×20 mL), yielding 2.08 g (63%) pure product. **(C=C isomer recorded).** ^{1}H-NMR (DMSO-d_6- 300 MHz Varian Unity): δ 13.25 (1H, s, NH), 9.73 (1H, s, NH), 8.12 (2H, d, J= 9.3 Hz), 6.82 (2H, d, J= 9.3 Hz), 3.15 (6H, s, dmba-CH_3), 2.63 (3H, s, CH_3).

Synthesis of 5-{1-[(2,4-Dinitro-phenyl)-hydrazono]-ethyl}-1,3-dimethyl-pyrimidine-2,4,6-trione (D25)

A methanol (200 mL) suspension of 5-acetyl-1,3-dimethylbarbituric acid (1.98 g, 10.0 mmol) and 2,4-dinitrophenylhydrazine (1.98 g, 10.0 mmol) was refluxed overnight. After cooling to room temperature, the solid was separated by filtration, slurred in hot water (~15 mL) and washed with methanol (3×20 mL), yielding 3.17 g (84%) pure product. **(C=C isomer recorded).** ^{1}H-NMR (DMSO-d_6- 300 MHz Varian Unity): δ 13.23 (1H, s, NH), 10.62 (1H, s, NH), 8.86 (1H, d, J= 2.7 Hz), 8.36 (1H, d of d, J_1= 9.6 Hz, J_2= 2.4 Hz), 7.16 (1H, d, J= 9.3 Hz), 3.16 (6H, s, dmba-CH_3), 2.63 (3H, s, CH_3). ^{13}C-NMR (DMSO-d_6- 300 MHz Varian Unity): δ 172.4, 161.6, 146.9, 143.3, 134.2, 127.2, 126.7, 119.2, 111.7, 86.7, 24.1, 13.1 ppm.

General Procedure M;

Preparation of 5,5'-(4-dimethylaminobenzylidene)dibarbituric acid (E1)

Into a clear trifluoroacetic acid solution (30 mL) of barbituric acid (0.270 mg; 0.0021 mol), 4-dimethylaminobenzaldehyde (0.149g 0.001mol) was added. Clear reaction mixture was left at room temperature and the solvent was slowly evaporated at room temperature almost to dryness (eight days). Formed white crystalline product 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 0º C. The NMR spectra were recorded in CF_3SO_3H with three drops of DMSO-d_6 as an internal standard and source of the deuterium lock signal. Product decomposition occurs at temperatures above 285º C. ^{1}H-NMR(CF_3SO_3H-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}C-NMR(CF_3SO_3H-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 5,5'-(4-nitrobenzylidene)dibarbituric acid (E2)

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 fitration, washed with cold trifluoroacetic acid (3×3 mL), with methanol (3×10 mL), and dried in vacuum at 60º 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 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}H-NMR spectra can be recorded. Product decomposes at temperatures above 200º C. ^{1}H-NMR (CF_3SO_3H-DMSO-d_6, 300 MHz) δ 7.66 (2H, d, *J*=

7.5Hz, 3H-benzene hydrogens), 6.88 (2H, d, *J*= 7.5 Hz, benzene 2H hydrogens), and 5.49 ppm (1H, benzyl hydrogen). ^{13}C-NMR (CF_3SO_3H-DMSO-d_6, 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 – CF_3SO_3H), 94.9 (benzyl carbon, and 34.8 ppm (barbituric *C-5* carbon).

Preparation of 5,5'-(4-nitrobenzylidene)di(1,3-dimethylbarbituric acid) (E2a)

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 (3× 2mL), ice-cold methanol (3×3 mL) and dried on 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 CF_3SO_3H at room temperature for approximately one hour. Two drops of DMSO-d_6 were added as both internal reference signal as well as solvent for the NMR signal lock. Product melting point is 179.2-181.1º C. ^{1}H-NMR (CF_3SO_3H-DMSO-d_6, 300 MHz), δ 7.67 (2H, d, *J*= 8.4 Hz, 3H aromatic hydrogens), 6.85 (2H, d, *J*= 8.4Hz, 2H aromatic hydrogens), 5.50 (1H, s, benzyl hydrogen), 3.05 ppm (12H, s, methyl hydrogens). ^{13}C-NMR (CF_3SO_3H-DMSO-d_6, 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 CF_3SO_3H), 96.2 (benzyl carbon), 37.3 (barbituric *C-5* carbon), and

34.0 ppm (methyl carbons). *Anal.* Calcd. for $C_{19}H_{19}N_5O_8$: 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 (E3). 4-Quinolinecarboxaldehyde (0.160 g; 0.001 mol) was added into refluxing methanol (400 mL) solution of barbituric acid (0.256 g; 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 (3×30 mL) and dried at 110º C for three hours to give 0.36 g (91%) product. Product decomposes at temperatures e×ceeding 280º C. ^{1}H-NMR(DMSO-d_6, 300 MHz) δ 10.32 (4H, s, NH), 9.09 (1H, d, *J*= 0.020, quinoline 2-H), 8.48 (1H, d, *J*= 0.030, quinoline 8-H), 8.15 (1H, d, *J*= 0.029, quinoline 5-H), 8.03 (1H, t, *J*= 0.024, quinoline 7-H), 8.40 (1H, t, *J*= 0.021, quinoline 6-H), 7.83 (1H, d, *J*= 0.019, quinoline 3-H), and 6.76 ppm (1H, s, benzyl H); ^{13}C-NMR (DMSO-d_6, 300 MHz) δ 161.1 and 161.0 (two different carbonyl carbons), 146.8, 139.9, 133.8, 130.0, 125.4, 123.6, 121.9, 117.9, 117.6 (nine quinoline carbons), 86.4 (benzyl carbon), and 27.4 ppm (barbituric *C-5*). *Anal.* Calcd. for $C_{22}H_{21}N_5O_6$: 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 (E4). 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 (3×1 mL), methanol

(3×5mL) and dried in vacuum at 90º C for one hour to afford 0.330 g (97%) of pure product. Product decomposition occurs at temperatures exceeding 290º C. ^{1}H-NMR (DMSO-d_6, 300 MHz) δ 10.32 (8H, s, NH), 8.60 (2H, d, *J*= 5.4Hz, 6H of pyridine ring), 8.03 (2H, s, 3H of pyridine ring) 7.47 (2H, d, *J*= 5.4Hz, 5H of pyridine ring), and 6.06 (2H, s, benzyl hydrogen). ^{13}C-NMR (DMSO-d_6, 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^{+} (CH_3COOH) m/z 115 (100%), 277 (50%), 387 (45%), 483 (83%), 505 (43%), and 689 (M+1, 70%). *Anal.* Calcd. for $C_{28}H_{20}N_{10}O_{12}$: 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 (E5)

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 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 167º C. ^{1}H-NMR (DMSO-d_6, 300 MHz) δ 8.60 (2H, d, *J*= 5.4Hz, 6H of pyridine ring), 8.02 (2H, s, 3H of pyridine ring) 7.56 (2H, d, *J*= 5.4Hz, 5H of pyridine ring), 6.37 (2H, s, benzyl hydrogen), and 3.14 ppm (24H, s, methyl hydrogens). ^{13}C-NMR (DMSO-d_6, 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$^+$ (CH_3COOH) *m/z* 143 (35%), 277 (50%), 415 (44%), 539 (83%), 661 (33%), 677 (22%), 801 (M+1, 42%). *Anal.* Calcd. for $C_{36}H_{36}N_{10}O_{12}$: C, 54.00; H, 4.53; N, 17.49 Found: C, 53.88; H, 4.61; N, 17.36.

Procedure M.

Preparation of 5-[(2,4,6-trioxohexahydropyrimidin-5-yl)(pyridin-3-yl)methyl]pyrimidine-2,4,6(1H,3H,5H)-trione (E7)

Into a hot (110º 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 (3×20 mL), acetone (3×20 mL) and dried at 80˚ C under reduced pressure for several hours. Product decomposition at temperatures above 250º C. MS-ES$^+$ (in acetic acid) 140 (38%), 209 (43%), 223 (100%), 251 (84%), 283 (26%), and 346 (M+1, 10%). ^{1}H-NMR(DMSO-d_6- 300 MHz Varian Unity) δ 10.21 (4H, s, NH), 8.64 (1H,d, J= 5.7 Hz, pyridine 6-H), 8.43 (1H, s, pyridine 2-H), 8.20 (1H, d, J= 5.7 Hz, pyridine 4-H), 7.89 (1H, d+d, J_1= 5.7 Hz, J_2= 5.7 Hz, pyridine 5-H), and 6.13 (1H, s, pyrilidene H). ^{13}C-NMR (DMSO-d_6- 300 MHz Varian Unity) δ 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). Yield 97%.

Preparation of 1,3-dimethyl-5-[(2,4,6-trioxohexahydropyrimidin-5-yl)(pyridin-3-yl)methyl]pyrimidine-2,4,6(1H,3H,5H)-trione (E8)

After 1,3-dimethylbarbituric acid (0.78 g; 5.0 mmol) was dissolved in refluxing methanol (100 mL) 3-pyridinecarboxaldehyde (0.27 g; 2.5 mmol) 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 (3×20 mL), ether (3×50 mL) and dried at 110º C for 30 minutes. Yield=92%. ^{1}H-NMR (DMSO-d_6- 300 MHz Varian Unity) δ 8.64 (1H, d, J= 6 Hz, pyridine 6-H), 8.56 (1H, s, pyridine 2-H), 8.29 (1H, d, J= 6 Hz, pyridine 4-H), 7.88 (1H, d, J_1= 7.8 Hz, J_2= 8.1 Hz, pyridine 5-H), 6.337 (1H, s, benzyl H), and 3.13 ppm (12H, s, CH_3); ^{13}C-NMR (DMSO-d_6- 300 MHz Varian Unity) δ 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).

Preparation of 1-methyl-5-[(2,4,6-trioxohexahydropyrimidin-5-yl)(pyridin-3-yl)methyl]pyrimidine-2,4,6(1H,3H,5H)-trione (E9)

After 1-methylbarbituric acid (0.71 g; 0.005 mol) was dissolved in refluxing methanol (100 mL) 3-pyridinecarboxaldehyde (0.27 g; 0.0025 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 (3×20 mL), ether (3×50 mL) and dried at 110º C for 30 minutes. Yield=97%. ^{1}H-NMR (DMSO-d_6- 300 MHz Varian Unity) δ 10.55 (2H, s, NH), 8.65 (1H, d, J= 5.7 Hz, pyridine 6-H), 8.49 (1H, s, pyridine 2-H), 8.24 (1H, d, J= 7.8 Hz, pyridine 4-H), 7.90 (1H,d+d, J_1= 8.4 Hz, J_2= 8.4 Hz, pyridine 5-H), 6.25 (1H, s, benzyl), and 3.08 (6H, s, CH_3). ^{13}C-NMR (DMSO-d_6- 300 MHz Varian Unity) δ 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).

Preparation of 1-butyl-5-[(2,4,6-trioxohexahydropyrimidin-5-yl)(pyridin-3-yl)methyl]pyrimidine-2,4,6(1H,3H,5H)-trione (E10)

Acetic acid solution (300 mL) of 1-butylbarbituric acid (920 mg; 5 mmol) and 3-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 (3×30 mL) and dried at 80º C under reduced pressure for five hours. Yield=81%. ^{1}H-NMR (DMSO-d_6- 300 MHz Varian Unity) δ 10.48 (2H, s, NH), 8.46 (1H, d, J= 4.2 Hz, pyridine 6-H), 8.33 (1H, s, pyridine 2-H), 7.79 (1H, d, J= 7.5 Hz), 7.56 (1H, t, J= 5.1 Hz), 6.164 (1H, s, CH), 3.70 (4H, J= 6.6 Hz, NCH_2), 1.46 (4H, m, $NCH_2C\mathbf{H}_2$), 1.24 (4H, m, $C\mathbf{H}_2CH_3$), and 0.86 ppm (6H, t, J= 6.6 Hz, CH_3). ^{13}C-NMR (DMSO-d_6- 300 MHz Varian Unity) δ 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).

Preparation of 1-phenyl-5-[(2,4,6-trioxohexahydropyrimidin-5-yl)(pyridin-3-yl)methyl]pyrimidine-2,4,6(1H,3H,5H)-trione (E11)

After 1-phenylbarbituric acid (1.02 g; 0.005 mol) was dissolved in refluxing methanol (100 mL) 3-pyridinecarboxaldehyde (0.27 g; 0.0025 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 (3×20 mL), ether (3×50 mL) and dried at 110º C for 30 minutes. Yield=93%. ^{1}H-NMR (DMSO-d_6- 300 MHz Varian Unity) δ 10.74 (2H, s, NH), 8.66 (1H, d, J= 6.3 Hz, pyridine 6-H), 8.63 (1H, s, pyridine 2-H), 8.40 (1H, d, J= 8.7 Hz, pyridine 4-H), 7.93 (1H, d+d, J_1=7.8 Hz, J_2=7.2 Hz, pyridine 5-H), 7.392 (4H, t, J= 0.023, phenyl *m*-H); 7.319 (2H, t, J= 6.9 Hz, phenyl *p*-H), 7.19 (4H, d, J= 6.9 Hz, *o*-H), and 6.23 (1H, s, CH). ^{13}C-NMR (DMSO-d_6- 300 MHz Varian Unity δ 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).

Preparation of 5-[(2,4,6-trioxohexahydropyrimidin-5-yl)(pyridin-4-yl)methyl]pyrimidine-2,4,6(1H,3H,5H)-trione (E12)

Into a hot (110º C) acetic acid (200 mL) solution of barbituric acid (1.28 g; 10 mmol) 4-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 (3×20 mL), acetone (3×20 mL) and dried at 80˚ C under reduced pressure for several hours. Product decomposition at temperatures above 250º C. Yield=97%. ^{1}H-NMR (DMSO-d_6- 300 MHz Varian Unity) δ 10.24 (4H, s, NH), 8.63 (2H, d, *J*= 6.4Hz, pyridine 2-H), 7.63 (2H, d, *J*= 6.9Hz, pyridine 3-H), and 6.18 ppm (1H, s, CH). ^{13}C-NMR (DMSO-d_6- 300 MHz Varian Unity) δ 163.5, 162.3 (carbonyl carbons), 145.5, 121.5, 113.3 (aromatic carbons), 87.3, and 33.5 ppm (aliphatic carbons).

Preparation of 1-methyl-5-[(2,4,6-trioxohexahydropyrimidin-5-yl)(pyridin-4-yl)methyl]pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (E13)

After 1-methylbarbituric acid (0.71 g; 0.005 mol) was dissolved in refluxing methanol (100 mL) 4-pyridinecarboxaldehyde (0.27 g; 0.0025 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 (3×20 mL), ether (3×50 mL) and dried at 110º C for 30 minutes. Yield=98%. ^{1}H-NMR (DMSO-d_6- 300 MHz Varian Unity) δ 10.60 (2H, s, NH), 8.64 (2H, d, *J*= 6.6

Hz, pyridine 2-H), 7.69 (2H, d, *J*= 5.7 Hz, pyridine 3H), 6.32 (1H, s, CH), and 3.09 ppm (6H, s, CH_3). ^{13}C-NMR (DMSO-d_6- 300 MHz Varian Unity) δ 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).

Preparation of 1-butyl-5-[(2,4,6-trioxohexahydropyrimidin-5-yl)(pyridin-4-yl)methyl]pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (E14)

Acetic acid solution (300 mL) of 1-butylbarbituric acid (920 mg; 5 mmol) and 4-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 (3×30 mL) and dried at 80º C under reduced pressure for five hours. Yield=92%. ^{1}H-NMR (DMSO-d_6- 300 MHz Varian Unity) δ 10.54 (2H, s, NH), 8.64 (2H, d, *J*= 6.9 Hz, pyridine 4-H), 7.63 (2H, d, *J*= 6.3 Hz, pyridine 3-H), 6.32 (1H, s), 3.70 (4H, t, *J*= 6.6 Hz), 1.46 (4H, m), 1.28 (4H, m), and 0.87 ppm (6H, t, *J*= 6.6 Hz, CH_3). ^{13}C-NMR (DMSO-d_6- 300 MHz Varian Unity) δ 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).

Synthesis of 1-phenyl-5-[(2,4,6-trioxohexahydropyrimidin-5-yl)(pyridin-4-yl)methyl]pyrimidine-2,4,6(1H,3H,5H)-trione (E15)

After 1-phenylbarbituric acid (g; 0.005 mol) was dissolved in refluxing methanol (100 mL) 4-pyridinecarboxaldehyde (0.27 g; 0.0025 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 (3×20 mL), ether (3×50 mL) and dried at 110º C for 30 minutes. Yield=92%. ^{1}H-NMR (DMSO-d_6- 300 MHz Varian Unity) δ 10.74 (2H, s, NH), 8.67 (2H, d, *J*= 6.9 Hz, pyridine 2-H), 7.84 (2H, d, *J*= 6.9 Hz, pyridine 3-H), 7.40 (4H, t, *J*= 6.9 Hz, phenyl *m*-H), 7.32 (2H, t, *J*= 6.9 Hz, phenyl *p*-H), 7.19 (4H, d, *J*= 6.9 Hz, *o*-H), 6.27 ppm (1H, s, CH). ^{13}C-NMR (DMSO-d_6- 300 MHz Varian Unity) δ 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.

Synthesis of 3,dimethyl-5-[(2,4,6-trioxohexahydropyrimidin-5-yl)(quinolin-3-yl)methyl]pyrimidine-2,4,6(1H,3H,5H)-trione (E16)

After 1,3-dimethylbarbituric acid (0.78 g; 0.005 mol) was dissolved in refluxing methanol (100 mL) 3-quinolinecarboxaldehyde (0.378 g; 0.0025 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 (3×20 mL), ether (3×50 mL) and dried at 110º C for 30 minutes. Yield=86%. ^{1}H-NMR (DMSO-d_6- 300 MHz Varian Unity) δ 9.02 (1H, s, quinoline 2-H), 8.80 (1H, s,q-2-H), 8.30 (2H, d, *J*= 8.1 Hz, q-8-H), 8.19 (1H, d, *J*= 6.0 Hz, q-5-H), 8.02 (1H, t. *J*= 8.1 Hz, q-7-H), 7.86 (1H, t, *J*= 7.2 Hz, q-6-H), 6.43 (1H, s, CH)), and 3.15 ppm (12H, s, CH_3). ^{13}C-NMR (DMSO-d_6- 300 MHz Varian Unity) δ 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).

Synthesis of 1-phenyl-5-[(2,4,6-trioxohexahydropyrimidin-5-yl)(quinolin-3-yl)methyl]pyrimidine-2,4,6(1H,3H,5H)-trione **(E17)**

After 1-phenylbarbituric acid (1.02 g; 0.005 mol) was dissolved in refluxing methanol (100 mL) 3-quinolinecarboxaldehyde (0.378 g; 0.0025 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 (3×20 mL), ether (3×50 mL) and dried at 110º C for 30 minutes. Yield=93%. ^{1}H-NMR (DMSO-d_6- 300 MHz Varian Unity) δ 10.78 (2H, s, NH), 9.05 (1H, s, q-2-H), 8.93 (1H, s, q-4-H), 8.36 (1H, d, *J*= 6.3 Hz, q-8-H), 8.20 (1H, d, *J*= 6.3 Hz, q-5-H), 8.00 (1H, t, *J*= 5.4 Hz, q-7-H), 7.88 (1H, t, *J*= 5.7 Hz, q-6-H), 7.39 (4H, t, *J*= 5.7, phenyl *m*-H), 7.31 (2H, t, *J*= 5.7 Hz, phenyl *p*-H), 7.24 (4H, d, *J*= 5.7 Hz, phenyl *o*-H), and 6.34 ppm (1H, s, CH). ^{13}C-NMR (DMSO-d_6- 300 MHz Varian Unity) δ 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).

Synthesis of 1,3-dimethyl-5-[(2,4,6-trioxohexahydropyrimidin-5-yl)(quinolin-4-yl)methyl]pyrimidine-2,4,6(1H,3H,5H)-trione **(E18)**

After 1,3-dimethylbarbituric acid (0.78 g; 0.005 mol) was dissolved in refluxing methanol (100 mL) 4-quinolinecarboxaldehyde (0.378 g; 0.0025 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 (3×20 mL), ether (3×50 mL) and dried at 110º C for 30 minutes. Yield=84%. ^{1}H-NMR (DMSO-d_6- 300 MHz Varian Unity) δ 9.07, d, *J*= 5.7 Hz, q-2-H), 8.39 (1H, d, *J*= 8.7 Hz, q-8-H), 8.16 (1H, d, *J*= 7.8 Hz, q-5-H), 8.03 (1H, t, *J*= 6.3 Hz, q-C-7), 7.92 (1H, d, *J*= 5.7 Hz, q-3-H), 7.84 (1H, t, *J*= 7.8 Hz, q-6-H), 6.97 (1H, s, CH), 3.69 (1H, s, CH), and 3.13 ppm (12H, s, CH_3). ^{13}C-NMR (DMSO-d_6- 300 MHz Varian Unity) δ 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).

Synthesis of 1-methyl-5-[(2,4,6-trioxohexahydropyrimidin-5-yl)(quinolin-4-yl)methyl]pyrimidine-2,4,6(1H,3H,5H)-trione **(E19)**

After 1-methylbarbituric acid (0.71 g; 0.005 mol) was dissolved in refluxing methanol (100 mL) 4-quinolinecarboxaldehyde (0.378 g; 0.0025 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 (3×20 mL), ether (3×50 mL) and dried at 110º C for 30 minutes. Yield=78%. ^{1}H-NMR (DMSO-d_6- 300 MHz Varian Unity) δ 10.63 (2H, s, NH), 9.06 (1H, d, J= 5.4 Hz, q-2-H), 8.42 (1H, d, J= 6.0 Hz, q-8-H), 8.14 (1H, d, J= 8.7 Hz, q-5-H), 8.00 (1H, t, J= 8.1 Hz, q-7-H), 7.83 (1H, d, J= 5.7 Hz, q-3-H), 7.83 (1H, t, J= 8.7 Hz, q-6-H), 6.87 (1H, s, CH), and 3.061 ppm (6H, s, CH_3). ^{13}C-NMR (DMSO-d_6- 300 MHz Varian Unity) δ 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).

Synthesis of 1-phenyl-5-[(2,4,6-trioxohexahydropyrimidin-5-yl)(quinolin-4-yl)methyl]pyrimidine-2,4,6(1H,3H,5H)-trione **(E20)**

After 1-phenylbarbituric acid (1.03 g; 0.005 mol) was dissolved in refluxing methanol (100 mL) 4-quinolinecarboxaldehyde (0.378 g; 0.0025 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 (3×20 mL), ether (3×50 mL) and dried at 110º C for 30 minutes. Yield=95%. ^{1}H-NMR (DMSO-d_6- 300 MHz Varian Unity) δ 10.83 (2H, s, NH), 912 (1H, d, J= 5.7

Hz, q-2-H), 8.49 (1H, d, *J*= 8.7 Hz, q-8-H), 8.17 (1H, d, *J*= 8.1 Hz, q-5-H), 8.05 (1H, t, *J*= 7.2 Hz, q-7-H), 7.98 (1H, d, *J*= 5.7 Hz, q-3-H), 7.90 (1H, t, *J*= 8.4 Hz, q-6-H), 7.39 (4H, t, *J*= 7.5 Hz, phenyl *m*-H), 7.32 (2H, t, *J*= 6.0 Hz, phenyl *p*-H), 7.14 (4H, d, *J*= 7.5 Hz, phenyl *o*-H), and 6.87 ppm (1H,s CH). ^{13}C-NMR (DMSO-d_6- 300 MHz Varian Unity) δ 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.

Preparation of Pyridinium-barbiturate Zwitterion (F1). A methanol solution (100 mL) of 1,3-dimethylbarbituric acid (1.56 g; 10 mmol) and 2-pyridinecarbaldehyde (1.1 g; 10 mmol) was refluxed for 45 min. The solution was then transferred to an open 300 mL beaker and left to stand at room temperature until the solvent evaporated to approximately 1/10 of its original volume. The product slowly crystallized from the methanol solution during the course of evaporation. Crystals were separated by filtration, washed with cold methanol (3×20 mL) and then ether (3×20 mL), and dried at room temperature to give 2.1 g (80%) of product. If necessary, further purification should be repeated by dissolving the product in a larger amount of methanol (~100 mL) and by leaving it at room temperature in open air to crystallize from the reduced volume (1/10) of the solvent. R_f = 0.505 in 1:1 CH_3OH-CH_3COOH. ^{1}H NMR (DMSO-d_6- 300 MHz Varian Unity) δ 9.00 (1H, d, *J* = 6.6 Hz, pyridinium 6-H), 8.41 (1H, t, *J* =7.8 Hz, pyridinium 5-H), 8.34 (1H, d, *J* = 5.1 Hz, pyridine 6-H), 7.90 (1H, t, *J* = 6.3 Hz, pyridinium, 4-H), 7.85 (1H, t, *J* = 7.8 Hz, pyridine 5-H), 7.71 (1H, d, *J* = 6.9 Hz, pyridinium 3-H), 7.61 (1H, d, *J* = 8.4 Hz, pyridine 3-H), 7.36 (1H, d + d, J_1 = 7.2 Hz, J_2 = 7.8 Hz, pyridine 4-H), 6.94 (1H, s, pyridinium), 5.82 (1H, s, pyridinebenzyl), 2.99 (6H,

1H, CH_3), 2.90 (3H, s, CH_3), and 2.83 (3H, s, CH_3); ^{13}C NMR (DMSO-d_6- 300 MHz Varian Unity) δ 162.9, 161.2, 158.5, 154.3, 150.2, 148.9, 147.5, 145.0, 141.8, 141.2, 135.9, 132.9, 122.0, 121.8, 121.1, 120.1 (six signals for carbonyl carbons and 10 signals for two pyridine rings), 70.8, 59.0, and 51.1 (signals for carbons from a five-membered ring), 25.4, 25.1, and 23.3 (three different CH_3 carbons); MS-ES (CH_3OH-CH_3COOH-NaCl), 491 (M + 1), 492 (M + 2), and (M + 22). *Anal.* Calcd. For $C_{24}H_{22}N_6O_6$: C, 58.77; H, 4.52; N, 17.13. Found: C, 58.71; H, 4.63; N 17.03.

Preparation of 5,5'-(2-Pyrimidine)bis(1,3-dimethyl-barbituric acid) (F3). A carbon tetrachloride solution (500 mL) of 1,3-dimethylbarbituric acid (780 mg; 5 mM) and 2-pyridinecarbaldehyde (270 mg; 2.5 mM) was stirred at room temperature for 7 days. The yellow precipitate was separated by filtration, washed with carbon tetrachloride (3×50 mL) and then ether (3×50 mL), and dried in air to afford 650 mg (65%) of product: R_f = 0.640 in 1:1 CH_3COOH-CH_3OH. ^1H NMR (DMSO-d_6- 300 MHz Varian Unity) δ 8.58 (1H, d, J = 6.0 Hz, pyridine 6-H), 8.40 (1H, t, J = 6.6 Hz, pyridine 5-H), 7.87 (1H, d, J =8.1 Hz, pyridine 3-H), 7.81 (1H, t, J =6.6 Hz, pyridine 4-H), 6.33 (1H, s, benzyl hydrogen), and 3.13 (12H, s, four methyl group hydrogens); ^{13}C NMR (DMSO-d_6- 300 MHz Varian Unity) δ 159.3 and 156.0 (two different barbituric acid carbonyls), 147.8, 142.3, 137.6, 122.3, and 120.5 (five carbons from the pyridine ring), 80.5 (benzylic carbon), 32.0 (barbituric acid 5-carbon), 24.5 (barbituric methyl carbon). ES-MS (CH_3OH + NaCl) 424 (M + Na). *Anal.* Calcd. For $C_{18}H_{19}N_5O_6$: C, 53.86; H, 4.77; N, 17.45. Found: C, 53.68; H, 4.85; N 17.32.

Preparation of Amide F6. Sodium hydroxide (80 mg; 2 mM) in water (1 mL) and compound **F1** (245 mg; 0.5 mmol) was kept at room temperature for 4 h with occasional stirring. In the beginning, the reaction mixture was a suspension that became a clear solution after ~10 min. Progress of the reaction was followed by TLC chromatography and ^{1}H NMR spectroscopy (D_2O as a solvent). After approximately 2 h, zwitterion **F1** was fully converted into amide **F6**. The R_f of the soluble product in ethanol is 0.295 in 1:1 CH_3COOH-CH_3OH. Into the water solution was added ethanol (200 mL), and the solution was dried over anhydrous calcium chloride. The solid was separated by filtration, and ethanol was evaporated in vacuo at room temperature. The oily residue was slurried in anhydrous 1:1 alcohol-benzene, and the solvent was again evaporated. This procedure was repeated several times. The solid residue left after evaporation of the solvent was slurried in dry ether, filtered, and dried in a vacuum to give 198 mg (85%) of amide. ^{1}H NMR (D_2O-KOH -300 MHz Varian Unity) δ 8.45 (1H, d-d, J = 6.0 Hz, J_2 = 0.1.2 Hz), 8.21 (1H, t, J = 7.2 Hz), 7.84 (1H, t-d, J_1 = 7.2 Hz, J_2 = 1.2 Hz), 7.64 (1H, t, J = 6.6 Hz), 7.60 (1H, d-d, J_1 = 7.2 Hz, J_2 = 1.2 Hz), 7.53 (1H, d-d, J_1 = 7.2 Hz, J_2 = 1.2 Hz), 7.49 (1H, t, J = 7.8 Hz), 7.38 (1H, d-d-d, J_1 = 7.2 Hz, J_2 = 6.0 Hz, J_3 = 1.2 Hz), 3.04 (6H, s), and 2.46 (6H, s). ^{13}C NMR (D_2O-KOH -300 MHz Varian Unity) δ 171.7, 170.4, 163.8, 157.4, 120.8, 120.7, 120, 0, 118.6, 85.7, 53.1, 43.6, 23.2, and 21.9; MS-ES (CH_3OH-H_2O-KOH), 502 (M + 38).

X-ray Single-Crystal Structure Determination of Compound F1 at 155(2) K. Crystal Data: $C_{24}H_{22}N_6O_6$, M_r = 490.48, monoclinic, space group $P2_1/n$, a = 11.6777(6) Å, b = 13.4416(7) Å, c = 15.0367(8) Å, α = 90°, β = 111.630(1)°, γ = 90°, V = 2194.1(2) Å^3, Z = 4, $\rho_{Calcd.}$ 1.485 Mg/m^3, F_{000} = 1024, wavelength (λ) = 0.71073 Å, absorption coefficient

(μ) = 0.110 mm^{-1}. **Data Collection and Reduction**: crystal size = 0.4×0.5×0.6 mm; theta range, 2.10-30.00°; index ranges, -16 ≤ *h* ≤16, -18 ≤ *k* ≤18, -21 ≤ *l* ≤20; reflections collected, 30679; independent reflections, 6390 [R_{int} = 0.0284]; refinement method, full-matrix least-squares on F^2; data/restraints/parameters, 6390/0/413; final *R* indices [*I* > 2σ(*I*)]: *R*1 = 0.0370, w*R*2 = 0.1041, GOF on F^2 = 1.035. *R* indices (all data) *R*1 = 0.0486, w*R*2 = 0.1067; largest difference peak and hole: 0.388 and -0.241 $eÅ^{-3}$. **Measurement, Computing, and Graphics**: *SMART 1K CDD* (Bruker, 2000); cell refinement, *SMART*; data reduction, *SAINT-Plus* (Bruker, 2000); programs(s) used to solve structure, *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure, *SHELX97* (Sheldrick, 1997); molecular graphics, *SHELXTL97* (Sheldrick, 1997); software used to prepare material for publication, *SHELXTL97*.

General Procedure N: Preparation of bis-barbiturate ammonium salts

Synthesis of 5-[(2,4,6-trioxohexahydropyrimidin-5-yl)(pyridin-3-yl)methyl]pyrimidine-2,4,6(1H,3H,5H)-trione piperidinium salt (G1)

A suspension of piperidine (0.148 mL, 0.128 g, 1.50 mmol) barbituric acid (0.256 g, 2.00 mmol), and 3-pyridinecarboxaldehyde (0.107 g, 1.00 mmol) in methanol (100 mL) was refluxed for approximately 12 h. The reaction mixture was cooled to room temperature and the volume of methanol reduced to ¼ its original volume, and diluted with anhydrous ethyl ether (100 mL). The resulting solid precipitate was filtered, washed with ether (3 x 15 mL), and oven dried at 110º C for 2-3 hours, yielding 0.400 g (93%) pure product. Product decomposes at temperatures above 250º C. ^{1}H-NMR (DMSO-d_6- 300 MHz Varian Unity) δ 10.09 (s, 4H), 8.21 (d, 1H, *J*= 4.8 Hz), 8.17 (d, 1H, *J*= 2.1 Hz), 7.34 (d, 1H, *J*= 7.5 Hz), 7.15 (m, 1H), 5.98 (s, 1H), 2.98 (t, 4H, *J*= 5.4 Hz), 1.60 (m, 4H), 1.51

(m, 2H). ^{13}C-NMR (DMSO-d_6- 300 MHz Varian Unity) δ 160.9, 147.0, 144.7, 142.0, 136.4, 130.6, 119.1, 86.7, 40.3, 25.1, 18.7, 18.1 ppm.

Synthesis of 5-[(2,4,6-trioxohexahydropyrimidin-5-yl)(pyridin-4-yl)methyl]pyrimidine-2,4,6(1H,3H,5H)-trione morpholinium salt (G2)

A suspension of morpholine (0.130 mL, 0.130 g, 1.50 mmol) barbituric acid (0.256 g, 2.00 mmol), and 4-pyridinecarboxaldehyde (0.107 g, 1.00 mmol) in methanol (100 mL) was refluxed for approximately 12 h. The reaction mixture was cooled to room temperature and the volume of methanol reduced to ¼ its original volume, and diluted with anhydrous ethyl ether (100 mL). The resulting solid precipitate was filtered, washed with ether (3×15 mL), and oven dried at 110º C for 2-3 hours, yielding 0.420 g (97%) pure product. Product decomposes at temperatures above 250º C. ^{1}H-NMR (DMSO-d_6- 300 MHz Varian Unity) δ 10.11 (s, 4H), 8.29 (d, 2H, *J*= 5.1 Hz), 6.98 (d, 2H, *J*= 5.1 Hz), 5.93 (s, 1H), 3.72 (t, 4H, *J*= 4.7 Hz), 3.07 (t, 4H, *J*= 5.1 Hz). ^{13}C-NMR (DMSO-d_6- 300 MHz Varian Unity) δ 161.3, 150.9, 147.1, 145.0, 118.8, 86.4, 59.8, 39.5, 27.0.

Synthesis of 5-[(2,4,6-trioxohexahydropyrimidin-5-yl)(quinolin-4-yl)methyl]pyrimidine-2,4,6(1H,3H,5H)-trione ethanolaminium salt (G3)

A suspension of ethanolamine (0.090 mL, 0.092 g, 1.50 mmol) barbituric acid (0.256 g, 2.00 mmol), and 4-quinolinecarboxaldehyde (0.159 g, 1.00 mmol) in methanol (100 mL) was refluxed for approximately 12 h. The reaction mixture was cooled to room temperature and the volume of methanol reduced to ¼ its original volume, and diluted with anhydrous ethyl ether (100 mL). The resulting solid precipitate was filtered, washed

with ether (3×15 mL), and oven dried at 110º C for 2-3 hours, yielding 0.420 g (92%) pure product. Product decomposes at temperatures above 250º C. ^{1}H-NMR (DMSO-d_6- 300 MHz Varian Unity) δ 10.08 (s, 4H), 8.66 (d, 1H, *J*= 4.8 Hz), 8.14 (d, 1H, *J*= 7.8 Hz), 7.91 (d, 1H, *J*= 8.1 Hz), 7.60 (t, 1H, *J*= 8.1 Hz), 7.42 (t, 1H, *J*= 7.2 Hz), 7.28 (d, 1H, *J*= 4.5 Hz), 6.48 (s, 1H), 3.54 (t, 2H, *J*= 5.0 Hz), 2.83 (t, 2H, *J*= 5.3 Hz). ^{13}C-NMR (DMSO-d_6- 300 MHz Varian Unity) δ 161.1, 147.7, 146.9, 145.7, 144.1, 125.6, 124.6, 123.8, 121.9, 121.3, 117.0, 87.2, 53.8, 37.6, 25.6.

Synthesis of 5-[(2,4,6-trioxohexahydropyrimidin-5-yl)(quinolin-3-yl)methyl]pyrimidine-2,4,6(1H,3H,5H)-trione morpholinium salt (G4)

A suspension of morpholine (0.130 mL, 0.130 g, 1.50 mmol) barbituric acid (0.256 g, 2.00 mmol), and 3-quinolinecarboxaldehyde (0.159 g, 1.00 mmol) in methanol (100 mL) was refluxed for approximately 12 h. The reaction mixture was cooled to room temperature and the volume of methanol reduced to ¼ its original volume, and diluted with anhydrous ethyl ether (100 mL). The resulting solid precipitate was filtered, washed with ether (3×15 mL), and oven dried at 110º C for 2-3 hours, yielding 0.396 g (82%) pure product. Product decomposes at temperatures above 250º C. ^{1}H-NMR (DMSO-d_6- 300 MHz Varian Unity) δ 10.09 (s, 4H), 8.52 (d, 1H, *J*= 2.1 Hz), 7.88 (d of d, 2H), 7.78 (s, 1H), 7.60 (t, 1H, *J*= 8.1 Hz), 7.48 (t, 1H, *J*= 8.1 Hz), 6.17 (s, 1H), 3.73 (t, 4H, *J*= 5.1 Hz), 3.09 (t, 4H, *J*= 5.1 Hz). ^{13}C-NMR (DMSO-d_6- 300 MHz Varian Unity) δ 161.1, 148.1, 147.7, 147.1, 142.1, 134.0, 128.1, 124.7, 124.4, 124.0, 122.6, 86.7, 59.8, 39.5, 25.6.

Synthesis of 5-[(2,4,6-trioxohexahydropyrimidin-5-yl)(2-nitrobenzyl)methyl]pyrimidine-2,4,6(1H,3H,5H)-trione morpholinium salt (G5)

A suspension of morpholine (0.130 mL, 0.130 g, 1.50 mmol) barbituric acid (0.256 g, 2.00 mmol), and 2-nitrobenzaldehyde (0.151 g, 1.00 mmol) in methanol (100 mL) was refluxed for approximately 12 h. The reaction mixture was cooled to room temperature and the volume of methanol reduced to ¼ its original volume, and diluted with anhydrous ethyl ether (100 mL). The resulting solid precipitate was filtered, washed with ether (3×15 mL), and oven dried at 110º C for 2-3 hours, yielding 0.439 g (92%) pure product. Product decomposes at temperatures above 250º C. ^{1}H-NMR (DMSO-d_6- 300 MHz Varian Unity) δ 10.00 (s. 4H), 7.43 (t, 2H, J= 8.3 Hz), 7.24 (m, 2H), 6.08 (s, 1H), 3.75 (t, 4H, J= 4.8 Hz), 3.09 (t, 4H, J= 4.8 Hz). ^{13}C-NMR (DMSO-d_6- 300 MHz Varian Unity) δ 160.7, 147.1, 146.4, 134.1, 126.9, 126.0, 122.3, 119.6, 86.5, 59.8, 39.4, 25.2 ppm.

Synthesis of 1,3-dimethyl-5-[(2,4,6-trioxohexahydropyrimidin-5-yl)(quinolin-4-yl)methyl]pyrimidine-2,4,6(1H,3H,5H)-trione piperidinium salt (G6)

A suspension of piperidine (0.148 mL, 0.128 g, 1.50 mmol) 1,3-dimethylbarbituric acid (0.312 g, 2.00 mmol), and 4-quinolinecarboxaldehyde (0.159 g, 1.00 mmol) in methanol (100 mL) was refluxed for approximately 12 h. The reaction mixture was cooled to room temperature and the volume of methanol reduced to ¼ its original volume, and diluted with anhydrous ethyl ether (100 mL). The resulting solid precipitate was filtered, washed with ether (3×15 mL), and oven dried at 110º C for 2-3 hours, yielding 0.520 g (97%) pure product. Product decomposes at temperatures above 200º C. ^{1}H-NMR (DMSO-d_6-

300 MHz Varian Unity) δ 8.65 (d, 1H, *J*= 4.5 Hz), 8.21 (s, 2H), 8.03 (d, 1H, *J*= 7.5 Hz), 7.90 (d, 1H, *J*= 7.5 Hz), 7.59 (t, 1H, *J*= 8.3 Hz), 7.42 (t, 1H, *J*= 8.3 Hz), 7.32 (d, 1H, *J*= 3.9 Hz), 6.73 (s, 1H), 3.11 (s, 12H), 2.98 (t, 4H, *J*= 5.7 Hz), 1.61 (m, 4H), 1.53 (m, 2H). ^{13}C-NMR (DMSO-d_6- 300 MHz Varian Unity) δ 159.0, 147.6, 146.8, 145.9, 144.3, 125.8, 124.5, 123.7, 122.0, 121.0, 117.2, 87.0, 40.2, 28.4, 24.0, 18.6, 18.0

Synthesis of 1,3-dimethyl-5-[(2,4,6-trioxohexahydropyrimidin-5-yl)(pyridin-4-yl)methyl]pyrimidine-2,4,6(1H,3H,5H)-trione morpholinium salt (G7)

A suspension of morpholine (0.130 mL, 0.130 g, 1.50 mmol) 1,3-dimethylbarbituric acid (0.312 g, 2.00 mmol), and 4-pyridinecarboxaldehyde (0.107 g, 1.00 mmol) in methanol (100 mL) was refluxed for approximately 12 h. The reaction mixture was cooled to room temperature and the volume of methanol reduced to ¼ its original volume, and diluted with anhydrous ethyl ether (100 mL). The resulting solid precipitate was filtered, washed with ether (3×15 mL), and oven dried at 110º C for 2-3 hours, yielding 0.454 g (93%) pure product. Product decomposes at temperatures above 200º C. ^{1}H-NMR (DMSO-d_6- 300 MHz Varian Unity) δ 8.34 (d, 2H, *J*= 6.0 Hz), 7.14 (d, 2H, *J*= 6.0 Hz), 3.73 (t, 4H, *J*= 4.5 Hz), 3.12 (s, 12H), 3.08 (t, 4H, *J*= 4.5 Hz). ^{13}C-NMR (DMSO-d_6- 300 MHz Varian Unity) δ 158.9, 153.4, 147.7, 143.2, 119.4, 86.2, 59.7, 39.4, 30.2, 24.4 ppm.

Synthesis of 1,3-dimethyl-5-[(2,4,6-trioxohexahydropyrimidin-5-yl)(pyridin-3-yl)methyl]pyrimidine-2,4,6(1H,3H,5H)-trione piperidinium salt (G8)

A suspension of piperidine (0.148 mL, 0.128 g, 1.50 mmol) 1,3-dimethylbarbituric acid (0.312 g, 2.00 mmol), and 3-pyridinecarboxaldehyde (0.107 g, 1.00 mmol) in methanol (100 mL) was refluxed for approximately 12 h. The reaction mixture was cooled to room temperature and the volume of methanol reduced to ¼ its original volume, and diluted with anhydrous ethyl ether (100 mL). The resulting solid precipitate was filtered, washed with ether (3×15 mL), and oven dried at 110º C for 2-3 hours, yielding 0.462 g (95%) pure product. Product decomposes at temperatures above 200º C. ^{1}H-NMR (DMSO-d_6- 300 MHz Varian Unity) δ 8.25 (s, 2H), 8.22 (d, 1H, J= 4.8 Hz), 8.19 (d, 1H, J= 2.1 Hz), 7.37 (d, 1H, J= 7.8 Hz), 7.14 (m, 1H), 3.13 (s, 12H), 3.00 (t, 4H, J= 5.7 Hz), 1.62(m, 4H), 1.53 (m, 2H). ^{13}C-NMR (DMSO-d_6- 300 MHz Varian Unity) δ 159.0, 147.7, 144.8, 142.0, 135.7, 130.7, 119.1, 86.5, 40.3, 28.0, 24.4, 18.6, 18.0 ppm.

Synthesis of 1,3-dimethyl-5-[(2,4,6-trioxohexahydropyrimidin-5-yl)(quinolin-3-yl)methyl]pyrimidine-2,4,6(1H,3H,5H)-trione piperidinium salt (G9)

A suspension of piperidine (0.148 mL, 0.128 g, 1.50 mmol) 1,3-dimethylbarbituric acid (0.312 g, 2.00 mmol), and 3-quinolinecarboxaldehyde (0.159 g, 1.00 mmol) in methanol (100 mL) was refluxed for approximately 12 h. The reaction mixture was cooled to room temperature and the volume of methanol reduced to ¼ its original volume, and diluted with anhydrous ethyl ether (100 mL). The resulting solid precipitate was filtered, washed with ether (3×15 mL), and oven dried at 110º C for 2-3 hours, yielding 0.440 g (82%) pure product. Product decomposes at temperatures above 200º C. ^{1}H-NMR (DMSO-d_6-

300 MHz Varian Unity) δ 8.54 (d, 1H, *J*= 2.1 Hz), 8.21 (s, 2H), 7.87 (t, 3H, *J*= 9.3 Hz), 7.60 (t, 1H, *J*= 6.9 Hz), 7.48 (t, 1H, *J*= 6.9 Hz), 6.40 (s, 1H), 3.15 (s, 12H), 3.00 (t, 4H, *J*= 5.7 Hz), 1.62 (m, 4H), 1.54 (m, 2H). ^{13}C-NMR (DMSO-d_6- 300 MHz Varian Unity) δ 159.2, 148.0, 147.9, 142.3, 133.8, 128.4, 124.8, 124.5, 124.3, 122.7, 86.7, 40.4, 28.6, 24.6, 18.8, and 18.2 ppm.

Synthesis of 1,3-dimethyl-5-[(2,4,6-trioxohexahydropyrimidin-5-yl)(3-nitrobenzyl)methyl]pyrimidine-2,4,6(1H,3H,5H)-trione morpholinium salt (G10)

A suspension of morpholine (0.130 mL, 0.130 g, 1.50 mmol) 1,3-dimethylbarbituric acid (0.312 g, 2.00 mmol), and 3-nitrobenzaldehyde (0.151 g, 1.00 mmol) in methanol (100 mL) was refluxed for approximately 12 h. The reaction mixture was cooled to room temperature and the volume of methanol reduced to ¼ its original volume, and diluted with anhydrous ethyl ether (100 mL). The resulting solid precipitate was filtered, washed with ether (3×15 mL), and oven dried at 110º C for 2-3 hours, yielding 0.447 g (84%) pure product. Product decomposes at temperatures above 200º C. ^{1}H-NMR (DMSO-d_6- 300 MHz Varian Unity) δ 8.67 (s, 2H), 7.94 (d, 1H, *J*= 7.8 Hz), 7.82 (s, 1H), 7.48 (m, 2H), 6.32 (s, 1H), 3.77 (t, 4H, *J*= 5.1 Hz), 3.12 (t, 4H, *J*= 5.1 Hz). ^{13}C-NMR (DMSO-d_6, 300 MHz) δ 159.1, 147.8, 144.1, 123.6, 130.3, 125.4, 117.5, 116.3, 86.5, 59.7, 39.4, 30.1, and 24.4 ppm

Synthesis of 1-methyl-5-[(2,4,6-trioxohexahydropyrimidin-5-yl)(pyridin-3-yl)methyl]pyrimidine-2,4,6(1H,3H,5H)-trione ethanolaminium salt (G11)

A suspension of ethanolamine (0.090 mL, 0.092 g, 1.50 mmol) 1-methylbarbituric acid (0.284 g, 2.00 mmol), and 3-pyridinecarboxaldehyde (0.107 g, 1.00 mmol) in methanol (100 mL) was refluxed for approximately 12 h. The reaction mixture was cooled to room temperature and the volume of methanol reduced to ¼ its original volume, and diluted with anhydrous ethyl ether (100 mL). The resulting solid precipitate was filtered, washed with ether (3×15 mL), and oven dried at 110º C for 2-3 hours, yielding 0.378 g (87%) pure product. Product decomposes at temperatures above 200º C. ^{1}H-NMR (DMSO-d_6- 300 MHz Varian Unity) δ 10.40 (s, 2H), 8.22 (d, 1H, *J*= 4.5 Hz), 8.19 (s, 1H), 7.37 (d, 1H, *J*= 8.1 Hz), 7.16 (m, 1H), 6.10 (s, 1H), 3.56 (t, 2H, *J*= 5.4 Hz), 3.08 (s, 6H), 2.80 (t, 2H, *J*= 5.4 Hz). ^{13}C-NMR (DMSO-d_6- 300 MHz Varian Unity) δ 160.9, 158.0, 147.3, 144.7, 142.0, 136.2, 130.6, 119.0, 86.6, 54.5, 37.9, 26.8, and 23.3 ppm.

Synthesis of 1-methyl-5-[(2,4,6-trioxohexahydropyrimidin-5-yl)(pyridin-4-yl)methyl]pyrimidine-2,4,6(1H,3H,5H)-trione piperidinium salt (G12)

A suspension of piperidine (0.148 mL, 0.128 g, 1.50 mmol) 1-methylbarbituric acid (0.284 g, 2.00 mmol), and 4-pyridinecarboxaldehyde (0.107 g, 1.00 mmol) in methanol (100 mL) was refluxed for approximately 12 h. The reaction mixture was cooled to room temperature and the volume of methanol reduced to ¼ its original volume, and diluted with anhydrous ethyl ether (100 mL). The resulting solid precipitate was filtered, washed with ether (3×15 mL), and oven dried at 110º C for 2-3 hours, yielding 0.399 g (87%) pure product. Product decomposes at temperatures above 200º C. ^{1}H-NMR (DMSO-d_6-

300 MHz Varian Unity) δ 10.30 (s, 2H), 8.27 (d, 2H, *J*= 6.0 Hz), 6.96 (d, 2H, *J*= 6.0 Hz), 6.07 (s, 1H), 3.06 (s, 6H), 2.99 (t, 4H, *J*= 5.7 Hz), 1.61 (m, 4H), 1.54 (m, 2H). ^{13}C-NMR (DMSO-d_6- 300 MHz Varian Unity) δ 160.4, 159.0, 150.1, 146.8, 144.6, 118.2, 85.9, 39.8, 28.3, 22.9, 18.2, and 17.6 ppm.

Synthesis of 1-methyl-5-[(2,4,6-trioxohexahydropyrimidin-5-yl)(quinolin-3-yl)methyl]pyrimidine-2,4,6(1H,3H,5H)-trione piperidinium salt (G13) A suspension of piperidine (0.148 mL, 0.128 g, 1.50 mmol) 1-methylbarbituric acid (0.284 g, 2.00 mmol), and 3-quinolinecarboxaldehyde (0.159 g, 1.00 mmol) in methanol (100 mL) was refluxed for approximately 12 h. The reaction mixture was cooled to room temperature and the volume of methanol reduced to ¼ its original volume, and diluted with anhydrous ethyl ether (100 mL). The resulting solid precipitate was filtered, washed with ether (3×15 mL), and oven dried at 110º C for 2-3 hours, yielding 0.351 g (69%) pure product. Product decomposes at temperatures above 200º C. ^{1}H-NMR (DMSO-d_6- 300 MHz Varian Unity) δ 10.41 (s, 2H), 8.53 (d, 1H, *J*= 2.1 Hz), 8.40 (s, 2H), 7.87 (m, 3H), 7.99 (s, 1H), 7.59 (t, 1H, *J*= 6.9 Hz), 7.47 (t, 1H, *J*= 6.9 Hz), 6.28 (s, 1H), 3.09 (s, 6H), 2.98 (t, 4H, *J*= 5.1), 1.59 (m, 4H), 1.52 (m, 2H). ^{13}C-NMR (DMSO-d_6- 300 MHz Varian Unity) δ 161.0, 158.8, 158.3, 147.7, 147.3, 142.0, 133.9, 128.0, 124.6, 124.3, 124.0, 122.5, 86.6, 40.3, 27.3, 23.4, 18.7, and 18.1 ppm.

Synthesis of 1-methyl-5-[(2,4,6-trioxohexahydropyrimidin-5-yl)(pyridin-4-yl)methyl]pyrimidine-2,4,6(1H,3H,5H)-trione morpholinium salt (G14)

A suspension of morpholine (0.130 mL, 0.130 g, 1.50 mmol) 1-methylbarbituric acid (0.284 g, 2.00 mmol), and 4-pyridinecarboxaldehyde (0.107 g, 1.00 mmol) in methanol (100 mL) was refluxed for approximately 12 h. The reaction mixture was cooled to room temperature and the volume of methanol reduced to ¼ its original volume, and diluted with anhydrous ethyl ether (100 mL). The resulting solid precipitate was filtered, washed with ether (3×15 mL), and oven dried at 110º C for 2-3 hours, yielding 0.410 g (89%) pure product. Product decomposes at temperatures above 200º C. ^{1}H-NMR (DMSO-d_6- 300 MHz Varian Unity) δ 10.40 (s, 2H), 8.31 (d, 2H, *J*= 6.0 Hz), 7.04 (d, 2H, *J*= 6.0 Hz), 6.10 (s, 1H), 3.74 (t, 4H, *J*= 5.7 Hz), 3.10 (t, 4H, *J*= 5.7 Hz), 3.07 (s, 6H). ^{13}C-NMR (DMSO-d_6- 300 MHz Varian Unity) δ 160.9, 151.9, 147.3, 144.3, 119.0, 86.3, 59.7, 39.4, 28.9, 23.3 ppm.

Synthesis of 1-methyl-5-[(2,4,6-trioxohexahydropyrimidin-5-yl)(quinolin-4-yl)methyl]pyrimidine-2,4,6(1H,3H,5H)-trione piperidinium salt (G15)

A suspension of piperidine (0.148 mL, 0.128 g, 1.50 mmol) 1-methylbarbituric acid (0.284 g, 2.00 mmol), and 4-quinolinecarboxaldehyde (0.159 g, 1.00 mmol) in methanol (100 mL) was refluxed for approximately 12 h. The reaction mixture was cooled to room temperature and the volume of methanol reduced to ¼ its original volume, and diluted with anhydrous ethyl ether (100 mL). The resulting solid precipitate was filtered, washed with ether (3×15 mL), and oven dried at 110º C for 2-3 hours, yielding 0.478 g (94%) pure product. Product decomposes at temperatures above 200º C. ^{1}H-NMR (DMSO-d_6-

300 MHz Varian Unity) δ 8.67 (d, 1H, *J*= 3.3 Hz), 8.10 (d, 1H, *J*= 6.0 Hz), 7.92 (d, 1H, *J*= 6.0 Hz), 7.60 (t, 1H, *J*= 5.7 Hz), 7.43 (t, 1H, *J*= 5.7 Hz), 7.30 (d, 1H, *J*= 3.3 Hz), 6.62 (s, 1H), 2.98 (t, 4H, *J*= 3.3 Hz), 1.60 (m, 4H), 1.51(m, 2H). ^{13}C-NMR (DMSO-d_6- 300 MHz Varian Unity) δ 160.9, 159.2, 147.3, 146.0, 144.4, 125.9, 124.7, 123.9, 122.0, 121.3, 117.2, 87.4, 40.3, 27.3, 23.4, 18.7, 18.1 ppm.

Synthesis of 1-phenyl-5-[(2,4,6-trioxohexahydropyrimidin-5-yl)(quinolin-4-yl)methyl]pyrimidine-2,4,6(1H,3H,5H)-trione piperidinium salt (G16)

A suspension of piperidine (0.148 mL, 0.128 g, 1.50 mmol) 1-phenylbarbituric acid (0.408 g, 2.00 mmol), and 4-quinolinecarboxaldehyde (0.159 g, 1.00 mmol) in methanol (100 mL) was refluxed for approximately 12 h. The reaction mixture was cooled to room temperature and the volume of methanol reduced to ¼ its original volume, and diluted with anhydrous ethyl ether (100 mL). The resulting solid precipitate was filtered, washed with ether (3×15 mL), and oven dried at 110º C for 2-3 hours, yielding 0.601 g (95%) pure product. Product decomposes at temperatures above 200º C. ^{1}H-NMR (DMSO-d_6- 300 MHz Varian Unity) δ 10.56 (s, 2H), 8.71 (d, 1H, *J*= 4.8 Hz), 8.20 (s, 2H), 8.14 (d, 1H, *J*= 8.4 Hz), 7.93 (d, 1H, *J*= 8.4 Hz), 7.62 (t, 1H, *J*= 7.5 Hz), 7.48 (t, 1H, *J*= 7.5 Hz), 7.40 (t, 4H, *J*= 5.1 Hz), 7.29 (m, 3H), 7.11 (d, 4H, *J*= 7.5 Hz), 6.59 (s, 1H), 2.95 (t, 4H, *J*= 5.1 Hz), 1.58 (m, 4H), 1.51 (m, 2H). ^{13}C-NMR (DMSO-d_6- 300 MHz Varian Unity) δ 160.6, 159.6, 147.0, 146.8, 145.9, 144.3, 133.2, 125.8, 125.7, 124.7, 124.6, 123.8, 123.6, 121.9, 121.1, 117.1, 87.1, 40.2, 27.2, 18.6, 18.0 ppm.

Synthesis of 1-phenyl-5-[(2,4,6-trioxohexahydropyrimidin-5-yl)(pyridin-3-yl)methyl]pyrimidine-2,4,6(1H,3H,5H)-trione morpholinium salt (G17)

A suspension of morpholine (0.130 mL, 0.130 g, 1.50 mmol) 1-phenylbarbituric acid (0.408 g, 2.00 mmol), and 3-pyridinecarboxaldehyde (0.107 g, 1.00 mmol) in methanol (100 mL) was refluxed for approximately 12 h. The reaction mixture was cooled to room temperature and the volume of methanol reduced to ¼ its original volume, and diluted with anhydrous ethyl ether (100 mL). The resulting solid precipitate was filtered, washed with ether (3×15 mL), and oven dried at 110º C for 2-3 hours, yielding 0.520 g (89%) pure product. Product decomposes at temperatures above 200º C. ^{1}H-NMR (DMSO-d_6- 300 MHz Varian Unity) δ 10.60 (s, 2H), 8.36 (s, 1H), 8.30 (d, 1H, *J*= 3.3 Hz), 7.59 (d, 1H, *J*= 5.7 Hz), 7.39 (t, 4H, *J*= 5.7 Hz), 7.29 (m, 3H), 7.18 (d, 4H, *J*= 5.7 Hz), 6.10 (s, 1H), 3.68 (t, 4H, *J*= 3.6 Hz), 3.02 (t, 4H, *J*= 3.6 Hz). ^{13}C-NMR (DMSO-d_6- 300 MHz Varian Unity) δ 160.9, 159.0, 147.0, 144.3, 141.7, 136.4, 133.4, 131.6, 125.8, 124.7, 123.7, 119.5, 87.7, 59.7, 39.4, 27.0 ppm.

Synthesis of 5-[(2,4,6-trioxohexahydropyrimidin-5-yl)(4-methylbenzyl)methyl]pyrimidine-2,4,6(1H,3H,5H)-trione morpholinium salt (G18)

Into 50 mL of methanol, 4-tolualdehyde (0.121 g; 1.00 mmol), barbituric acid (0.256 g; 2.00 mmol), and morpholine (0.130 mL; 0.130 g; 1.5 mmol) were added and stirred. The resulting reaction suspension was refluxed overnight. The reaction mixture was cooled to room temperature and the volume reduced to ¼ the original volume, resulting in the formation of a precipitate. The precipitate was removed by filtration and washed with ether (3×20 mL). Solid was oven dried at 105º C for 3 hours, to afford 0.424 g (95%)

pure product. Product decomposes at temperatures above 200º C. ^{1}H-NMR (DMSO-d_6- 300 MHz Varian Unity) δ 10.22 (s, 4H), 6.89 (m, 4H), 5.89 (s, 1H), 3.71 (t, 4H, *J*= 4.8 Hz), 3.04 (t, 4H, *J*= 4.8 Hz), 2.19 (s, 3H). ^{13}C-NMR (DMSO-d_6- 300 MHz Varian Unity) δ 161.9, 147.2, 137.7, 129.6, 124.5, 123.0, 87.7, 59.9, 39.6, 26.6, 16.9 ppm.

Synthesis of 5-[(2,4,6-trioxohexahydropyrimidin-5-yl)(3-methylbenzyl)methyl]pyrimidine-2,4,6(1H,3H,5H)-trione morpholinium salt (G19)

Into 50 mL of methanol, 3-tolualdehyde (0.121 g; 1.00 mmol), barbituric acid (0.256 g; 2.00 mmol), and morpholine (0.130 mL; 0.130 g; 1.5 mmol) were added and stirred. The resulting reaction suspension was refluxed overnight. The reaction mixture was cooled to room temperature and the volume reduced to ¼ the original volume, resulting in the formation of a precipitate. The precipitate was removed by filtration and washed with ether (3×20 mL). Solid was oven dried at 105º C for 3 hours, to afford 0.401 g (90%) pure product. Product decomposes at temperatures above 200º C. ^{1}H-NMR (DMSO-d_6- 300 MHz Varian Unity) δ 10.12 (s, 4H), 7.02 (t, 1H, *J*= 7.8 Hz), 6.83 (m, 3H), 5.89 (s, 1H), 3.72 (t, 4H, *J*= 4.8 Hz), 3.06 (t, 4H, *J*= 4.8 Hz), 2.19 (s, 3H). ^{13}C-NMR (DMSO-d_6- 300 MHz Varian Unity) δ 162.9, 147.2, 141.0, 132.6, 123.8, 123.7, 121.7, 120.3, 87.6, 60.0, 39.7, 26.8, 17.8 ppm.

Synthesis of 5-[(2,4,6-trioxohexahydropyrimidin-5-yl)(3-methoxybenzyl)methyl]pyrimidine-2,4,6(1H,3H,5H)-trione morpholinium salt (G2)

Into 50 mL of methanol, 3-methoxybenzaldehyde (0.136 g; 1.00 mmol), barbituric acid (0.256 g; 2.00 mmol), and morpholine (0.130 mL; 0.130 g; 1.5 mmol) were added and

stirred. The resulting reaction suspension was refluxed overnight. The reaction mixture was cooled to room temperature and the volume reduced to ¼ the original volume, resulting in the formation of a precipitate. The precipitate was removed by filtration and washed with ether (3×20 mL). Solid was oven dried at 105º C for 3 hours, to afford 0.439 g (95%) pure product. Product decomposes at temperatures above 200º C. ^{1}H-NMR (DMSO-d_6- 300 MHz Varian Unity) δ 10.12 (s, 4H), 7.06 (t, 1H, *J*= 7.8 Hz), 6.59 (m, 3H), 5.92 (s, 1H), 3.73 (t, 4H, *J*= 4.9 Hz), 3.65 (s, 3H), 3.10 (t, 4H, *J*= 5.1 Hz). ^{13}C-NMR (DMSO-d_6- 300 MHz Varian Unity) δ 161.7, 155.4, 147.1, 143.0, 124.8, 115.8, 109.7, 105.5, 87.4, 59.8, 51.2, 39.5, 27.0 ppm.

Synthesis of 5-[(2,4,6-trioxohexahydropyrimidin-5-yl)(4-(dimethylamino)benzyl)methyl]pyrimidine-2,4,6(1H,3H,5H)-trione morpholinium salt (G21)

Into 50 mL of methanol, 4-(dimethylamino)benzaldehyde (0.149 g; 1.00 mmol), barbituric acid (0.256 g; 2.00 mmol), and morpholine (0.130 mL; 0.130 g; 1.5 mmol) were added and stirred. The resulting reaction suspension was refluxed overnight. The reaction mixture was cooled to room temperature and the volume reduced to ¼ the original volume, resulting in the formation of a precipitate. The precipitate was removed by filtration and washed with ether (3×20 mL). Solid was oven dried at 105º C for 3 hours, to afford 0.456 g (96%) pure product. Product decomposes at temperatures above 200º C. ^{1}H-NMR (DMSO-d_6- 300 MHz Varian Unity) δ 6.86 (d, 2H, *J*= 8.4 Hz), 6.56 (d, 2H, *J*= 8.7 Hz), 5.84 (s, 1H), 3.73 (t, 4H, *J*= 4.8 Hz), 3.09 (t, 4H, *J*= 4.8 Hz), 2.79 (s,

6H). ^{13}C-NMR (DMSO-d_6- 300 MHz Varian Unity) δ 160.0, 147.3, 144.6, 128.6, 123.6, 108.9, 87.9, 59.9, 39.6, 37.1, 26.0 ppm.

Synthesis of 5-[(2,4,6-trioxohexahydropyrimidin-5-yl)(naphthyl)methyl]pyrimidine-2,4,6(1H,3H,5H)-trione morpholinium salt (G22)

Into 50 mL of methanol, 2-naphthaldehyde (0.158 g; 1.00 mmol), barbituric acid (0.256 g; 2.00 mmol), and morpholine (0.130 mL; 0.130 g; 1.5 mmol) were added and stirred. The resulting reaction suspension was refluxed overnight. The reaction mixture was cooled to room temperature and the volume reduced to ¼ the original volume, resulting in the formation of a precipitate. The precipitate was removed by filtration and washed with ether (3×20 mL). Solid was oven dried at 105º C for 3 hours, to afford 0.458 g (95%) pure product. Product decomposes at temperatures above 200º C. ^{1}H-NMR (DMSO-d_6- 300 MHz Varian Unity) δ 10.04 (s, 4H), 8.13 (d, 1H, *J*= 8.1 Hz), 7.78 (d, 1H, *J*= 8.1 Hz), 7.60 (d, 1H, *J*= 8.1 Hz), 7.33 (m, 4H), 6.45 (s, 1H), 3.73 (t, 4H, *J*= 4.8 Hz), 3.08 (t, 4H, *J*= 4.8 Hz). ^{13}C-NMR (DMSO-d_6- 300 MHz Varian Unity) δ 161.2, 147.0, 137.5, 130.0, 128.4, 124.7, 121.9, 121.8, 121.4, 121.3, 121.2, 121.1, 88.3, 59.8, 39.5, 25.7 ppm.

Synthesis of 5-[(2,4,6-trioxohexahydropyrimidin-5-yl)(2-hydroxybenzyl)methyl]pyrimidine-2,4,6(1H,3H,5H)-trione morpholinium salt (G23)

Into 50 mL of methanol, 2-hydroxybenzaldehyde (0.122 g; 1.00 mmol), barbituric acid (0.256 g; 2.00 mmol), and morpholine (0.130 mL; 0.130 g; 1.5 mmol) were added and stirred. The resulting reaction suspension was refluxed overnight. The reaction mixture

was cooled to room temperature and the volume reduced to ¼ the original volume, resulting in the formation of a precipitate. The precipitate was removed by filtration and washed with ether (3×20 mL). Solid was oven dried at 105º C for 3 hours, to afford 0.403 g (90%) pure product. Product decomposes at temperatures above 200º C. ^{1}H-NMR (DMSO-d_6- 300 MHz Varian Unity) δ 10.16 (s, 4H), 7.19 (d, 1H, *J*= 7.8 Hz), 6.88 (t, 1H, *J*= 7.7 Hz), 6.59 (m, 2H), 5.94 (s, 1H), 3.75 (t, 4H, *J*= 4.8 Hz), 3.10 (t, 4H, *J*= 4.8 Hz). ^{13}C-NMR (DMSO-d_6- 300 MHz Varian Unity) δ 161.8, 151.5, 146.9, 126.9, 125.2, 122.3, 114.2, 111.4, 87.1, 59.8, 45.0, 39.6 ppm.

Synthesis of 5-[(2,4,6-trioxohexahydropyrimidin-5-yl)(4-hydroxybenzyl)methyl]pyrimidine-2,4,6(1H,3H,5H)-trione morpholinium salt (G24)

Into 50 mL of methanol, 4-hydroxybenzaldehyde (0.122 g; 1.00 mmol), barbituric acid (0.256 g; 2.00 mmol), and morpholine (0.130 mL; 0.130 g; 1.5 mmol) were added and stirred. The resulting reaction suspension was refluxed overnight. The reaction mixture was cooled to room temperature and the volume reduced to ¼ the original volume, resulting in the formation of a precipitate. The precipitate was removed by filtration and washed with ether (3×20 mL). Solid was oven dried at 105º C for 3 hours, to afford 0.358 g (80%) pure product. Product decomposes at temperatures above 200º C. ^{1}H-NMR (DMSO-d_6- 300 MHz Varian Unity) δ 10.02 (s, 4H), 6.79 (d, 2H, *J*= 8.4 Hz), 6.53 (d, 2H, *J*= 8.4 Hz), 5.82 (s, 1H), 3.72 (t, 4H, *J*= 4.8 Hz), 3.06 (t, 4H, *J*= 4.8 Hz). ^{13}C-NMR (DMSO-d_6- 300 MHz Varian Unity) δ 161.1, 150.7, 147.1, 131.1, 123.9, 110.7, 87.7, 60.0, 39.7, 26.0 ppm.

Synthesis of 5-[(2,4,6-trioxohexahydropyrimidin-5-yl)(2,3,4-trimethoxybenzyl)methyl]pyrimidine-2,4,6(1H,3H,5H)-trione morpholinium salt (G25)

Into 50 mL of methanol, 2,3,4-trimethoxybenzaldehyde (0.198 g; 1.00 mmol), barbituric acid (0.256 g; 2.00 mmol), and morpholine (0.130 mL; 0.130 g; 1.5 mmol) were added and stirred. The resulting reaction suspension was refluxed overnight. The reaction mixture was cooled to room temperature and the volume reduced to ¼ the original volume, resulting in the formation of a precipitate. The precipitate was removed by filtration and washed with ether (3×20 mL). Solid was oven dried at 105º C for 3 hours, to afford 0.501 g (96%) pure product. Product decomposes at temperatures above 200º C. ^{1}H-NMR (DMSO-d_6- 300 MHz Varian Unity) δ 10.00 (s, 4H), 6.78 (d, 1H, J= 9.0 Hz), 6.55 (d, 1H, J= 9.0 Hz), 5.86 (s, 1H), 3.72 (t, 4H, J= 4.8 Hz), 3.69 (s, 3H), 3.65 (s, 3H), 3.52 (s, 3H), 3.08 (t, 4H, J= 4.8 Hz). ^{13}C-NMR (DMSO-d_6- 300 MHz Varian Unity) δ 160.9, 147.6, 147.3, 147.1, 138.2, 127.1, 119.4, 102.7, 87.5, 59.9, 56.3, 56.2, 52.1, 39.5, 23.3 ppm.

Synthesis of 1,3-dimethyl-5-[(2,4,6-trioxohexahydropyrimidin-5-yl)(2-methoxybenzyl)methyl]pyrimidine-2,4,6(1H,3H,5H)-trione morpholinium salt (G26)

Into 50 mL of methanol, 2-methoxybenzaldehyde (0.136 g; 1.00 mmol), 1,3-dimethylbarbituric acid (0.312 g; 2.00 mmol), and morpholine (0.130 mL; 0.130 g; 1.5 mmol) were added and stirred. The resulting reaction suspension was refluxed overnight. The reaction mixture was cooled to room temperature and the volume reduced to ¼ the original volume, resulting in the formation of a precipitate. The precipitate was removed by filtration and washed with ether (3×20 mL). Solid was oven dried at 105º C for 3

hours, to afford 0.481 g (93%) pure product. Product decomposes at temperatures above 200º C. ^{1}H-NMR (DMSO-d_6- 300 MHz Varian Unity) δ 7.15 (d, 1H, *J*= 7.8 Hz), 7.03 (t, 1H, *J*= 7.7 Hz), 6.74 (m, 2H), 6.01 (s, 1H), 3.77 (t, 4H, *J*= 4.7 Hz), 3.57 (s, 3H), 3.16 (t, 4H), 3.12 (s, 12H). ^{13}C-NMR (DMSO-d_6- 300 MHz Varian Unity) δ 159.4, 153.6, 148.0, 128.9, 125.6, 122.6, 115.9, 107.3, 86.7, 59.8, 52.0, 39.6, 27.6, 24.3 ppm.

Synthesis of 1,3-dimethyl-5-[(2,4,6-trioxohexahydropyrimidin-5-yl)(3,4,5-trimethoxybenzyl)methyl]pyrimidine-2,4,6(1H,3H,5H)-trione ethanolaminium salt (G27) Into 50 mL of methanol, 3,4,5-trimethoxybenzaldehyde (0.198 g; 1.00 mmol), 1,3-dimethylbarbituric acid (0.312 g; 2.00 mmol), and ethanolamine (0.090 mL; 0.092 g; 1.5 mmol) were added and stirred. The resulting reaction suspension was refluxed overnight. The reaction mixture was cooled to room temperature and the volume reduced to ¼ the original volume, resulting in the formation of a precipitate. The precipitate was removed by filtration and washed with ether (3×20 mL). Solid was oven dried at 105º C for 3 hours, to afford).513 g (93%) pure product. Product decomposes at temperatures above 200º C. ^{1}H-NMR (DMSO-d_6- 300 MHz Varian Unity) δ 6.34 (s, 2H), 6.12 (s, 1H), 3.61 (s, 6H), 3.60 (s, 3H), 3.57 (t, 2H, *J*= 5.5 Hz), 3.15 (s, 12H), 2.87 (t, 2H, *J*= 5.3 Hz). ^{13}C-NMR (DMSO-d_6- 300 MHz Varian Unity) δ 158.6, 148.6, 147.9, 136.5, 131.6, 101.1, 87.4, 56.4, 54.0, 52.4, 37.8, 24.5, 23.3 ppm.

Synthesis of 1,3-dimethyl-5-[(2,4,6-trioxohexahydropyrimidin-5-yl)(4-hydroxybenzyl)methyl]pyrimidine-2,4,6(1H,3H,5H)-trione morpholinium salt (G28)

Into 50 mL of methanol, 4-hydroxybenzaldehyde (0.122 g; 1.00 mmol), 1,3-dimethylbarbituric acid (0.312 g; 2.00 mmol), and morpholine (0.130 mL; 0.130 g; 1.5 mmol) were added and stirred. The resulting reaction suspension was refluxed overnight. The reaction mixture was cooled to room temperature and the volume reduced to ¼ the original volume, resulting in the formation of a precipitate. The precipitate was removed by filtration and washed with ether (3×20 mL). Solid was oven dried at 105º C for 3 hours, to afford 0.463 g (92%) pure product. ^{1}H-NMR (DMSO-d_6- 300 MHz Varian Unity) δ 6.81 (d, 2H, *J*= 8.1 Hz), 6.54 (d, 2H, *J*= 8.4 Hz), 6.08 (s, 1H), 3.74 (t, 4H), 3.15 (t, 4H), 3.11 (s, 12H). ^{13}C-NMR (DMSO-d_6- 300 MHz Varian Unity) δ 158.4, 150.9, 147.9, 130.4, 124.0, 111.7, 110.8, 59.9, 39.6, 29.1, 24.4 ppm.

Synthesis of 5-[(2,4,6-trioxohexahydropyrimidin-5-yl)(butyl)methyl]pyrimidine-2,4,6(1H,3H,5H)-trione morpholinium salt (G29) Into 100 mL methanol barbituric acid (2.56 g; 0.02 mol), valeraldehyde (1.04 mL; 0.840 g; 0.01 mol), and morpholine (1.1 mL; 1.00 g, 0.011 mol) were mixed with stirring. The reaction suspension was refluxed overnight. The volume of the mixture was reduced to 1/5 the original volume (~20 mL) and was cooled to room temperature. The white solid precipitate was filtered and washed with ether (3×25 mL). The solid was oven dried at 110 C for 3 hours, affording 3.8 g (92%) pure product. ^{1}H-NMR (DMSO-d_6- 300 MHz Varian Unity) δ 9.86 (s, 4H), 4.46 (t, 1H, *J*= 8.5 Hz), 3.73 (t, 4H, *J*= 5.0 Hz), 3.06 (t, 4H, *J*= 5.0 Hz), 1.65 (m, 2H), 1.18

(m, 2H), 1.02 (m, 2H). ^{13}C-NMR (DMSO-d_6- 300 MHz Varian Unity) δ 161.1, 147.0, 87.5, 60.2, 39.8, 27.0, 26.6, 22.3, 18.7, 10.6 ppm.

Synthesis of 5-[(2,4,6-trioxohexahydropyrimidin-5-yl)(hexyl)methyl]pyrimidine-2,4,6(1H,3H,5H)-trione morpholinium salt (G30) Into 100 mL methanol barbituric acid (2.56 g; 0.02 mol), heptaldehyde (1.39 mL, 1.14 g; 0.01 mol), and morpholine (1.10 mL; 1.00 g, 0.011 mol) were mixed with stirring. The reaction suspension was refluxed overnight. The volume of the mixture was reduced to 1/5 the original volume (~20 mL) and cooled to room temperature. The solid precipitate was filtered and washed with ether (3×25 mL). The solid was oven dried at 110º C for 3 hours, affording 3.30 g (75%) pure product. Product decomposes at temperatures above 160º C. ^{1}H-NMR (DMSO-d_6- 300 MHz Varian Unity) δ 9.84 (s, 4H), 4.46 (t, 1H, J= 8.4 Hz), 3.75 (t, 4H, J= 4.8 Hz), 3.09 (t, 4H, J= 4.8 Hz), 1.64 (m, 2H), 1.22 (m, 2H), 1.17 (m, 4H), 1.03 (m, 2H), 0.82 (t, 3H, J= 6.6 Hz). ^{13}C-NMR (DMSO-d_6- 300 MHz Varian Unity) δ 151.4, 147.0, 87.6, 59.9, 39.6, 27.9, 27.4, 25.2, 24.2, 22.4, 18.5, 10.4 ppm.

Synthesis of 5-[(2,4,6-trioxohexahydropyrimidin-5-yl)(nonyl)methyl]pyrimidine-2,4,6(1H,3H,5H)-trione morpholinium salt (G31) Into 100 mL methanol barbituric acid (2.56 g; 0.02 mol), decanal (1.88 mL, 1.56 g; 0.01 mol), and morpholine (1.10 mL; 1.00 g, 0.011 mol) were mixed with stirring. The reaction suspension was refluxed overnight. The volume of the mixture was reduced to 1/5 the original volume (~20 mL) and cooled to room temperature. The solid precipitate was filtered and washed with ether (3×25 mL). The solid was oven dried at 110º C for 3 hours, affording 4.53 g (94%) pure

product. Product decomposes at temperatures above 160º C. ^{1}H-NMR (DMSO-d_6- 300 MHz Varian Unity) δ 9.90 (s, 4H), 4.44 (t, 1H, *J*= 8.1 Hz), 3.73 (t, 4H, *J*= 4.5 Hz), 3.07 (t, 4H, *J*= 4.5 Hz), 1.63 (m, 2H), 1.19 (m, 12H), 1.03 (m, 2H), 0.82 (t, 3H, *J*= 6.9 Hz) ppm. ^{13}C-NMR (DMSO-d_6- 300 MHz Varian Unity) δ 161.5, 147.2, 87.9, 60.2, 39.8, 27.9, 27.4, 25.8, 25.7, 25.6, 25.3, 24.4, 22.5, 18.7, 10.5 ppm.

Synthesis of 5-[(2,4,6-trioxohexahydropyrimidin-5-yl)(heptyl)methyl]pyrimidine-2,4,6(1H,3H,5H)-trione piperidinium salt (G32) Into 100 mL methanol barbituric acid (2.56 g; 0.02 mol), octanal (1.56 mL, 1.28 g; 0.01 mol), and piperidine (1.08 mL; 0.937 g, 0.011 mol) were mixed with stirring. The reaction suspension was refluxed overnight. The volume of the mixture was reduced to 1/5 the original volume (~20 mL) and cooled to room temperature. The solid precipitate was filtered and washed with ether (3×25 mL). The solid was oven dried at 110º C for 3 hours, affording 3.70 g (82%) pure product. Product decomposes at temperatures above 160º C. ^{1}H-NMR (DMSO-d_6- 300 MHz Varian Unity) δ 9.85 (s, 4H), 4.46 (t, 1H, *J*= 8.1 Hz), 3.00 (t, 4H, *J*= 5.6 Hz), 1.64 (m, 4H), 1.55 (m, 2H), 1.17 (m, 10H), 1.03 (m, 2H), 0.83 (t, 3H, *J*= 6.8 Hz). ^{13}C-NMR (DMSO-d_6- 300 MHz Varian Unity) δ 161.7, 147.2, 87.9, 40.4, 27.8, 27.2, 25.6, 25.3, 24.4, 22.4, 18.7, 18.6, 18.2, 10.4 ppm.

Synthesis of 1-phenyl-5-[(2,4,6-trioxohexahydropyrimidin-5-yl)(nonyl)methyl]pyrimidine-2,4,6(1H,3H,5H)-trione morpholinium salt (G33) Into 50 mL methanol 1-phenylbarbituric acid (0.408 g; 0.002 mol), decanal (0.188 mL, 0.156 g; 0.001 mol), and morpholine (0.110 mL; 0.100 g, 0.0011 mol) were mixed with stirring.

The reaction suspension was refluxed overnight. The volume of the mixture was reduced to 1/5 the original volume (~10 mL) and cooled to room temperature. The solid precipitate was filtered and washed with ether (3×25 mL). The solid was oven dried at 110º C for 3 hours, affording 0.462 g (73%) pure product. Product decomposes at temperatures above 200º C. ^{1}H-NMR (DMSO-d_6- 300 MHz Varian Unity) δ 10.36 (s, 2H), 7.37 (t, 4H, *J*= 7.4 Hz), 7.30 (t, 2H, *J*= 7.2 Hz), 7.10 (d, 4H, *J*= 7.2 Hz), 4.52 (t, 1H, *J*= 8.1 Hz), 3.69 (t, 4H, *J*= 4.8 Hz), 3.02 (t, 4H, *J*= 4.8 Hz), 1.76 (m, 2H), 1.22 (m, 12H), 1.13 (m, 2H), 0.85 (t, 3H, *J*= 6.6 Hz) ppm. ^{13}C-NMR (DMSO-d_6- 300 MHz Varian Unity) δ 161.2, 159.2, 147.1, 133.6, 125.9, 124.8, 123.7, 88.2, 59.7, 39.4, 27.9, 27.3, 27.2, 27.0, 25.7, 25.6, 25.3, 24.4, 18.6, 10.5 ppm.

Synthesis of 5-[(2-thio-4,6-dioxohexahydropyrimidin-5-yl)(2-nitrobenzyl)methyl]pyrimidine-2-thio-4,6-(1H,3H,5H)-dione piperidinium salt (G34)

Into 100 mL methanol, 4,6-dihydroxy-2-mercaptopyrimidine (2.88 g; 0.02 mol), 2-nitrocarboxaldehyde (1.51g; 0.01 mol), and piperidine (1.1 mL; 1.00 g; 0.011 mol) were mixed while stirring. The reaction suspension was refluxed overnight. The reaction suspension was cooled to room temperature and the pale yellow solid was filtered and washed with ether (3×20 mL). The solid was oven dried at 105 C for 3 hours to afford 5.10 g (90%) pure product. Product decomposes at temperatures above 200º C. ^{1}H-NMR (DMSO-d_6- 300 MHz Varian Unity) δ 7.50 (d, 1H, *J*= 7.5 Hz), 7.43 (t, 1H, *J*= 7.4 Hz), 7.26 (m, 2H), 6.05 (s, 1H), 2.95 (t, 4H, *J*= 5.4 Hz), 1.60 (m, 4H), 1.50 (m, 2H). ^{13}C-NMR (DMSO-d_6- 300 MHz Varian Unity) δ 169.4, 159.2, 146.2, 133.1, 127.4, 126.1, 122.7, 119.8, 90.7, 40.4, 25.7, 18.7, 18.3 ppm.

Synthesis of 5-[(2-thio-4,6-dioxohexahydropyrimidin-5-yl)(2, 4, 5-trimethoxybenzyl)methyl]pyrimidine-2-thio-4,6-(1H,3H,5H)-dione morpholinium salt (G35) Into 100 mL methanol, 4,6-dihydroxy-2-mercaptopyrimidine (2.88 g; 0.02 mol), 2,4,5-trimethoxybenzaldehyde (1.98 g; 0.01 mol), and morpholine (1.10 mL; 1.00 g; 0.011 mol) were mixed while stirring. The reaction suspension was refluxed overnight. The reaction suspension was cooled to room temperature and the pale yellow solid was filtered and washed with ether (3×20 mL). The solid was oven dried at 105º C for 3 hours to afford 5.04 g (91%) pure product. Product decomposes at temperatures above 200º C. ^{1}H-NMR (DMSO-d_6- 300 MHz Varian Unity) δ 6.71 (s, 1H), 6.51 (s, 1H), 5.87 (s, 1H), 3.74 (t, 4H), 3.71 (s, 3H), 3.58 (s, 3H), 3.57 (s, 3H), 3.09 (t, 4H). ^{13}C-NMR (DMSO-d_6- 300 MHz Varian Unity) δ 168.9, 159.2, 148.0, 144.1, 138.0, 120.0, 112.0, 95.6, 92.7, 60.1, 53.6, 52.9, 52.2, 39.7, 23.1 ppm.

Synthesis of 5-[(2-thio-4,6-dioxohexahydropyrimidin-5-yl)(4-(dimethylamino)benzyl)methyl]pyrimidine-2-thio-4,6-(1H,3H,5H)-dione lysine salt (G36) Into 100 mL methanol, 4,6-dihydroxy-2-mercaptopyrimidine (2.88 g; 0.02 mol), 4-dimethylaminobenzaldehyde (1.49 g; 0.01 mol), and lysine monohydrate (1.80 g. 0.011 mol) were mixed while stirring. The reaction suspension was refluxed overnight. The reaction suspension was cooled to room temperature and the pale yellow solid was filtered and washed with ether (3×20 mL). The solid was oven dried at 105º C for 3 hours to afford 3.77 g (90%) pure product. Product decomposes at temperatures above 200º C. ^{1}H-NMR (DMSO-d_6- 300 MHz Varian Unity) δ 6.79 (d, 2H, J= 8.4 Hz), 6.55 (d, 2H, J= 9.0 Hz), 5.85 (s, 1H), 3.35 (t, 1H, J= 5.9 Hz), 2.78 (s, 6H), 2.75 (t, 2H, J= 7.8

Hz), 1.66 (m, 2H), 1.52 (m, 2H), 1.39 (m, 2H). ^{13}C-NMR (DMSO-d_6- 300 MHz Varian Unity) δ 169.1, 167.5, 160.1, 144.7, 127.3, 123.5, 108.9, 92.7, 49.9, 37.0, 36.8, 26.5, 25.9, 23.0, 18.2 ppm.

Preparation 5-Benzoyl-1-butylpyrimidine-2,4,6-trione (H5). 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). The resulting reaction mixture was stirred at room temperature for an additional two hours. The pyridine reaction mixture was then slowly added over thirty minutes into a stirring solution of methanol (60 mL), water (50 mL) and concentrated hydrochloric acid (150 mL). The resulting suspension was stirred at room temperature for an additional half an hour and then at 0º C for an additional hour. Solid precipitate was separated by filtration, washed (3×15 mL) with diluted hydrochloric acid (one part of concentrated hydrochloric acid and nine parts of water). Solid product was dried at 110º C for half an hour to afford pure **1e** in 28.0 g (97%). m.p. 138.9-139.7 º C. ^{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 (H1). Benzoyl chloride (14.1 g; 0.1 mol) was slowly added over 10 minutes into a stirring pyridine (60 mL) solution of barbituric acid (12.8 g; 0.1 mol). The resulting reaction mixture was stirred at room temperature for additional two hours. The 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). The resulting suspension was stirred at room temperature for additional half an hour and at 0º C for an additional hour. The solid precipitate was separated by filtration, washed (3×15 mL) with diluted hydrochloric acid (one part of concentrated hydrochloric acid and nine parts of water). The solid product was dried at 110º C for half an hour to afford 20.9 g **(**90%) of pure product. ^{1}H-NMR (DMSO-d_6, 500 MHz) δ 11.48 (2H, s), 7.5 6(2H, d, J= 8.7 Hz), 7.53 (1H, t, J= 6.3 Hz), 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 91 ppm. *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 (H2). Benzoyl chloride (14.1 g; 0.1 mol) was slowly added over 10 minutes into a stirring pyridine (60 mL) solution of 1-phenylbarbituric acid (20.4 g; 0.1 mol). The resulting reaction mixture was stirred at room temperature for additional two hours. The 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). The resulting suspension was stirred at room temperature for additional half an hour and at 0º C for an additional hour. The solid precipitate was separated by filtration, washed (3×15 mL) with diluted hydrochloric

acid (one part of concentrated hydrochloric acid and nine parts of water). Thesolid product was dried at 110º C for half an hour to afford 25.5 g (83%) pure product. ^{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 (H3). Benzoyl chloride (14.1 g; 0.1 mol) was slowly added over 10 minutes into stirring pyridine (60 mL) solution of 1-methylbarbituric acid (14.2 g; 0.1 mol). The resulting reaction mixture was stirred at room temperature for additional two hours. The 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). The resulting suspension was stirred at room temperature for additional half an hour and at 0º C for an additional hour. The solid precipitate was separated by filtration, washed (3×15 mL) with diluted hydrochloric acid (one part of concentrated hydrochloric acid and nine parts of water). The solid product was dried at 110º C for half an hour to afford 77%. ^{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 (H6). 4-methoxybenzoyl chloride (17.1 g; 0.1 mol) was slowly added over 10 minutes into stirring pyridine (60 mL) solution of barbituric acid (12.8 g; 0.1 mol). The resulting reaction mixture was stirred at room temperature for additional two hours. The 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). The resulting suspension was stirred at room temperature for additional half an hour and at 0º C for an additional hour. The solid precipitate was separated by filtration, washed (3×15 mL) with diluted hydrochloric acid (one part of concentrated hydrochloric acid and nine parts of water). The solid product was dried at 110º C for half an hour to afford 22.8 g (87%) pure product. ^{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.

Preparation 5-(4-methoxybenzoyl)-1,3-dimethylpyrimidine-2,4,6-trione (H7). 4-Methoxybenzoyl chloride (17.1 g; 0.1 mol) was slowly added to stirring pyridine (60 mL) solution of 1,3-dimethylbarbituric acid (15.6 g; 0.1 mol). The 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). The resulting suspension was stirred at room temperature for thirty minutes and then at 70º C for 30 minutes. After heating, reaction suspension became clear water solution. Water solution was extracted (4×100mL) with ethyl acetate. Combined ethyl

acetate extracts were dried over anhydrous magnesium sulfate and evaporated to an oily residue. Oily residue was dissolved in ethanol (10 mL) and kept at 0º C to form yellow crystals that were separated by filtration, washed with ice cold ethanol (3×5 mL) and dried on the air to give 26.1 g (90%). m.p. 143.8-145.1 º C. ^{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 (H4). Benzoyl chloride (14.1 g; 0.1 mol) was slowly added to stirring pyridine (60 mL) solution of 1,3-dimethylbarbituric acid (15.6 g; 0.1 mol). The 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). The resulting suspension was stirred at room temperature for thirty minutes and then at 70º C for 30 minutes. After heating, reaction suspension became clear water solution. Water solution was extracted (4×100mL) with ethyl acetate. The combined ethyl acetate extracts were dried over anhydrous magnesium sulfate and evaporated to an oily residue. Oily residue was dissolved in ethanol (10 mL) and kept at 0º C to form yellow crystals that were separated by filtration, washed with ice cold ethanol (3×5 mL) and dried on the air to give 21.8 g (84%) pure product. ^{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.

Preparation of 5-(4-nitrobenzyl)-1,3-dimethylbarbituric acid (H9). 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 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 (3×20 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 (3×15 mL) and dried at 110º C for half an hour to afford 27.8 g (91%) pure product. Product decomposes at temperatures above 190º C. ^{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-ESI$^+$ (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-(3-nitrobenzoyl)-pyrimidine-2,4,6-trione (H8). Into tetrahydrofuran solution (200 mL) of barbituric acid (14.1 g; 0.11 mol) and 3-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 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 (3×20 mL). Product contains ~3% 3-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 (3×15 mL) and dried at 110º C for half an hour to afford 25.7 g (93%) pure product. ^{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-(3-nitrobenzoyl)pyrimidine-2,4,6-trione (H11). Into tetrahydrofuran solution (200 mL) of 1,3-dimethylbarbituric acid (17.2 g; 0.11 mol) and 3-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 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 (3×20 mL). Product contains ~3% 3-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 (3×15 mL) and dried at 110º C for half an hour to afford 28.9 g (95%) pure product. ^{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 (H10). Into tetrahydrofuran solution (200 mL) of barbituric acid (14.1 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 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). The yellow precipitate was separated by filtration and washed with ice water (3×20 mL). Product contains ~3% 4-nitrobenzoic acid. The 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. The solid was separated by filtration, washed with ice water and added to aqueous ammonium chloride (4 g =NH_4Cl in 100 mL water). The resulting suspension was refluxed for five minutes, cooled in ice-water. White crystalline product was separated by filtration, washed with ice water (3×15 mL) and dried at 110º C for half an hour to afford 25.7 g (93%) pure product. ^{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 (H12). Into tetrahydrofuran solution (200 mL) of barbituric acid (14.1 g; 0.11 mol) and 3,5-dinitrobenzoyl chloride (23.0 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 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). The yellow precipitate was separated by filtration and washed with ice water (3×20 mL). The product contains ~3% 3,5-dinitrobenzoic acid. The 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). The resulting suspension was refluxed for five minutes, cooled in ice-water. White crystalline product was separated by filtration, washed with ice water (3×15 mL) and dried at 110º C for half an hour to afford 29.0 g (90%) pure product. ^{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 (H13).

Into tetrahydrofuran solution (200 mL) of 1-methylbarbituric acid (15.6 g; 0.11 mol) and 3,5-dinitrobenzoyl chloride (23.0 g; 0.1 mol) with stirring *N*-methylmorpholine (15.15 g; 0.15 mol) was added. The 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 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). The yellow precipitate was separated by filtration and washed with ice water (3×20 mL). Product contains ~3% 3,5-dinitrobenzoic acid. The 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. The solid was separated by filtration, washed with ice water and added to aqueous ammonium chloride (4 g =NH_4Cl in 100 mL water). The resulting suspension was refluxed for five minutes, cooled in ice-water. White crystalline

product was separated by filtration, washed with ice water (3×15 mL) and dried at 110º C for half an hour to afford 31.2 g (93%) pure product. ^{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.

Preparation of 5-(3-hydroxybenzoyl)barbituric acid (**H14**). 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). The resulting dark red reaction mixture was stirred at room temperature for additional hour and then added slowly over of 20 minutes into stirring aqueous hydrochloride (10 mL water, 20 mL concentrated hydrochloric acid, and 5 mL methanol). The resulting suspension was stirred at room temperature for additional half an hour and kept at 0º C for one hour. The solid material was separated by filtration and it contains both 5-(3-acetyloxybenzoyl)barbituric acid and 5-(3-hydroxybenzoyl)barbituric acid. 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 70º C for half an hour. The resulting reaction mixture was acidified to pH=2 at ice-water bath temperature. The formed white solid precipitate was separated by filtration, washed with ice-cooled water (3×5 mL) and dried at 110º C for 30 minutes. Isolated yield of 5-(3-hydroxybenzoyl)barbituric acid is 91% (2.26 g). Product

decomposes at temperatures above 270º C. ^{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 (H15). Chloroform solution (150 mL) of 4-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 1-butylbarbituric acid (1.84 g; 0.01 mol). Resulting dark red reaction mixture was stirred at room temperature for additional hour and then added slowly over of 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 0º C for one hour. 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 70º C 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 (3×5 mL) and dried at 110º C for 30 minutes to yield 2.34 g (77%) pure product. ^{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 (H16). Chloroform solution (150 mL) of 4-acetoxybenzoic acid (18.0 g; 0.1 mol) and oxalyl chloride (25.0 g 0.2 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 1,3-dimethylbarbituric acid (15.6 g; 0.1 mol). Resulting dark red reaction mixture was stirred at room temperature for additional hour and then added slowly over of 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 0º C for one hour. To complete the ester hydrolysis solid material was mixed with aqueous sodium hydroxide (6.00 g; 0.15 mol of NaOH in 30 mL water) and heated at 70º C 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 (3×5 mL) and dried at 110º C for 30 minutes yielding 23.4 g (85%) pure product. ^{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 (H17). Chloroform solution (150 mL) of 4-acetoxybenzoic acid (18.0 g; 0.1 mol) and oxalyl chloride (25.0 g 0.2 mol) was stirred at room temperature for four hours. After evaporation of solvent the oily residue was dissolved in benzene (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 (12.8 g; 0.1 mol). Resulting dark red reaction mixture was stirred at room temperature for additional hour and then added slowly over of 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 0º C for one hour. To complete the ester hydrolysis solid material was mixed with aqueous sodium hydroxide (6.00 g; 0.15 mol of NaOH in 30 mL water) and heated at 70º C 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 (3×5 mL) and dried at 110º C for 30 minutes yielding 19.8 g (80%) pure product. ^{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 (H18). Chloroform solution (150 mL) of 4-acetoxybenzoic acid (18.0 g; 0.1 mol) and oxalyl chloride (25.0 g 0.2 mol) was stirred at room temperature for four hours. After evaporation of solvent the oily residue was dissolved in benzene (70 mL) and solvent was again evaporated. Chloroform (~30 mL) of this oily residue was slowly added into

stirring pyridine (30 mL) suspension of 1-phenylbarbituric acid (20.4 g; 0.1 mol). Resulting dark red reaction mixture was stirred at room temperature for additional hour and then added slowly over of 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 0º C for one hour. To complete the ester hydrolysis solid material was mixed with aqueous sodium hydroxide (6.00 g; 0.15 mol of NaOH in 30 mL water) and heated at 70º C 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 (3×5 mL) and dried at 110º C for 30 minutes yielding 27.0 g (83%) pure product. ^{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.

Preparation of 5-[[2,4-dinitrophenyl)hydrozono]-(4-methoxyphenyl)methyl]-1,3-dimethylpyrimidine-2,4,6-trione (H26). To a 1-propanol (20 mL) suspension of 5-(4-methoxybenzoyl)-1,3-dimethylpyrimidine-2,4,6-trione (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 0º C for one hour. Resulting orange precipitate was separated by filtration, washed with 1-propanol (3×5 mL), ether (3×10 mL) and dried at 50º C for twenty minutes. The isolated yield of pure

product is 1.30 g (81%). m.p: 98-99.2º C. ^{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 (H19). To a 1-propanol (20 mL) suspension of 5-(benzoyl)-pyrimidine-2,4,6-trione (0.792 g; 3.4 mmol) and 4-nitrophenylhydrazine (0.520 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 0º C for one hour. Resulting brown precipitate was separated by filtration, washed with 1-propanol (3 x 5 mL), ether (3 x 10 mL) and dried at 50º C for twenty minutes. The isolated yield of pure is 0.913 g (73%). ^{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 (H20). 1-Propanol (20 mL) mixture of 5-benzoyl-1-phenylpyrimidine-2,4,6-trione (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 110º C for 2 hours. Isolated yield of pure product is 1.10 g (79 %). Product decomposes at temperatures above 200º C. ^{1}H-NMR(CF_3CO_2H-DMSO-d_6, 500 MHz), δ 7.57 (d, 2H, *J*= 4.5 Hz, Ar), 7.06 (d of t, 3H, *J*= 3.0 Hz, Ar), 7.01 (t, 1H, *J*= 7.0 Hz, Ar), 6.93 (t, 2H, *J*= 7.0 Hz, Ar), 6.86 (d of t, 4H, *J*= 3.5 Hz, Ar), 6.37 (d, 2H, *J*= 4.5 Hz, 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 (H21). To a 1-propanol (20 mL) suspension of 5-(benzoyl)-1,3-dimethylpyrimidine-2,4,6-trione (0.887 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 0º C for one hour. Resulting orange precipitate was separated by filtration, washed with 1-propanol (3×5 mL), ether (3×10 mL) and dried at 50º C for twenty minutes to yield 1.24 g (83%) pure product. Mp: 92.2-94.5º C. ^{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), 6.90 (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 (H22). To a 1-propanol (20 mL) suspension of 5-(benzoyl)-1-phenylpyrimidine-2,4,6-trione (1.05 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 0º C for one hour. Resulting orange precipitate was separated by filtration, washed with 1-propanol (3×5 mL), ether (3×10 mL) and dried at 50º C for twenty minutes. The isolated yield is 1.46 g (88%). ^{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 (H23). To a 1-propanol (20 mL) suspension of 5-(benzoyl)-pyrimidine-2,4,6-trione (0.792 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 0º C for one hour. Resulting orange precipitate was separated by filtration, washed with 1-propanol (3×5 mL), ether (3×10 mL) and dried at 50º C for twenty minutes. The isolated yield is 1.17 g (84%). ^{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 (H24). To a 1-propanol (20 mL) suspension of 5-(benzoyl)-1,3-dimethylpyrimidine-2,4,6-trione (0.887 g; 3.4 mmol) and 4-hydrazinobenzoic acid (0.520 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 0º C for one hour. Resulting brown precipitate was separated by filtration, washed with 1-propanol (3×5 mL), ether (3×10 mL) and dried at 50º C for twenty minutes. The isolated yield is 79%. ^{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 (H25). To a 1-propanol (20 mL) suspension of 5-(4-methoxybenzoyl)-1,3-dimethylpyrimidine-2,4,6-trione (1.0 g; 3.4 mmol) and 4-nitrophenylhydrazine (0.520 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 0º C for one hour. Resulting brown precipitate was separated by filtration, washed with 1-propanol (3×5 mL), ether (3×10 mL) and dried at 50º C for twenty minutes. The isolated yield is 82%. ^{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-methylpyrimidine-2,4,6-trione (H27). To a 1-propanol (20 mL) suspension of 5-(4-methoxybenzoyl)-1-methylpyrimidine-2,4,6-trione (0.942 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 0º C for one hour.

Resulting orange precipitate was separated by filtration, washed with 1-propanol (3×5 mL), ether (3×10 mL) and dried at 50º C for twenty minutes. The isolated yield is 81%. ^{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 (H28). To a 1-propanol (20 mL) suspension of 5-(3-hydroxybenzoyl)-1-methylpyrimidine-2,4,6-trione (0.894 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 0º C for one hour. Resulting orange precipitate was separated by filtration, washed with 1-propanol (3×5 mL), ether (3×10 mL) and dried at 50º C for twenty minutes. The isolated yield is 1.30 g (88%). ^{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 (H29). To a 1-propanol (20 mL) suspension of 5-(4-hydroxybenzoyl)-1-methylpyrimidine-2,4,6-trione (0.894 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 0º C for one hour. Resulting orange precipitate was separated by filtration, washed with 1-propanol (3×5 mL), ether (3×10 mL) and dried at 50º C for twenty minutes. The isolated yield is 1.32 g (88%). ^{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 (H30). To a 1-propanol (20 mL) suspension of 5-(4-hydroxybenzoyl)-pyrimidine-2,4,6-trione (0.894 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 0º C for one hour. Resulting orange precipitate was separated by filtration, washed with 1-propanol (3×5 mL), ether (3×10 mL) and dried at 50º C for twenty minutes. The isolated yield is 1.20 g (80%). ^{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 (H31). To a 1-propanol (20 mL) suspension of 5-(4-hydroxybenzoyl)-pyrimidine-2,4,6-trione (0.846 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 0º C for one hour. Resulting orange precipitate was separated by filtration, washed with 1-propanol (3×5 mL), ether (3×10 mL) and dried at 50º C for twenty minutes. The isolated yield is 1.32 g (91%). ^{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 (H32). To a 1-propanol (20 mL) suspension of 5-(4-hydroxybenzoyl)-1-phenylpyrimidine-2,4,6-trione (1.10 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 0º C for one hour. Resulting orange precipitate was separated by filtration, washed with 1-propanol (3×5 mL), ether (3×10 mL) and dried at 50º C for twenty minutes. The isolated yield is 1.42 g (83%). ^{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 (H33). To a 1-propanol (20 mL) suspension of 5-(4-hydroxybenzoyl)-1-methylpyrimidine-2,4,6-trione (0.894 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 0º C for one hour. Resulting orange precipitate was separated by filtration, washed with 1-propanol (3×5 mL), ether (3×10 mL) and dried at 50º C for twenty minutes. The isolated yield is 84%. ^{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 (H34). To a 1-propanol (20 mL) suspension of 5-(4-hydroxybenzoyl)-1,3-dimethylpyrimidine-2,4,6-trione (0.941 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 0º C for one hour. Resulting orange precipitate was separated by filtration, washed with 1-propanol (3×5 mL), ether (3×10 mL) and dried at 50º C for twenty minutes. The isolated yield is 91%. ^{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 (H35). To a 250 mL round bottom flask charged with 20 mL propanol, 5(4-nitro-benzoyl)-pyrimidine-2,4,6-trione (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 (3×15 mL) and dried at 110º C for two hours. The yield of pure product was 0.409 g (89%). Product decomposes at temperatures above 275º C. ^{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, and 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 (H36). To a 1-propanol (20 mL) suspension of 5-(4-nitrobenzoyl)-pyrimidine-2,4,6-trione (0.945 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 0º C for one hour. Resulting orange precipitate was separated by filtration, washed with 1-propanol (3×5 mL), ether (3×10 mL) and dried at 50º C for twenty minutes. The isolated yield is 91%. ^{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.

Preparation of 5-(4-nitrobenzoyl)-1,3-dimethylpyrimidine-2,4,6-trione morpholinium salt (H47). Tetrahydrofuran (200 mL) solution of 5-(4-nitrobenzoyl)-1,3-dimethylpyrimidine-2,4,6-trione (610 mg; 2 mmol) and morpholine (191 mg; 2.2 mmol) was stirred at room temperature for half an hour. Solvent was evaporated. 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 (3×15 mL)

and dried at 110º C for half an hour. The yield of product is 740 mg (94%). Product decomposes at temperatures above 220º C. ^{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 salt (H37).

Tetrahydrofuran (200 mL) solution of 5-benzoyl-1,3-dimethylpyrimidine-2,4,6-trione (522 mg; 2 mmol) and piperidine (191 mg; 2.2 mmol) was stirred at room temperature for half an hour. Solvent was evaporated. 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 (3×15 mL) and dried at 110º C for half an hour. The yield of product is 556 mg (80%). Product decomposes at temperatures above 220º C. ^{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 salt (H38).

Tetrahydrofuran (200 mL) solution of 5-benzoyl-1-methylpyrimidine-2,4,6-trione (494 mg; 2 mmol) and piperidine (191 mg; 2.2 mmol) was stirred at room temperature for half an hour. Solvent was evaporated. 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 (3×15 mL) and dried at 110º C for half an hour. The yield of product is 317 mg (95%). Product decomposes at temperatures above 220º C. ^{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 (H39). Tetrahydrofuran (200 mL) solution of 5-(4-methoxybenzoyl)-pyrimidine-2,4,6-trione (610 mg; 2 mmol) and piperidine (191 mg; 2.2 mmol) was stirred at room temperature for half an hour. Solvent was evaporated. 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 (3×15 mL) and dried at 110º C for half an hour. The yield of product is 88%. Product decomposes at temperatures above 220º C. ^{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 (H40). Tetrahydrofuran (200 mL) solution of 5-(4-methoxybenzoyl)-1,3-dimethylpyrimidine-2,4,6-trione (582 mg; 2 mmol) and piperidine (191 mg; 2.2 mmol)

was stirred at room temperature for half an hour. Solvent was evaporated. 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 (3×15 mL) and dried at 110º C for half an hour. The yield of product is 93%. Product decomposes at temperatures above 220º C. ^{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 (H41). Tetrahydrofuran (200 mL) solution of 5-(4-nitrobenzoyl)-pyrimidine-2,4,6-trione (558 mg; 2 mmol) and piperidine (191 mg; 2.2 mmol) was stirred at room temperature for half an hour. Solvent was evaporated. 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 (3×15 mL) and dried at 110º C for half an hour. The yield of product is 95%. Product decomposes at temperatures above 220º C. ^{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 (H42). Tetrahydrofuran (200 mL) solution of 5-(4-nitrobenzoyl)- pyrimidine-2,4,6-trione (558 mg; 2 mmol) and morpholine (191 mg; 2.2 mmol) was stirred at room temperature for half an hour. Solvent was evaporated. 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 (3×15 mL) and dried at 110º C for half an hour. The yield of product is 90%. Product decomposes at temperatures above 220º C. ^{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 (H43). Tetrahydrofuran (200 mL) solution of 5-(4-nitrobenzoyl)-pyrimidine-2,4,6-trione (558 mg; 2 mmol) and *N*-methylmorpholine (224 mg; 2.2 mmol) was stirred at room temperature for half an hour. Solvent was evaporated. 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 (3×15 mL) and dried at 110º C for half an hour. The yield of product is 91%. Product decomposes at temperatures above 220º C. ^{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 (H44). Tetrahydrofuran (200 mL) solution of 5-(4-nitrobenzoyl)-pyrimidine-2,4,6-trione (558 mg; 2 mmol) and ethanolamine (140 mg; 2.2 mmol) was stirred at room temperature for half an hour. Solvent was evaporated. 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 (3×15 mL) and dried at 110º C for half an hour. The yield of product is 98%. Product decomposes at temperatures above 220º C. ^{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 (H45). Tetrahydrofuran (200 mL) solution of 5-(4-nitrobenzoyl)-pyrimidine-2,4,6-trione (558 mg; 2 mmol) and 4-(dimethylamino)benzaldehyde (328 mg; 2.2 mmol) was stirred at room temperature for half an hour. Solvent was evaporated. 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 (3×15 mL) and dried at 110º C for half an hour. The yield of product is 97%. Product decomposes at temperatures above 220º C. ^{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 (H46). Tetrahydrofuran (200 mL) solution of 5-(4-nitrobenzoyl)-1,3-dimethylpyrimidine-2,4,6-trione (610 mg; 2 mmol) and piperidine (187 mg; 2.2 mmol) was stirred at room temperature for half an hour. Solvent was evaporated. 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 (3×15 mL) and dried at 110º C for half an hour. The yield of product is 92%. Product decomposes at temperatures above 220º C. ^{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 (H48). Tetrahydrofuran (200 mL) solution of 5-(4-nitrobenzoyl)-1,3-dimethylpyrimidine-2,4,6-trione (610 mg; 2 mmol) and *N*-methylmorpholine (224 mg; 2.2 mmol) was stirred at room temperature for half an hour. Solvent was evaporated. 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 (3×15 mL) and dried at 110º C for half an hour. The yield of product is 89%. Product decomposes at temperatures above 220º C. ^{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 (H49). Tetrahydrofuran (200 mL) solution of 5-(4-nitrobenzoyl)-1,3-dimethylpyrimidine-2,4,6-trione (610 mg; 2 mmol) and ethanolamine (140 mg; 2.2 mmol) was stirred at room temperature for half an hour. Solvent was evaporated. 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 (3×15 mL) and dried at 110º C for half an hour. The yield of product 92%. Product decomposes at temperatures above 220º C. ^{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 (H50). Tetrahydrofuran (200 mL) solution of 5-(4-nitrobenzoyl)-1,3-dimethylpyrimidine-2,4,6-trione (610 mg; 2 mmol) and *N*-4-dimethylaminopyridine (328 mg; 2.2 mmol) was stirred at room temperature for half an hour. Solvent was evaporated. 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 (3×15 mL) and dried at 110º C for half an hour. The yield of product 93%. Product decomposes at temperatures above 220º C. ^{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 O. ***Preparation of piperidinium salt of 5-[[2,4-dinitrophenyl)hydrazono]-(4-hydroxyphenyl)methyl]-1,3-dimethyl-pyrimidine-2,4,6-trione (H52).*** 1-Propanol (20 mL) suspension of 5-[[2,4-dinitrophenyl)hydrazono]-(4-hydroxyphenyl)methyl]-1,3-dimethyl-pyrimidine-2,4,6-trione (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 m), and dried at 110º C for 2 hours to give 0.535 g (98%) of pure product. Product decomposes at temperatures above 250º C. ^{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 (H51). This compound was prepared in 93% isolated yield by following **General Procedure O**. ^{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 (H53). This compound was prepared in 81% isolated yield by following **General Procedure O**. ^{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.

Synthesis of methyl L-lysine salt of 5-{(4-methoxyphenyl)[2-(4-nitrophenyl)hydrazino]methylene}pyrimidine-2,4,6-trione (H54). Methanol (500 mL) suspension of 5-{(4-methoxyphenyl)[2-(4-nitrophenyl)hydrazino]methylene}pyrimidine-2,4,6-trione (0.397 g; 1.00 mmol) and *L*-lysine (0.146 g; 1.00 mmol) was stirred at 50º C 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 (3×20 mL) and dried at 110º C for ten minutes to give 0.525 g (97%). Product decomposes at temperatures above 200º C. ^{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.

Synthesis of 5,5'-(2-pyrilidene)bis(1,3-dimethylbarbituric acid)**(I-1)** A methanol solution (400 mL) of 2,2'-pyridil (0.212 g, 1.00 mmol) and 1,3-dimethylbarbituric acid (0.468 g, 3.00 mmol) was refluxed for 5 h. The resulting dark reaction mixture was concentrated to a 50 mL volume at atmospheric pressure and left at room temperature in an open beaker overnight. The resulting crystalline product was slurred in ice-cold methanol (3 x 10 mL), separated by filtration, washed with cold methanol (3 x 10 mL), and dried at 90º C for 30 min to afford 0.350 g (87%) pure product. If necessary further crystallization can be performed in acetic acid. ^{1}H NMR (DMSO-d_6) δ 8.58 (1H, d, *J*= 5.2 Hz), 8.41 (1H, t, *J*= 7.1 Hz), 7.88 (1H, d, *J*= 5.4 Hz), 7.81 (1H, t, *J*= 7.1 Hz), 6.33 (1H, s), 3.13 (12H, s) ppm. ^{13}C-NMR (DMSO-d_6) δ 159.3, 155.9, 147.9, 142.4, 137.5, 122.3, 120.6, 81.1, 32.0, 24.5 ppm. MS-ESI$^+$ in methanol 424 (M + Na)$^+$. *Anal.* Calcd. . For $C_{18}H_{19}N_5O_6$: C, 53.75; H, 4.83; N, 17.33. Found: C, 53.86; H, 4.77; N, 17.45.

Synthesis of 5,5'-(2-pyrilidene)bis(1-phenylbarbituric acid)**(I-2)** A methanol solution (400 mL) of 2,2'-pyridil (0.212 g, 1.00 mmol) and 1-phenylbarbituric acid (0.612 g, 3.00 mmol) was refluxed for 5 h. The resulting dark reaction mixture was concentrated to a 50 mL volume at atmospheric pressure and left at room temperature in an open beaker overnight. The resulting crystalline product was slurred in ice-cold methanol (3 x 10 mL), separated by filtration, washed with cold methanol (3 x 10 mL), and dried at 90º C. Yield=78%. ^{1}H-NMR(DMSO-d_6) δ 10.84 (2H, s, NH), 8.64 (2H, d, *J*= 6.9Hz, pyridine 6-H), 8.44 (1H, t, *J*= 6.9 Hz, pyridine 4-H), 7.98 (1H, d, *J*= 6.9Hz, pyridine 3-H), 7.83 (1H, t, *J*= 6.9Hz, pyridine 4-H), 7.40 (4H, t, *J*= 6.9 Hz, phenyl *m*-H), 7.32 (2H, t, *J*= 6.9 Hz, phenyl *p*-H), 7.20 (4H, d, *J*= 6.9 Hz, phenyl *o*-H), 6.23 (1H, benzyl). ^{13}C-NMR (DMSO-d_6) δ 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).

APPENDIX

X-ray Crystallographic Data, Positional Parameters, General Displacement, Parameter Expressions, Bond Distances and Bond Angles

for

5-{(4-Methoxyphenyl)-[N'-(4-nitrophenyl)hydrazino]methylene}-1,3-dimethylpyrimidine-2,4,6-trione (**H25**)

piperidinium salt of 5-[[2,4-dinitrophenyl)hydrazono]-(4-hydroxyphenyl)methyl]-1,3-dimethyl-pyrimidine-2,4,6-trione (**H52**)

Pyridinium-barbiturate Zwitterion (**F1**)

1,3-dimethyl-5-[(2,4,6-trioxohexahydropyrimidin-5-yl)(quinolin-4-yl)methyl]pyrimidine-2,4,6(1H,3H,5H)-trione morpholinium salt (**G37**)

and

5,5'-(2-pyrilidene)bis(1,3-dimethylbarbituric acid)(**I-1**)

X-ray crystallographic Data- Compound H25

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

Table 1: Crystal data and structure refinement for compound **H25**.

Empirical formula	$C_{20.55}H_{21.98}N_5O_{7.07}$	
Formula weight	452.20	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system, space group	Triclinic, P-1	
Unit cell dimensions	a = 10.7707(11) Å	α = 92.675(2) deg.
	b = 13.4704(14) Å	β = 90.176(3) deg.
	c = 15.4021(16) Å	γ = 112.341(2) deg.
Volume	2064.1(4) $Å^3$	
Z, Calculated density	4, 1.455 Mg/m^3	
Absorption coefficient	0.112 mm^{-1}	
F(000)	947	
Crystal size	0.15 x 0.15 x 0.4 mm	
Theta range for data collection	2.04 to 22.50 deg.	
Limiting indices -	8<=h<=11, -14<=k<=13, -14<=l<=16	
Reflections collected / unique	8652 / 5362 [R(int) = 0.0471]	
Completeness to theta = 22.50	99.1 %	
Absorption correction	Empirical	
Max. and min. transmission	1.000000 and 0.779916	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5362 / 1269 / 748	
Goodness-of-fit on F^2	1.280	
Final R indices [I^2sigma(I)]	R1 = 0.0798, wR2 = 0.1643	
R indices (all data)	R1 = 0.0918, wR2 = 0.1814	
Largest diff. peak and hole	0.706 and -0.426 e. $Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for **H25**

U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
C(1)	8448(10)	727(7)	164(5)	65(2)
N(2)	8350(7)	-71(6)	-472(4)	55(2)
C(3)	8172(9)	-1090(7)	-307(5)	60(2)
N(4)	8085(7)	-1366(5)	555(4)	58(2)
C(5)	8110(8)	-645(6)	1237(5)	48(2)
C(6)	8352(8)	435(6)	1068(5)	48(2)
C(7)	8615(7)	1233(6)	1734(4)	46(2)
N(8)	8645(6)	995(5)	2559(3)	45(2)
N(9)	8935(6)	1754(5)	3246(3)	43(2)
C(10)	10242(6)	2176(5)	3619(4)	42(2)
C(11)	11341(6)	2125(5)	3180(4)	45(2)
C(12)	12595(6)	2571(5)	3551(4)	47(2)
C(13)	12790(6)	3091(6)	4367(4)	46(2)
C(14)	11691(6)	3143(6)	4810(4)	45(2)
C(15)	10442(6)	2704(5)	4436(4)	41(2)
O(16)	8582(10)	1598(6)	-71(4)	112(3)
C(17)	8457(11)	212(8)	-1404(5)	76(3)
O(18)	8072(8)	-1767(6)	-891(4)	91(2)
C(19)	7915(11)	-2467(7)	762(6)	80(3)
O(20)	7912(6)	-1013(4)	1976(3)	57(2)
N(21)	14101(6)	3538(5)	4757(4)	55(2)
O(22)	15063(6)	3495(5)	4338(4)	67(2)
O(23)	14241(6)	3972(5)	5498(4)	78(2)
C(24)	8846(8)	2372(6)	1583(5)	50(2)
C(25)	10175(9)	3135(7)	1560(5)	58(2)
C(26)	10384(10)	4205(7)	1425(5)	62(2)
C(27)	9349(10)	4504(7)	1290(5)	61(2)
C(28)	8032(9)	3771(7)	1330(5)	64(2)
C(29)	7831(9)	2692(7)	1464(5)	59(2)
O(30)	9499(7)	5545(5)	1140(4)	79(2)
C(31)	10836(12)	6312(8)	1040(7)	91(3)
C(51)	5840(7)	1529(5)	4741(4)	36(2)
N(52)	5049(6)	1205(4)	3985(3)	37(1)
C(53)	3688(7)	690(5)	3948(5)	37(2)
N(54)	3040(6)	527(4)	4728(4)	38(1)
C(55)	3701(7)	847(6)	5534(4)	38(2)
C(56)	5112(7)	1411(5)	5540(4)	35(2)
C(57)	5809(7)	1898(6)	6334(4)	42(2)

N(58A)	5080(80)	1880(70)	7030(40)	52(3)
N(58)	5149(17)	1747(14)	7078(7)	51(3)
N(59)	5709(7)	2380(6)	7834(4)	53(2)
N(59A)	5430(40)	2190(20)	7935(11)	61(3)
C(60)	5616(6)	3401(6)	8032(5)	81(2)
C(60A)	5260(30)	3163(17)	7785(9)	75(3)
C(61)	5125(8)	3903(6)	7419(5)	84(2)
C(61A)	4000(30)	3219(18)	7751(16)	77(4)
C(62A)	3860(20)	4160(20)	7606(16)	84(3)
C(62)	5043(8)	4868(7)	7613(5)	87(2)
C(63)	5445(7)	5384(6)	8427(5)	92(3)
C(63A)	4990(30)	5090(17)	7491(10)	93(3)
C(64)	5932(9)	4889(7)	9038(5)	95(3)
C(64A)	6250(20)	5035(18)	7526(16)	90(3)
C(65A)	6380(20)	4090(20)	7669(16)	86(3)
C(65)	6016(8)	3921(7)	8845(5)	89(3)
O(66)	7067(5)	1868(4)	4668(3)	45(1)
C(67)	5722(8)	1428(7)	3138(4)	50(2)
O(68)	3073(5)	370(4)	3257(3)	47(1)
C(69)	1574(7)	-25(7)	4699(5)	55(2)
O(70)	3002(5)	615(4)	6191(3)	49(1)
N(71A)	4900(30)	6093(19)	7339(14)	112(4)
N(71)	5354(10)	6388(8)	8624(6)	108(3)
O(72A)	5970(30)	6870(20)	7240(20)	122(6)
O(72)	5493(13)	6736(9)	9395(6)	137(4)
O(73A)	3800(30)	6170(30)	7300(20)	129(7)
O(73)	5140(12)	6918(8)	8052(7)	124(3)
C(74)	7250(7)	2639(6)	6399(4)	39(2)
C(75)	8176(7)	2288(6)	6742(4)	41(2)
C(76)	9514(7)	2978(6)	6803(4)	43(2)
C(77)	9913(7)	4020(6)	6531(4)	41(2)
C(78)	8987(7)	4373(6)	6213(5)	45(2)
C(79)	7627(8)	3672(6)	6128(5)	45(2)
O(80)	11256(5)	4613(4)	6617(3)	48(1)
C(81)	11727(8)	5698(7)	6364(5)	60(2)
O(101)	5494(15)	1532(13)	8541(10)	58(3)
C(102)	5320(30)	1960(30)	9320(20)	50(4)
C(103)	5160(30)	1260(20)	10056(19)	45(3)
C(104)	5220(20)	187(18)	9949(19)	30(4)
O(105)	4978(11)	1389(11)	9526(9)	67(3)
O(106)	5252(10)	184(10)	8659(9)	76(3)
O(107)	4996(12)	447(11)	9399(11)	67(4)

Table 3: Bond lengths [Å] and angles [deg] for **H25**

C(1)-O(16)	1.200(10)
C(1)-N(2)	1.394(10)
C(1)-C(6)	1.457(11)
N(2)-C(3)	1.348(11)
N(2)-C(17)	1.497(10)
C(3)-O(18)	1.226(10)
C(3)-N(4)	1.389(11)
N(4)-C(5)	1.389(10)
N(4)-C(19)	1.474(11)
C(5)-O(20)	1.249(9)
C(5)-C(6)	1.415(11)
C(6)-C(7)	1.396(10)
C(7)-N(8)	1.328(7)
C(7)-C(24)	1.488(11)
N(8)-N(9)	1.384(7)
N(9)-C(10)	1.412(7)
C(10)-C(11)	1.388(6)
C(10)-C(15)	1.391(6)
C(11)-C(12)	1.363(7)
C(12)-C(13)	1.385(6)
C(13)-C(14)	1.391(6)
C(13)-N(21)	1.426(8)
C(14)-C(15)	1.360(7)
N(21)-O(23)	1.239(6)
N(21)-O(22)	1.241(6)
C(24)-C(29)	1.334(12)
C(24)-C(25)	1.411(11)
C(25)-C(26)	1.397(11)
C(26)-C(27)	1.340(12)
C(27)-O(30)	1.380(10)
C(27)-C(28)	1.390(12)
C(28)-C(29)	1.411(11)
O(30)-C(31)	1.432(12)
C(51)-O(66)	1.230(8)
C(51)-N(52)	1.391(9)
C(51)-C(56)	1.445(9)
N(52)-C(53)	1.362(9)
N(52)-C(67)	1.481(9)
C(53)-O(68)	1.222(8)
C(53)-N(54)	1.375(9)
N(54)-C(55)	1.394(9)
N(54)-C(69)	1.467(9)

Table 3 (H25) cont.

C(55)-O(70)	1.243(8)
C(55)-C(56)	1.417(10)
C(56)-C(57)	1.426(10)
C(57)-N(58A)	1.331(11)
C(57)-N(58)	1.333(8)
C(57)-C(74)	1.492(10)
N(58A)-N(59A)	1.44(8)
N(58)-N(59)	1.399(16)
N(59)-C(60)	1.435(8)
N(59A)-O(101)	1.33(3)
N(59A)-C(60A)	1.425(10)
C(60)-C(65)	1.388(7)
C(60)-C(61)	1.399(7)
C(60A)-C(61A)	1.389(8)
C(60A)-C(65A)	1.393(8)
C(61)-C(62)	1.355(8)
C(61A)-C(62A)	1.362(9)
C(62A)-C(63A)	1.387(8)
C(62)-C(63)	1.389(7)
C(63)-C(64)	1.387(7)
C(63)-N(71)	1.412(10)
C(63A)-C(64A)	1.390(8)
C(63A)-N(71A)	1.419(11)
C(64)-C(65)	1.360(8)
C(64A)-C(65A)	1.357(9)
N(71A)-O(73A)	1.236(9)
N(71A)-O(72A)	1.243(9)
N(71)-O(73)	1.233(8)
N(71)-O(72)	1.243(8)
C(74)-C(75)	1.370(10)
C(74)-C(79)	1.379(10)
C(75)-C(76)	1.386(10)
C(76)-C(77)	1.389(10)
C(77)-C(78)	1.356(11)
C(77)-O(80)	1.364(9)
C(78)-C(79)	1.411(10)
O(80)-C(81)	1.426(9)
O(101)-C(102)	1.35(4)
C(102)-C(103)	1.47(3)
C(103)-C(104)	1.47(3)
O(16)-C(1)-N(2)	117.8(7)
O(16)-C(1)-C(6)	124.8(8)
N(2)-C(1)-C(6)	117.4(8)

Table 3 (H25) cont.

C(3)-N(2)-C(1)	124.5(7)
C(3)-N(2)-C(17)	117.2(7)
C(1)-N(2)-C(17)	118.4(7)
O(18)-C(3)-N(2)	121.9(8)
O(18)-C(3)-N(4)	120.0(9)
N(2)-C(3)-N(4)	118.0(7)
C(3)-N(4)-C(5)	122.2(7)
C(3)-N(4)-C(19)	119.6(7)
C(5)-N(4)-C(19)	118.2(7)
O(20)-C(5)-N(4)	116.2(7)
O(20)-C(5)-C(6)	124.0(7)
N(4)-C(5)-C(6)	119.7(7)
C(7)-C(6)-C(5)	122.1(7)
C(7)-C(6)-C(1)	119.7(7)
C(5)-C(6)-C(1)	117.9(7)
N(8)-C(7)-C(6)	120.5(7)
N(8)-C(7)-C(24)	115.9(7)
C(6)-C(7)-C(24)	123.7(6)
C(7)-N(8)-N(9)	123.2(6)
N(8)-N(9)-C(10)	119.2(5)
C(11)-C(10)-C(15)	119.1(5)
C(11)-C(10)-N(9)	122.1(5)
C(15)-C(10)-N(9)	118.8(5)
C(12)-C(11)-C(10)	120.4(4)
C(11)-C(12)-C(13)	120.4(4)
C(12)-C(13)-C(14)	119.4(5)
C(12)-C(13)-N(21)	120.0(5)
C(14)-C(13)-N(21)	120.5(5)
C(15)-C(14)-C(13)	120.1(4)
C(14)-C(15)-C(10)	120.6(4)
O(23)-N(21)-O(22)	122.4(7)
O(23)-N(21)-C(13)	118.7(5)
O(22)-N(21)-C(13)	118.9(5)
C(29)-C(24)-C(25)	119.0(8)
C(29)-C(24)-C(7)	121.8(7)
C(25)-C(24)-C(7)	119.2(8)
C(26)-C(25)-C(24)	118.9(9)
C(27)-C(26)-C(25)	121.0(9)
C(26)-C(27)-O(30)	123.4(9)
C(26)-C(27)-C(28)	121.0(9)
O(30)-C(27)-C(28)	115.6(9)
C(27)-C(28)-C(29)	117.5(9)
C(24)-C(29)-C(28)	122.5(8)
C(27)-O(30)-C(31)	117.4(8)

Table 3 (H25) cont.

O(66)-C(51)-N(52)	117.9(6)
O(66)-C(51)-C(56)	126.7(6)
N(52)-C(51)-C(56)	115.4(6)
C(53)-N(52)-C(51)	125.7(6)
C(53)-N(52)-C(67)	116.0(6)
C(51)-N(52)-C(67)	118.3(6)
O(68)-C(53)-N(52)	121.7(7)
O(68)-C(53)-N(54)	121.5(6)
N(52)-C(53)-N(54)	116.8(6)
C(53)-N(54)-C(55)	123.6(6)
C(53)-N(54)-C(69)	117.4(6)
C(55)-N(54)-C(69)	119.0(6)
O(70)-C(55)-N(54)	117.2(6)
O(70)-C(55)-C(56)	125.1(6)
N(54)-C(55)-C(56)	117.7(6)
C(55)-C(56)-C(57)	119.9(6)
C(55)-C(56)-C(51)	120.2(6)
C(57)-C(56)-C(51)	119.8(6)
N(58A)-C(57)-C(56)	118(4)
N(58)-C(57)-C(56)	119.8(10)
N(58A)-C(57)-C(74)	116(4)
N(58)-C(57)-C(74)	115.6(10)
C(56)-C(57)-C(74)	124.5(6)
C(57)-N(58A)-N(59A)	133(7)
C(57)-N(58)-N(59)	121.5(13)
N(58)-N(59)-C(60)	123.1(10)
O(101)-N(59A)-C(60A)	144.8(13)
O(101)-N(59A)-N(58A)	125(4)
C(60A)-N(59A)-N(58A)	88(4)
C(65)-C(60)-C(61)	118.0(6)
C(65)-C(60)-N(59)	120.5(6)
C(61)-C(60)-N(59)	121.5(6)
C(61A)-C(60A)-C(65A)	118.6(7)
C(61A)-C(60A)-N(59A)	122.0(10)
C(65A)-C(60A)-N(59A)	119.4(10)
C(62)-C(61)-C(60)	121.0(5)
C(62A)-C(61A)-C(60A)	120.7(6)
C(61A)-C(62A)-C(63A)	120.6(6)
C(61)-C(62)-C(63)	120.8(5)
C(64)-C(63)-C(62)	118.5(6)
C(64)-C(63)-N(71)	121.1(6)
C(62)-C(63)-N(71)	120.4(6)
C(62A)-C(63A)-C(64A)	118.8(7)

Table 3 (H25) cont.

C(62A)-C(63A)-N(71A)	122.7(9)
C(64A)-C(63A)-N(71A)	118.5(9)
C(65)-C(64)-C(63)	120.9(5)
C(65A)-C(64A)-C(63A)	120.7(6)
C(64A)-C(65A)-C(60A)	120.6(6)
C(64)-C(65)-C(60)	120.9(5)
O(73A)-N(71A)-O(72A)	122.2(16)
O(73A)-N(71A)-C(63A)	120.4(12)
O(72A)-N(71A)-C(63A)	117.4(12)
O(73)-N(71)-O(72)	119.9(10)
O(73)-N(71)-C(63)	121.6(8)
O(72)-N(71)-C(63)	118.5(8)
N(71A)-O(72A)-C(12)#1	141.8(17)
C(75)-C(74)-C(79)	121.0(7)
C(75)-C(74)-C(57)	119.4(7)
C(79)-C(74)-C(57)	119.6(7)
C(74)-C(75)-C(76)	119.3(7)
C(75)-C(76)-C(77)	120.5(7)
C(78)-C(77)-O(80)	125.3(7)
C(78)-C(77)-C(76)	119.9(7)
O(80)-C(77)-C(76)	114.8(7)
C(77)-C(78)-C(79)	120.2(7)
C(74)-C(79)-C(78)	119.0(7)
C(77)-O(80)-C(81)	117.5(6)
N(59A)-O(101)-C(102)	108(2)
O(101)-C(102)-C(103)	115(3)
C(104)-C(103)-C(102)	122(3)

Symmetry transformations used to generate equivalent atoms:
#1 -x+2,-y+1,-z+1

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for **H25**.
The anisotropic displacement factor exponent takes the form:
$-2\ pi^2\ [\ h^2\ a^*2\ U11 + ... + 2\ h\ k\ a^*\ b^*\ U12\ ]$

	U11	U22	U33	U23	U13	U12
C(1)	98(5)	52(4)	28(3)	-5(3)	2(4)	10(4)
N(2)	69(4)	63(3)	25(3)	-9(3)	0(3)	17(3)
C(3)	70(4)	63(4)	42(3)	-11(3)	6(4)	21(4)
N(4)	72(4)	49(3)	45(3)	-12(3)	5(3)	16(3)
C(5)	50(4)	43(3)	39(3)	-5(3)	0(3)	3(3)
C(6)	57(4)	45(3)	31(3)	0(3)	-1(3)	8(3)
C(7)	51(4)	46(3)	30(3)	2(3)	5(3)	7(3)
N(8)	58(4)	39(3)	29(3)	-4(2)	0(3)	9(3)
N(9)	52(3)	44(3)	28(3)	-10(2)	7(2)	13(3)
C(10)	53(3)	36(4)	32(3)	-2(3)	5(3)	12(3)
C(11)	53(3)	36(4)	39(4)	-5(3)	3(3)	11(3)
C(12)	55(4)	36(4)	48(4)	6(3)	7(3)	15(3)
C(13)	52(3)	39(4)	43(3)	6(3)	1(3)	13(3)
C(14)	55(3)	44(4)	34(4)	-2(3)	2(3)	15(3)
C(15)	49(3)	36(4)	32(3)	1(3)	5(3)	10(3)
O(16)	220(7)	60(4)	38(3)	1(3)	-3(4)	34(5)
C(17)	108(7)	87(6)	28(4)	-8(4)	-4(4)	33(5)
O(18)	124(5)	84(4)	63(4)	-24(3)	12(4)	39(4)
C(19)	116(7)	54(5)	69(6)	-13(4)	2(5)	32(5)
O(20)	75(4)	37(3)	47(3)	4(2)	9(3)	8(3)
N(21)	57(3)	53(4)	55(4)	1(3)	-2(3)	21(3)
O(22)	59(3)	68(4)	77(4)	-3(3)	-1(3)	32(3)
O(23)	69(4)	93(5)	61(4)	-8(3)	-12(3)	20(3)
C(24)	65(4)	45(3)	33(3)	5(3)	9(3)	11(3)
C(25)	66(4)	46(4)	52(4)	5(4)	4(4)	11(3)
C(26)	77(4)	46(4)	53(4)	4(4)	2(4)	12(3)
C(27)	90(4)	54(3)	37(4)	7(3)	9(4)	26(3)
C(28)	81(4)	65(4)	52(4)	10(4)	8(4)	32(4)
C(29)	68(4)	60(4)	43(4)	10(4)	10(4)	17(3)
O(30)	120(4)	57(3)	57(3)	13(3)	12(3)	32(3)
C(31)	132(7)	59(6)	65(6)	11(5)	9(6)	17(5)
C(51)	47(3)	22(3)	34(3)	1(3)	3(3)	9(3)
N(52)	48(3)	28(3)	33(3)	0(2)	2(2)	14(2)
C(53)	50(3)	26(3)	31(3)	-2(3)	-3(3)	11(3)
N(54)	42(3)	36(3)	32(3)	-1(2)	-2(2)	10(2)
C(55)	46(3)	32(3)	31(3)	-1(3)	-1(3)	9(3)
C(56)	45(3)	28(3)	28(3)	4(3)	3(2)	9(3)
C(57)	49(3)	39(3)	30(3)	5(3)	2(2)	8(3)
N(58A)	58(5)	57(6)	30(4)	5(5)	2(4)	8(5)
N(58)	58(4)	56(5)	27(3)	7(3)	0(3)	6(4)

Table 4 (H25) cont.

N(59)	63(4)	60(4)	26(3)	5(3)	-1(3)	13(3)
N(59A)	70(5)	66(5)	34(4)	0(4)	-1(4)	12(4)
C(60)	97(5)	77(4)	55(4)	-2(3)	-3(4)	17(4)
C(60A)	91(5)	73(5)	52(5)	2(4)	-1(5)	21(4)
C(61)	105(5)	76(4)	66(4)	5(4)	0(4)	28(4)
C(61A)	95(6)	78(6)	55(7)	2(7)	3(7)	29(5)
C(62A)	105(6)	81(6)	64(6)	3(6)	5(6)	32(5)
C(62)	110(5)	80(5)	65(4)	2(4)	10(5)	29(4)
C(63)	114(6)	87(5)	68(5)	-3(4)	13(5)	32(4)
C(63A)	113(5)	86(5)	72(5)	2(5)	8(5)	28(5)
C(64)	119(7)	88(6)	65(5)	-8(5)	5(5)	28(5)
C(64A)	110(6)	80(6)	70(6)	5(6)	3(6)	23(5)
C(65A)	102(6)	77(5)	65(6)	4(6)	1(6)	18(5)
C(65)	109(7)	87(6)	60(5)	-10(5)	1(5)	26(5)
O(66)	48(3)	42(3)	38(3)	-1(2)	2(2)	9(2)
C(67)	55(5)	62(5)	29(4)	9(4)	5(3)	18(4)
O(68)	57(3)	40(3)	34(3)	-6(2)	-5(2)	10(2)
C(69)	42(4)	56(5)	52(5)	5(4)	0(3)	3(4)
O(70)	49(3)	49(3)	33(3)	4(2)	7(2)	2(2)
N(71A)	132(7)	98(6)	106(8)	9(7)	10(8)	42(6)
N(71)	143(7)	103(6)	85(5)	-5(4)	22(6)	55(5)
O(72A)	138(8)	107(8)	116(9)	11(8)	14(8)	39(7)
O(72)	180(8)	134(7)	101(6)	-20(5)	14(6)	69(6)
O(73A)	135(9)	120(12)	134(13)	5(11)	4(11)	51(8)
O(73)	146(6)	123(6)	115(6)	11(5)	17(5)	63(5)
C(74)	50(3)	33(3)	27(3)	-3(3)	-3(3)	8(3)
C(75)	53(3)	30(3)	34(4)	1(3)	0(3)	9(3)
C(76)	53(3)	44(3)	30(4)	1(3)	-1(3)	16(3)
C(77)	48(3)	37(3)	29(3)	-4(3)	1(3)	8(3)
C(78)	55(4)	32(3)	41(4)	3(3)	3(3)	10(3)
C(79)	56(4)	38(3)	37(4)	6(3)	-2(3)	12(3)
O(80)	47(3)	42(3)	46(3)	-1(2)	3(2)	6(2)
C(81)	58(5)	49(4)	53(5)	3(4)	2(4)	-1(4)
O(101)	60(5)	68(5)	36(4)	0(4)	2(4)	13(4)
C(102)	52(7)	56(7)	36(5)	-2(5)	2(6)	14(6)
C(103)	49(6)	55(6)	32(5)	-8(6)	1(6)	24(5)
C(104)	30(8)	52(7)	7(6)	-14(6)	-10(6)	17(6)
O(105)	64(5)	73(5)	59(5)	-12(5)	-1(4)	23(4)
O(106)	64(6)	80(6)	80(6)	-63(5)	-1(5)	30(5)
O(107)	58(5)	70(6)	61(6)	-16(5)	-3(5)	12(4)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for **H25**.

	x	y	z	U(eq)
H(8)	8472	322	2674	54
H(9)	8311	1970	3447	52
H(11)	11219	1778	2617	54
H(12)	13340	2524	3249	56
H(14)	11813	3484	5376	55
H(15)	9699	2759	4736	49
H(17A)	9227	99	-1660	113
H(17B)	8578	968	-1440	113
H(17C)	7634	-245	-1724	113
H(19A)	6956	-2910	797	121
H(19B)	8362	-2448	1321	121
H(19C)	8313	-2774	305	121
H(25)	10915	2925	1634	70
H(26)	11274	4729	1429	74
H(28)	7296	3988	1268	77
H(29)	6938	2174	1470	71
H(31A)	11342	6421	1589	136
H(31B)	10802	6995	876	136
H(31C)	11280	6043	584	136
H(58A)	4211	1620	6923	63
H(58)	4343	1238	7094	62
H(59)	6138	2141	8206	63
H(61)	4845	3563	6859	101
H(61A)	3218	2592	7828	93
H(62A)	2996	4190	7584	101
H(62)	4707	5195	7187	104
H(64)	6209	5230	9598	114
H(64A)	7026	5663	7448	108
H(65A)	7252	4069	7691	103
H(65)	6353	3596	9272	107
H(67A)	6044	857	2973	75
H(67B)	6484	2120	3188	75
H(67C)	5083	1454	2694	75
H(69A)	1212	134	4161	82
H(69B)	1193	224	5201	82
H(69C)	1337	-802	4714	82
H(75)	7904	1578	6936	49
H(76)	10163	2736	7033	51
H(78)	9255	5095	6048	53
H(79)	6980	3908	5886	54
H(81A)	11440	5712	5762	90

Table 5 (H25) cont.

H(81B)	12709	6015	6410	90
H(81C)	11353	6112	6746	90
H(10A)	4521	2147	9283	60
H(10B)	6108	2635	9453	60
H(10C)	5845	1669	10502	54
H(10D)	4274	1150	10309	54
H(10E)	4775	-167	9400	45
H(10F)	4772	-247	10433	45
H(10G)	6164	262	9943	45
H(101)	5580(150)	1920(120)	9300(150)	80
H(102)	5200(200)	1150(190)	9980(100)	80
H(103)	5810(190)	610(140)	8220(120)	91
H(104)	4500(80)	260(130)	8710(110)	91
H(105)	5700(300)	490(170)	8260(160)	80
H(106)	5360(190)	-50(120)	9190(120)	80

Table 6. Torsion angles [deg] for **H25**.

O(16)-C(1)-N(2)-C(3)	-178.7(10)
C(6)-C(1)-N(2)-C(3)	0.0(13)
O(16)-C(1)-N(2)-C(17)	1.8(14)
C(6)-C(1)-N(2)-C(17)	-179.5(8)
C(1)-N(2)-C(3)-O(18)	178.9(9)
C(17)-N(2)-C(3)-O(18)	-1.5(13)
C(1)-N(2)-C(3)-N(4)	-0.2(13)
C(17)-N(2)-C(3)-N(4)	179.4(8)
O(18)-C(3)-N(4)-C(5)	-176.0(8)
N(2)-C(3)-N(4)-C(5)	3.1(12)
O(18)-C(3)-N(4)-C(19)	2.0(13)
N(2)-C(3)-N(4)-C(19)	-178.9(8)
C(3)-N(4)-C(5)-O(20)	174.3(7)
C(19)-N(4)-C(5)-O(20)	-3.7(11)
C(3)-N(4)-C(5)-C(6)	-5.8(12)
C(19)-N(4)-C(5)-C(6)	176.2(8)
O(20)-C(5)-C(6)-C(7)	11.1(13)
N(4)-C(5)-C(6)-C(7)	-168.9(7)
O(20)-C(5)-C(6)-C(1)	-174.7(8)
N(4)-C(5)-C(6)-C(1)	5.4(12)
O(16)-C(1)-C(6)-C(7)	-9.6(15)
N(2)-C(1)-C(6)-C(7)	171.8(8)
O(16)-C(1)-C(6)-C(5)	176.0(10)
N(2)-C(1)-C(6)-C(5)	-2.6(12)
C(5)-C(6)-C(7)-N(8)	-0.1(12)
C(1)-C(6)-C(7)-N(8)	-174.2(8)
C(5)-C(6)-C(7)-C(24)	-178.7(8)
C(1)-C(6)-C(7)-C(24)	7.2(12)
C(6)-C(7)-N(8)-N(9)	178.3(7)
C(24)-C(7)-N(8)-N(9)	-3.0(10)
C(7)-N(8)-N(9)-C(10)	-99.5(8)
N(8)-N(9)-C(10)-C(11)	20.1(10)
N(8)-N(9)-C(10)-C(15)	-163.0(6)
C(15)-C(10)-C(11)-C(12)	1.1(11)
N(9)-C(10)-C(11)-C(12)	178.0(7)
C(10)-C(11)-C(12)-C(13)	-0.8(11)
C(10)-C(11)-C(12)-O(72A)#1	-148.2(11)
C(11)-C(12)-C(13)-C(14)	0.9(11)
O(72A)#1-C(12)-C(13)-C(14)	148.0(12)
C(11)-C(12)-C(13)-N(21)	178.8(7)
O(72A)#1-C(12)-C(13)-N(21)	-34.1(14)
C(12)-C(13)-C(14)-C(15)	-1.4(11)
N(21)-C(13)-C(14)-C(15)	-179.3(7)
C(13)-C(14)-C(15)-C(10)	1.8(11)

Table 6 (H25) cont.

C(11)-C(10)-C(15)-C(14)	-1.6(11)
N(9)-C(10)-C(15)-C(14)	-178.6(7)
C(12)-C(13)-N(21)-O(23)	-177.9(7)
C(14)-C(13)-N(21)-O(23)	-0.1(11)
C(12)-C(13)-N(21)-O(22)	3.3(11)
C(14)-C(13)-N(21)-O(22)	-178.8(7)
N(8)-C(7)-C(24)-C(29)	-96.8(9)
C(6)-C(7)-C(24)-C(29)	81.8(11)
N(8)-C(7)-C(24)-C(25)	83.6(9)
C(6)-C(7)-C(24)-C(25)	-97.8(9)
C(29)-C(24)-C(25)-C(26)	0.9(12)
C(7)-C(24)-C(25)-C(26)	-179.5(7)
C(24)-C(25)-C(26)-C(27)	-2.3(12)
C(25)-C(26)-C(27)-O(30)	-178.9(7)
C(25)-C(26)-C(27)-C(28)	3.8(13)
C(26)-C(27)-C(28)-C(29)	-3.7(13)
O(30)-C(27)-C(28)-C(29)	178.8(7)
C(25)-C(24)-C(29)-C(28)	-1.1(12)
C(7)-C(24)-C(29)-C(28)	179.3(7)
C(27)-C(28)-C(29)-C(24)	2.4(13)
C(26)-C(27)-O(30)-C(31)	6.5(12)
C(28)-C(27)-O(30)-C(31)	-176.1(8)
O(66)-C(51)-N(52)-C(53)	171.3(6)
C(56)-C(51)-N(52)-C(53)	-7.7(9)
O(66)-C(51)-N(52)-C(67)	-8.5(9)
C(56)-C(51)-N(52)-C(67)	172.5(6)
C(51)-N(52)-C(53)-O(68)	-175.2(6)
C(67)-N(52)-C(53)-O(68)	4.6(10)
C(51)-N(52)-C(53)-N(54)	3.5(10)
C(67)-N(52)-C(53)-N(54)	-176.7(6)
O(68)-C(53)-N(54)-C(55)	177.9(6)
N(52)-C(53)-N(54)-C(55)	-0.8(10)
O(68)-C(53)-N(54)-C(69)	-1.4(10)
N(52)-C(53)-N(54)-C(69)	179.9(6)
C(53)-N(54)-C(55)-O(70)	-177.3(6)
C(69)-N(54)-C(55)-O(70)	1.9(10)
C(53)-N(54)-C(55)-C(56)	2.9(10)
C(69)-N(54)-C(55)-C(56)	-177.8(6)
O(70)-C(55)-C(56)-C(57)	-9.3(11)
N(54)-C(55)-C(56)-C(57)	170.4(6)
O(70)-C(55)-C(56)-C(51)	172.9(7)
N(54)-C(55)-C(56)-C(51)	-7.3(10)
O(66)-C(51)-C(56)-C(55)	-169.5(7)
N(52)-C(51)-C(56)-C(55)	9.4(9)

Table 6 (H25) cont.

O(66)-C(51)-C(56)-C(57)	12.7(11)
N(52)-C(51)-C(56)-C(57)	-168.4(6)
C(55)-C(56)-C(57)-N(58A)	-5(5)
C(51)-C(56)-C(57)-N(58A)	172(5)
C(55)-C(56)-C(57)-N(58)	5.4(14)
C(51)-C(56)-C(57)-N(58)	-176.9(10)
C(55)-C(56)-C(57)-C(74)	-170.9(7)
C(51)-C(56)-C(57)-C(74)	6.9(11)
N(58)-C(57)-N(58A)-N(59A)	68(28)
C(56)-C(57)-N(58A)-N(59A)	173(7)
C(74)-C(57)-N(58A)-N(59A)	-20(11)
N(58A)-C(57)-N(58)-N(59)	-86(28)
C(56)-C(57)-N(58)-N(59)	-166.2(11)
C(74)-C(57)-N(58)-N(59)	10.3(19)
C(57)-N(58)-N(59)-C(60)	85.3(16)
C(57)-N(58A)-N(59A)-O(101)	-94(10)
C(57)-N(58A)-N(59A)-C(60A)	100(9)
N(58)-N(59)-C(60)-C(65)	170.6(8)
N(58)-N(59)-C(60)-C(61)	-9.4(8)
O(101)-N(59A)-C(60A)-C(61A)	-82(4)
N(58A)-N(59A)-C(60A)-C(61A)	80(3)
O(101)-N(59A)-C(60A)-C(65A)	98(4)
N(58A)-N(59A)-C(60A)-C(65A)	-100(3)
C(65)-C(60)-C(61)-C(62)	0.1(2)
N(59)-C(60)-C(61)-C(62)	-179.95(14)
C(65A)-C(60A)-C(61A)-C(62A)	0.0(2)
N(59A)-C(60A)-C(61A)-C(62A)	-179.99(14)
C(60A)-C(61A)-C(62A)-C(63A)	0.0(2)
C(60)-C(61)-C(62)-C(63)	0.0(2)
C(61)-C(62)-C(63)-C(64)	-0.1(2)
C(61)-C(62)-C(63)-N(71)	-179.87(17)
C(61A)-C(62A)-C(63A)-C(64A)	0.0(3)
C(61A)-C(62A)-C(63A)-N(71A)	180.00(17)
C(62)-C(63)-C(64)-C(65)	0.1(2)
N(71)-C(63)-C(64)-C(65)	179.92(18)
C(62A)-C(63A)-C(64A)-C(65A)	0.0(3)
N(71A)-C(63A)-C(64A)-C(65A)	180.00(17)
C(63A)-C(64A)-C(65A)-C(60A)	0.0(2)
C(61A)-C(60A)-C(65A)-C(64A)	0.0(2)
N(59A)-C(60A)-C(65A)-C(64A)	179.99(14)
C(63)-C(64)-C(65)-C(60)	-0.1(2)
C(61)-C(60)-C(65)-C(64)	0.0(2)
N(59)-C(60)-C(65)-C(64)	180.00(14)

Table 6 (H25) cont.

C(62A)-C(63A)-N(71A)-O(73A)	0.0(3)
C(64A)-C(63A)-N(71A)-O(73A)	-180.0(2)
C(62A)-C(63A)-N(71A)-O(72A)	-180.0(2)
C(64A)-C(63A)-N(71A)-O(72A)	0.0(3)
C(64)-C(63)-N(71)-O(73)	167.7(10)
C(62)-C(63)-N(71)-O(73)	-12.5(10)
C(64)-C(63)-N(71)-O(72)	-12.4(10)
C(62)-C(63)-N(71)-O(72)	167.4(9)
O(73A)-N(71A)-O(72A)-C(12)#1	-110(3)
C(63A)-N(71A)-O(72A)-C(12)#1	70(3)
N(58A)-C(57)-C(74)-C(75)	86(5)
N(58)-C(57)-C(74)-C(75)	75.6(12)
C(56)-C(57)-C(74)-C(75)	-108.0(9)
N(58A)-C(57)-C(74)-C(79)	-93(5)
N(58)-C(57)-C(74)-C(79)	-103.3(11)
C(56)-C(57)-C(74)-C(79)	73.1(10)
C(79)-C(74)-C(75)-C(76)	-1.0(11)
C(57)-C(74)-C(75)-C(76)	-180.0(6)
C(74)-C(75)-C(76)-C(77)	0.8(10)
C(75)-C(76)-C(77)-C(78)	0.9(10)
C(75)-C(76)-C(77)-O(80)	-179.4(6)
O(80)-C(77)-C(78)-C(79)	177.9(6)
C(76)-C(77)-C(78)-C(79)	-2.5(11)
C(75)-C(74)-C(79)-C(78)	-0.5(11)
C(57)-C(74)-C(79)-C(78)	178.4(6)
C(77)-C(78)-C(79)-C(74)	2.3(11)
C(78)-C(77)-O(80)-C(81)	0.9(10)
C(76)-C(77)-O(80)-C(81)	-178.8(6)
C(60A)-N(59A)-O(101)-C(102)	1(5)
N(58A)-N(59A)-O(101)-C(102)	-156(4)
N(59A)-O(101)-C(102)-C(103)	171(3)
O(101)-C(102)-C(103)-C(104)	2(5)

Symmetry transformations used to generate equivalent atoms:
#1 -x+2,-y+1,-z+1

X-ray crystallographic Data- Compound H52

(piperidinium salt of 5-[[2,4-dinitrophenyl)hydrazono]-(4-hydroxyphenyl)methyl]-1,3-dimethyl-pyrimidine-2,4,6-trione)

Table 7. Crystal data and structure refinement for compound **H52.**

Empirical formula	C_{24} H_{27} N_7 O_8
Formula weight	541.53
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system, space group	Monoclinic, P2(1)/n
Unit cell dimensions	a = 8.5917(3) Å alpha = 90 deg. b = 17.4016(5) Å beta = 101.8980(10) deg. c = 16.8982(5) Å gamma = 90 deg.
Volume	2472.16(13) $Å^3$
Z, Calculated density	4, 1.455 Mg/m^3
Absorption coefficient	0.112 mm^{-1}
F(000)	1136
Crystal size	0.3 x 0.4 x 0.5 mm
Theta range for data collection	2.34 to 27.50 deg.
Limiting indices	-11<=h<=11, -22<=k<=22, -21<=l<=21
Reflections collected / unique	34222 / 5677 [R(int) = 0.0348]
Completeness to theta = 27.50	100.0 %
Absorption correction	Empirical
Max. and min. transmission	1.000000 and 0.705996
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5677 / 374 / 474
Goodness-of-fit on F^2	1.100
Final R indices [I>2sigma(I)]	R1 = 0.0470, wR2 = 0.1526
R indices (all data)	R1 = 0.0568, wR2 = 0.1689
Extinction coefficient	0.013(3)
Largest diff. peak and hole	0.683 and -0.548 $e.A^{-3}$

Table 8. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for **H52**.
U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
C(1)	11042(2)	701(1)	1889(1)	29(1)
N(3)	11211(2)	1472(1)	1651(1)	31(1)
C(3)	9975(2)	1983(1)	1480(1)	31(1)
N(5)	8530(2)	1746(1)	1615(1)	30(1)
C(5)	8258(2)	1016(1)	1928(1)	28(1)
C(6)	9562(2)	506(1)	2082(1)	27(1)
C(7)	9318(2)	-283(1)	2364(1)	27(1)
N(8)	8904(2)	-436(1)	3048(1)	30(1)
N(9)	8842(2)	188(1)	3538(1)	30(1)
C(10)	8267(2)	117(1)	4221(1)	28(1)
C(11)	8226(2)	740(1)	4761(1)	29(1)
C(12)	7569(2)	664(1)	5441(1)	32(1)
C(13)	6975(2)	-36(1)	5605(1)	34(1)
C(14)	7047(2)	-679(1)	5113(1)	36(1)
C(15)	7680(2)	-598(1)	4435(1)	32(1)
N(16)	8865(2)	1490(1)	4632(1)	36(1)
O(17)	9177(2)	1638(1)	3965(1)	49(1)
O(18)	9079(2)	1957(1)	5190(1)	48(1)
N(19)	6202(2)	-93(1)	6293(1)	47(1)
O(20)	5750(3)	-718(1)	6466(1)	76(1)
O(21)	6010(2)	497(1)	6654(1)	65(1)
O(22)	12173(1)	261(1)	1916(1)	39(1)
C(23)	12802(2)	1739(1)	1580(1)	41(1)
O(24)	10141(2)	2631(1)	1200(1)	39(1)
C(25)	7188(2)	2284(1)	1408(1)	39(1)
O(26)	6890(1)	868(1)	2022(1)	34(1)
C(27)	9445(2)	-945(1)	1839(1)	27(1)
C(28)	9645(2)	-1697(1)	2144(1)	30(1)
C(29)	9649(2)	-2321(1)	1640(1)	33(1)
C(30)	9495(2)	-2211(1)	810(1)	31(1)
C(31)	9325(2)	-1468(1)	495(1)	31(1)
C(32)	9294(2)	-847(1)	1008(1)	29(1)
O(33)	9551(2)	-2845(1)	347(1)	38(1)
N(34)	4978(2)	447(1)	8184(1)	30(1)
C(35)	5280(2)	353(1)	9083(1)	35(1)
C(36)	6642(2)	861(1)	9489(1)	38(1)
C(37)	6355(2)	1702(1)	9237(1)	40(1)
C(38)	6014(2)	1770(1)	8318(1)	40(1)
C(39)	4634(2)	1268(1)	7938(1)	35(1)

Table 9. Bond lengths [A] and angles [deg] for **H52**.

C(1)-O(22)	1.231(2)
C(1)-N(3)	1.416(2)
C(1)-C(6)	1.417(2)
N(3)-C(3)	1.370(2)
N(3)-C(23)	1.472(2)
C(3)-O(24)	1.241(2)
C(3)-N(5)	1.372(2)
N(5)-C(5)	1.413(2)
N(5)-C(25)	1.469(2)
C(5)-O(26)	1.246(2)
C(5)-C(6)	1.411(2)
C(6)-C(7)	1.483(2)
C(7)-N(8)	1.303(2)
C(7)-C(27)	1.473(2)
N(8)-N(9)	1.3729(19)
N(9)-C(10)	1.352(2)
C(10)-C(15)	1.418(2)
C(10)-C(11)	1.422(2)
C(11)-C(12)	1.387(2)
C(11)-N(16)	1.449(2)
C(12)-C(13)	1.370(3)
C(13)-C(14)	1.403(3)
C(13)-N(19)	1.457(2)
C(14)-C(15)	1.373(2)
N(16)-O(18)	1.230(2)
N(16)-O(17)	1.237(2)
N(19)-O(20)	1.212(3)
N(19)-O(21)	1.223(3)
C(27)-C(32)	1.394(2)
C(27)-C(28)	1.403(2)
C(28)-C(29)	1.380(2)
C(29)-C(30)	1.395(2)
C(30)-O(33)	1.358(2)
C(30)-C(31)	1.395(2)
C(31)-C(32)	1.389(2)
N(34)-C(35)	1.497(2)
N(34)-C(39)	1.499(2)
C(35)-C(36)	1.514(3)
C(36)-C(37)	1.529(3)
C(37)-C(38)	1.524(3)
C(38)-C(39)	1.507(3)
O(22)-C(1)-N(3)	118.29(14)
O(22)-C(1)-C(6)	125.50(15)
N(3)-C(1)-C(6)	116.21(14)

Table 9 (H52) cont.

C(3)-N(3)-C(1)	123.68(14)
C(3)-N(3)-C(23)	118.09(15)
C(1)-N(3)-C(23)	118.24(15)
O(24)-C(3)-N(3)	121.65(15)
O(24)-C(3)-N(5)	121.04(16)
N(3)-C(3)-N(5)	117.30(14)
C(3)-N(5)-C(5)	123.89(14)
C(3)-N(5)-C(25)	117.50(14)
C(5)-N(5)-C(25)	118.60(14)
O(26)-C(5)-C(6)	125.46(15)
O(26)-C(5)-N(5)	117.87(14)
C(6)-C(5)-N(5)	116.63(14)
C(5)-C(6)-C(1)	121.51(14)
C(5)-C(6)-C(7)	118.82(14)
C(1)-C(6)-C(7)	119.30(14)
N(8)-C(7)-C(27)	116.23(14)
N(8)-C(7)-C(6)	123.84(14)
C(27)-C(7)-C(6)	119.83(13)
C(7)-N(8)-N(9)	115.11(14)
C(10)-N(9)-N(8)	120.65(14)
N(9)-C(10)-C(15)	120.64(15)
N(9)-C(10)-C(11)	122.73(14)
C(15)-C(10)-C(11)	116.62(14)
C(12)-C(11)-C(10)	121.80(15)
C(12)-C(11)-N(16)	116.28(15)
C(10)-C(11)-N(16)	121.92(14)
C(13)-C(12)-C(11)	118.96(16)
C(12)-C(13)-C(14)	121.76(16)
C(12)-C(13)-N(19)	118.12(16)
C(14)-C(13)-N(19)	120.08(17)
C(15)-C(14)-C(13)	119.02(16)
C(14)-C(15)-C(10)	121.74(16)
O(18)-N(16)-O(17)	122.29(15)
O(18)-N(16)-C(11)	118.71(15)
O(17)-N(16)-C(11)	119.01(14)
O(20)-N(19)-O(21)	123.42(18)
O(20)-N(19)-C(13)	118.37(18)
O(21)-N(19)-C(13)	118.19(18)
C(32)-C(27)-C(28)	117.62(14)
C(32)-C(27)-C(7)	120.55(14)
C(28)-C(27)-C(7)	121.76(14)
C(29)-C(28)-C(27)	121.48(15)
C(28)-C(29)-C(30)	120.09(15)

Table 9 (H52) cont.

O(33)-C(30)-C(31)	123.15(15)
O(33)-C(30)-C(29)	117.43(15)
C(31)-C(30)-C(29)	119.41(15)
C(32)-C(31)-C(30)	119.82(15)
C(31)-C(32)-C(27)	121.57(15)
C(35)-N(34)-C(39)	111.66(13)
N(34)-C(35)-C(36)	110.58(15)
C(35)-C(36)-C(37)	111.51(15)
C(38)-C(37)-C(36)	110.19(15)
C(39)-C(38)-C(37)	110.95(15)
N(34)-C(39)-C(38)	109.97(14)

Symmetry transformations used to generate equivalent atoms: #1 -x+2,-y+1,-z+1

Table 10. Anisotropic displacement parameters ($A^2 \times 10^3$) for **H52**.
The anisotropic displacement factor exponent takes the form:
$-2\,pi^2\,[\,h^2\,a^{*2}\,U11 + ... + 2\,h\,k\,a^*\,b^*\,U12\,]$

	U11	U22	U33	U23	U13	U12
C(1)	30(1)	33(1)	25(1)	-2(1)	8(1)	-1(1)
N(3)	32(1)	35(1)	28(1)	-2(1)	9(1)	-5(1)
C(3)	39(1)	29(1)	25(1)	-3(1)	8(1)	-5(1)
N(5)	36(1)	27(1)	28(1)	0(1)	9(1)	2(1)
C(5)	32(1)	29(1)	24(1)	-3(1)	7(1)	0(1)
C(6)	29(1)	30(1)	24(1)	0(1)	7(1)	0(1)
C(7)	26(1)	30(1)	26(1)	0(1)	7(1)	2(1)
N(8)	33(1)	29(1)	29(1)	-2(1)	10(1)	1(1)
N(9)	36(1)	27(1)	27(1)	-2(1)	11(1)	-1(1)
C(10)	28(1)	30(1)	26(1)	0(1)	6(1)	2(1)
C(11)	31(1)	29(1)	28(1)	-2(1)	5(1)	0(1)
C(12)	31(1)	40(1)	25(1)	-4(1)	5(1)	4(1)
C(13)	32(1)	48(1)	24(1)	1(1)	8(1)	-1(1)
C(14)	40(1)	40(1)	29(1)	2(1)	9(1)	-6(1)
C(15)	36(1)	32(1)	28(1)	-1(1)	8(1)	-2(1)
N(16)	39(1)	32(1)	39(1)	-6(1)	10(1)	-3(1)
O(17)	72(1)	35(1)	43(1)	-1(1)	21(1)	-10(1)
O(18)	54(1)	41(1)	50(1)	-18(1)	15(1)	-9(1)
N(19)	41(1)	71(1)	28(1)	2(1)	9(1)	-2(1)
O(20)	102(2)	94(1)	41(1)	-11(1)	34(1)	-55(1)
O(21)	85(1)	79(1)	38(1)	7(1)	30(1)	35(1)
O(22)	29(1)	42(1)	47(1)	-2(1)	11(1)	4(1)
C(23)	34(1)	52(1)	37(1)	0(1)	9(1)	-13(1)
O(24)	56(1)	29(1)	34(1)	-1(1)	18(1)	-6(1)
C(25)	43(1)	32(1)	43(1)	1(1)	10(1)	7(1)
O(26)	29(1)	33(1)	41(1)	1(1)	11(1)	2(1)
C(27)	25(1)	30(1)	26(1)	-1(1)	9(1)	2(1)
C(28)	34(1)	32(1)	27(1)	2(1)	10(1)	3(1)
C(29)	38(1)	29(1)	33(1)	3(1)	11(1)	3(1)
C(30)	32(1)	30(1)	32(1)	-3(1)	9(1)	1(1)
C(31)	36(1)	33(1)	25(1)	0(1)	7(1)	0(1)
C(32)	30(1)	28(1)	29(1)	1(1)	8(1)	1(1)
O(33)	54(1)	29(1)	32(1)	-4(1)	11(1)	0(1)
N(34)	28(1)	35(1)	30(1)	-1(1)	9(1)	0(1)
C(35)	35(1)	42(1)	30(1)	3(1)	11(1)	0(1)
C(36)	37(1)	44(1)	33(1)	-2(1)	4(1)	1(1)
C(37)	41(1)	41(1)	39(1)	-8(1)	10(1)	-2(1)
C(38)	44(1)	35(1)	43(1)	2(1)	17(1)	-1(1)
C(39)	35(1)	38(1)	33(1)	3(1)	9(1)	8(1)

Table 11. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for **H52**.

	x	y	z	U(eq)
H(9)	9130(30)	660(14)	3415(13)	40(6)
H(12)	7600(30)	1072(13)	5805(15)	48(6)
H(14)	6550(30)	-1127(14)	5249(15)	48(6)
H(15)	7670(30)	-1044(13)	4050(15)	46(6)
H(23A)	12890(30)	2250(16)	1750(16)	55(7)
H(23B)	12920(40)	1710(16)	1023(19)	68(8)
H(23C)	13630(30)	1448(14)	1948(15)	48(6)
H(25A)	7030(40)	2403(18)	832(10)	46(12)
H(25B)	7480(40)	2745(13)	1738(15)	39(11)
H(25C)	6250(20)	2046(15)	1544(17)	27(9)
H(25F)	6330(40)	2000(20)	1050(30)	13(16)
H(25E)	7450(80)	2750(30)	1130(30)	60(30)
H(25D)	6840(80)	2430(40)	1900(30)	110(40)
H(28)	9800(20)	-1787(10)	2728(12)	27(4)
H(29)	9810(30)	-2830(13)	1850(14)	38(5)
H(31)	9180(30)	-1388(13)	-95(14)	41(6)
H(32)	9190(20)	-328(12)	782(12)	30(5)
H(33)	9540(30)	-2686(15)	-196(17)	55(7)
H(34A)	5870(30)	279(13)	8007(13)	39(5)
H(34B)	4150(30)	86(13)	8008(14)	45(6)
H(35A)	5510(30)	-197(13)	9194(14)	42(6)
H(35B)	4370(30)	467(12)	9236(12)	30(5)
H(36A)	6810(30)	795(12)	10060(15)	41(6)
H(36B)	7680(30)	693(13)	9332(13)	45(6)
H(37A)	7300(30)	2029(12)	9473(13)	37(5)
H(37B)	5410(30)	1918(13)	9434(15)	47(6)
H(38A)	6930(30)	1623(14)	8146(15)	50(6)
H(38B)	5760(30)	2317(15)	8138(15)	55(7)
H(39A)	4480(20)	1276(12)	7369(14)	36(5)
H(39B)	3610(30)	1393(12)	8104(13)	34(5)

Table 12. Torsion angles [deg] for **H52**.

O(22)-C(1)-N(3)-C(3)	169.82(15)
C(6)-C(1)-N(3)-C(3)	-10.6(2)
O(22)-C(1)-N(3)-C(23)	-9.9(2)
C(6)-C(1)-N(3)-C(23)	169.69(15)
C(1)-N(3)-C(3)-O(24)	-173.12(14)
C(23)-N(3)-C(3)-O(24)	6.6(2)
C(1)-N(3)-C(3)-N(5)	5.7(2)
C(23)-N(3)-C(3)-N(5)	-174.57(14)
O(24)-C(3)-N(5)-C(5)	179.68(14)
N(3)-C(3)-N(5)-C(5)	0.9(2)
O(24)-C(3)-N(5)-C(25)	0.7(2)
N(3)-C(3)-N(5)-C(25)	-178.10(14)
C(3)-N(5)-C(5)-O(26)	-179.80(14)
C(25)-N(5)-C(5)-O(26)	-0.9(2)
C(3)-N(5)-C(5)-C(6)	-1.9(2)
C(25)-N(5)-C(5)-C(6)	177.07(14)
O(26)-C(5)-C(6)-C(1)	174.28(15)
N(5)-C(5)-C(6)-C(1)	-3.5(2)
O(26)-C(5)-C(6)-C(7)	1.3(2)
N(5)-C(5)-C(6)-C(7)	-176.45(13)
O(22)-C(1)-C(6)-C(5)	-171.20(16)
N(3)-C(1)-C(6)-C(5)	9.2(2)
O(22)-C(1)-C(6)-C(7)	1.7(2)
N(3)-C(1)-C(6)-C(7)	-177.83(13)
C(5)-C(6)-C(7)-N(8)	-63.2(2)
C(1)-C(6)-C(7)-N(8)	123.66(17)
C(5)-C(6)-C(7)-C(27)	112.97(16)
C(1)-C(6)-C(7)-C(27)	-60.2(2)
C(27)-C(7)-N(8)-N(9)	178.05(13)
C(6)-C(7)-N(8)-N(9)	-5.6(2)
C(7)-N(8)-N(9)-C(10)	172.95(15)
N(8)-N(9)-C(10)-C(15)	-1.6(2)
N(8)-N(9)-C(10)-C(11)	177.90(14)
N(9)-C(10)-C(11)-C(12)	177.13(16)
C(15)-C(10)-C(11)-C(12)	-3.3(2)
N(9)-C(10)-C(11)-N(16)	-2.7(2)
C(15)-C(10)-C(11)-N(16)	176.81(15)
C(10)-C(11)-C(12)-C(13)	1.5(2)
N(16)-C(11)-C(12)-C(13)	-178.65(15)
C(11)-C(12)-C(13)-C(14)	1.4(3)
C(11)-C(12)-C(13)-N(19)	-176.32(15)
C(12)-C(13)-C(14)-C(15)	-2.2(3)
N(19)-C(13)-C(14)-C(15)	175.42(16)
C(13)-C(14)-C(15)-C(10)	0.2(3)

Table 12 (H52) cont.

N(9)-C(10)-C(15)-C(14)	-178.01(16)
C(11)-C(10)-C(15)-C(14)	2.5(2)
C(12)-C(11)-N(16)-O(18)	14.1(2)
C(10)-C(11)-N(16)-O(18)	-166.04(16)
C(12)-C(11)-N(16)-O(17)	-165.92(16)
C(10)-C(11)-N(16)-O(17)	13.9(2)
C(12)-C(13)-N(19)-O(20)	-176.18(19)
C(14)-C(13)-N(19)-O(20)	6.1(3)
C(12)-C(13)-N(19)-O(21)	5.5(3)
C(14)-C(13)-N(19)-O(21)	-172.21(17)
N(8)-C(7)-C(27)-C(32)	156.20(15)
C(6)-C(7)-C(27)-C(32)	-20.3(2)
N(8)-C(7)-C(27)-C(28)	-20.7(2)
C(6)-C(7)-C(27)-C(28)	162.85(15)
C(32)-C(27)-C(28)-C(29)	-1.7(2)
C(7)-C(27)-C(28)-C(29)	175.28(15)
C(27)-C(28)-C(29)-C(30)	1.7(3)
C(28)-C(29)-C(30)-O(33)	178.28(15)
C(28)-C(29)-C(30)-C(31)	-0.5(3)
O(33)-C(30)-C(31)-C(32)	-179.35(15)
C(29)-C(30)-C(31)-C(32)	-0.6(3)
C(30)-C(31)-C(32)-C(27)	0.6(2)
C(28)-C(27)-C(32)-C(31)	0.5(2)
C(7)-C(27)-C(32)-C(31)	-176.49(15)
C(39)-N(34)-C(35)-C(36)	-57.28(19)
N(34)-C(35)-C(36)-C(37)	54.9(2)
C(35)-C(36)-C(37)-C(38)	-54.3(2)
C(36)-C(37)-C(38)-C(39)	55.9(2)
C(35)-N(34)-C(39)-C(38)	58.86(19)
C(37)-C(38)-C(39)-N(34)	-58.0(2)

Symmetry transformations used to generate equivalent atoms: #1 -x+2,-y+1,-z+1

X-ray crystallographic Data- Compound F1
(Pyridinium-barbiturate Zwitterion)

Table 13. Crystal data and structure refinement for compound **F1**

Empirical formula	$C_{24}\ H_{22}\ N_6\ O_6$
Formula weight	490.48
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system, space group	Monoclinic, P2(1)/n
Unit cell dimensions	a=11.6777(6) Å, alpha = 90.00 deg. b=13.4416(7) Å, beta = 111.6300(10) deg c=15.0367(8) Å, gamma = 90.00 deg
Volume	2194.1(2) $Å^3$
Z, calculated density	4, 1.485 Mg/m^3
Absorption coefficient	0.110 mm^{-1}
F(000)	1024
Crystal size	0.4 x 0.5 x 0.6 mm
Theta range for data collection	2.10 to 30.00 deg.
Limiting indices	-16<=h<=16, -18<=k<=18, -21<=l<=20
Reflections collected / unique	30679 / 6390 [R(int) = 0.0284]
Completeness to theta = 30.00	100.0%
Absorption correction	empirical
Max. and min. transmission	1.000000 and 0.811722
Refinement method	Full matrix least squares on F^2
Data / restraints/ parameters	6390 / 0 / 413
Goodness of fit on F^2	1.035
Final R indices [I>2sigma(I)]	R1=0.0486, wR2=0.1041
Largest diff. peak and hole	0.388 and -0.241 $e.A^3$

Table 14: Atomic coordinates and equivalent isotropic displacement parameters (A^2) for **F1.** U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
C(1)	0.40154(9)	0.76110(7)	0.32067(7)	0.01620(19)
C(2)	0.37268(9)	0.66438(7)	0.35879(7)	0.0173(2)
C(3)	0.37981(10)	0.56702(8)	0.33032(8)	0.0217(2)
C(4)	0.34872(10)	0.49033(8)	0.37943(9)	0.0247(2)
C(5)	0.31165(10)	0.51147(8)	0.45610(9)	0.0246(2)
C(6)	0.30312(10)	0.60879(8)	0.48059(8)	0.0215(2)
N(7)	0.33290(8)	0.68190(6)	0.43083(6)	0.01767(18)
C(8)	0.32301(9)	0.79020(7)	0.44947(8)	0.0177(2)
C(9)	0.42018(9)	0.83200(7)	0.41155(7)	0.01618(19)
C(10)	0.40282(9)	0.93899(8)	0.37796(7)	0.0179(2)
N(11)	0.50556(8)	0.97972(6)	0.36542(7)	0.01981(19)
C(12)	0.62265(10)	0.93615(8)	0.40039(8)	0.0203(2)
N(13)	0.64245(8)	0.86229(7)	0.46952(7)	0.01974(18)
C(14)	0.54844(9)	0.81456(7)	0.48722(7)	0.0178(2)
C(15)	0.49643(9)	0.75965(7)	0.27610(7)	0.0169(2)
C(16)	0.60439(9)	0.70148(7)	0.31489(7)	0.0175(2)
N(17)	0.68541(8)	0.70188(7)	0.26378(7)	0.02065(19)
C(18)	0.66641(10)	0.75685(8)	0.18230(8)	0.0203(2)
N(19)	0.56146(8)	0.81420(7)	0.14951(6)	0.02109(19)
C(20)	0.47389(9)	0.81994(8)	0.19443(7)	0.0176(2)
O(21)	0.30749(7)	0.98487(6)	0.35799(6)	0.02502(18)
C(22)	0.48702(11)	1.06806(8)	0.30363(9)	0.0247(2)
O(23)	0.70576(7)	0.96754(6)	0.37764(6)	0.02848(19)
C(24)	0.77081(10)	0.83330(10)	0.52487(10)	0.0264(2)
O(25)	0.56654(7)	0.76029(6)	0.55579(6)	0.02343(17)
O(26)	0.63307(7)	0.65141(6)	0.38941(6)	0.02345(17)
C(27)	0.79630(12)	0.63983(10)	0.29909(10)	0.0295(3)
O(28)	0.74013(7)	0.75544(7)	0.14071(6)	0.02804(19)
C(29)	0.54155(13)	0.87453(11)	0.06397(10)	0.0331(3)
O(30)	0.38443(7)	0.87667(6)	0.15982(6)	0.02363(17)
C(31)	0.18991(9)	0.82394(8)	0.39900(8)	0.0195(2)
N(32)	0.13528(8)	0.79654(7)	0.30716(7)	0.0230(2)
C(33)	0.01985(11)	0.82892(9)	0.25990(9)	0.0277(2)
C(34)	-0.04474(11)	0.88746(10)	0.30170(10)	0.0317(3)
C(35)	0.01122(11)	0.91232(9)	0.39715(10)	0.0319(3)
C(36)	0.13147(11)	0.87981(9)	0.44767(9)	0.0254(2)

Table 15: Bond lengths [Å] and angles [deg] for **F1.**

C1-C15	1.4915(13)
C1-C2	1.5083(14)
C1-C9	1.6136(14)
C2-N7	1.3475(13)
C2-C3	1.3889(14)
C3-C4	1.3918(15)
C4-C5	1.4018(17)
C5-C6	1.3725(16)
C6-N7	1.3559(13)
N7-C8	1.4948(13)
C8-C31	1.5257(15)
C8-C9	1.5510(13)
C9-C10	1.5128(14)
C9-C14	1.5286(14)
C10-O21	1.2097(13)
C10-N11	1.3934(13)
N11-C12	1.3996(14)
N11-C22	1.4738(14)
C12-O23	1.2173(13)
C12-N13	1.3938(14)
N13-C14	1.3794(13)
N13-C24	1.4737(14)
C14-O25	1.2163(13)
C15-C20	1.4128(14)
C15-C16	1.4138(14)
C16-O26	1.2425(12)
C16-N17	1.4220(13)
N17-C18	1.3769(14)
N17-C27	1.4654(14)
C18-O28	1.2367(13)
C18-N19	1.3763(14)
N19-C20	1.4202(13)
N19-C29	1.4648(14)
C20-O30	1.2421(12)
C31-N32	1.3418(14)
C31-C36	1.3905(15)
N32-C33	1.3435(15)
C33-C34	1.3902(17)
C34-C35	1.3810(19)
C35-C36	1.3976(17)

Symmetry transformations used to generate equivalent atoms: #1 -x+2,-y+1,-z+1

Table 16: Anisotropic displacement parameters (A^2) for **F1.** The anisotropic displacement factor exponent takes the form: -2 pi^2 [h^2 a^{*2}U11 + … + h k a*b* U12]

	U11	U22	U33	U23	U13	U12
C1	0.0174(4)	0.0158(4)	0.0172(5)	0.0002(4)	0.0085(4)	-0.0001(4)
C2	0.0160(4)	0.0188(5)	0.0182(5)	0.0005(4)	0.0076(4)	-0.0017(4)
C3	0.0215(5)	0.0197(5)	0.0248(6)	-0.0030(4)	0.0097(4)	-0.0032(4)
C4	0.0234(5)	0.0171(5)	0.0328(6)	-0.0007(4)	0.0092(5)	-0.0035(4)
C5	0.0226(5)	0.0226(5)	0.0271(6)	0.0056(4)	0.0073(4)	-0.0048(4)
C6	0.0209(5)	0.0248(5)	0.0201(5)	0.0040(4)	0.0091(4)	-0.0044(4)
N7	0.0183(4)	0.0175(4)	0.0190(4)	0.0013(3)	0.0090(3)	-0.0019(3)
C8	0.0200(5)	0.0178(5)	0.0186(5)	-0.0019(4)	0.0110(4)	-0.0021(4)
C9	0.0173(4)	0.0159(4)	0.0175(5)	-0.0001(4)	0.0090(4)	-0.0012(4)
C10	0.0197(5)	0.0172(4)	0.0185(5)	-0.0013(4)	0.0091(4)	-0.0012(4)
N11	0.0201(4)	0.0165(4)	0.0250(5)	0.0033(3)	0.0108(4)	-0.0007(3)
C12	0.0199(5)	0.0188(5)	0.0228(5)	-0.0012(4)	0.0085(4)	-0.0029(4)
N13	0.0165(4)	0.0198(4)	0.0225(5)	0.0011(3)	0.0068(4)	-0.0014(3)
C14	0.0201(5)	0.0171(4)	0.0176(5)	-0.0021(4)	0.0085(4)	-0.0008(4)
C15	0.0184(5)	0.0173(4)	0.0177(5)	0.0002(4)	0.0096(4)	-0.0001(4)
C16	0.0193(5)	0.0167(4)	0.0183(5)	-0.0011(4)	0.0091(4)	-0.0003(4)
N17	0.0199(4)	0.0235(4)	0.0221(5)	0.0031(3)	0.0120(4)	0.0051(3)
C18	0.0202(5)	0.0237(5)	0.0192(5)	-0.0016(4)	0.0100(4)	-0.0006(4)
N19	0.0214(4)	0.0267(5)	0.0184(4)	0.0052(4)	0.0111(4)	0.0026(4)
C20	0.0183(4)	0.0188(5)	0.0173(5)	-0.0014(4)	0.0085(4)	-0.0014(4)
O21	0.0233(4)	0.0207(4)	0.0343(5)	0.0031(3)	0.0145(3)	0.0035(3)
C22	0.0291(6)	0.0185(5)	0.0281(6)	0.0050(4)	0.0125(5)	-0.0012(4)
O23	0.0222(4)	0.0298(4)	0.0370(5)	0.0050(4)	0.0150(4)	-0.0039(3)
C24	0.0166(5)	0.0272(6)	0.0317(7)	0.0031(5)	0.0044(5)	0.0012(4)
O25	0.0258(4)	0.0250(4)	0.0199(4)	0.0044(3)	0.0089(3)	0.0005(3)
O26	0.0254(4)	0.0237(4)	0.0232(4)	0.0072(3)	0.0112(3)	0.0037(3)
C27	0.0261(6)	0.0335(6)	0.0326(7)	0.0078(5)	0.0152(5)	0.0120(5)
O28	0.0253(4)	0.0393(5)	0.0254(4)	0.0007(4)	0.0162(3)	0.0012(3)
C29	0.0326(6)	0.0459(7)	0.0260(6)	0.0165(6)	0.0168(5)	0.0078(6)
O30	0.0228(4)	0.0253(4)	0.0230(4)	0.0060(3)	0.0086(3)	0.0059(3)
C31	0.0197(5)	0.0190(5)	0.0236(5)	-0.0007(4)	0.0124(4)	-0.0026(4)
N32	0.0200(4)	0.0256(5)	0.0246(5)	-0.0034(4)	0.0096(4)	-0.0014(4)
C33	0.0226(5)	0.0303(6)	0.0291(6)	-0.0034(5)	0.0082(5)	-0.0019(5)
C34	0.0204(5)	0.0319(6)	0.0407(8)	-0.0041(5)	0.0086(5)	0.0019(5)
C35	0.0267(6)	0.0306(6)	0.0433(8)	-0.0085(5)	0.0185(6)	0.0020(5)
C36	0.0255(5)	0.0276(6)	0.0274(6)	-0.0058(5)	0.0147(5)	-0.0022(4)

Table 17: Hydrogen coordinates and isotropic displacement parameters (A^2) for **F1.**

	x	y	z	U(eq)
H1	0.3248(12)	0.7836(9)	0.2719(9)	0.021(3)
H3	0.4067(12)	0.5553(10)	0.2770(10)	0.023(3)
H4	0.3552(13)	0.4244(11)	0.3629(10)	0.033(4)
H5 H	0.2909(12)	0.4636(10)	0.4937(10)	0.028(3)
H6 H	0.2770(12)	0.6285(10)	0.5332(10)	0.026(3)
H8 H	0.3469(10)	0.7980(8)	0.5170(9)	0.010(3)
H22A H	0.5598(15)	1.1079(11)	0.3231(11)	0.041(4)
H22B H	0.4693(14)	1.0485(12)	0.2381(12)	0.039(4)
H22C H	0.4188(15)	1.1054(12)	0.3092(11)	0.041(4)
H24A H	0.8090(16)	0.8214(13)	0.4832(13)	0.054(5)
H24B H	0.8121(17)	0.8808(14)	0.5627(14)	0.057(5)
H24C H	0.7714(18)	0.7710(15)	0.5532(14)	0.065(6)
H27A H	0.7900(16)	0.5899(14)	0.2491(13)	0.054(5)
H27B H	0.7910(17)	0.6029(14)	0.3546(14)	0.059(5)
H27C H	0.8673(15)	0.6790(11)	0.3107(11)	0.038(4)
H29A H	0.6067(17)	0.9293(14)	0.0757(13)	0.059(5)
H29B H	0.5521(16)	0.8305(13)	0.0117(13)	0.051(5)
H29C H	0.4543(16)	0.9002(12)	0.0413(12)	0.050(5)
H33 H	-0.0176(14)	0.8088(11)	0.1926(11)	0.038(4)
H34 H	-0.1253(14)	0.9100(11)	0.2628(10)	0.035(4)
H35 H	-0.0328(14)	0.9549(12)	0.4260(11)	0.037(4)
H36 H	0.1752(13)	0.8971(11)	0.5157(11)	0.033(4)

Table 18: Torsion angles [deg] for **F1.**

C15 C1 C2	117.82(8)
C15 C1 C9	119.83(8)
C2 C1 C9	99.58(8)
N7 C2 C3	119.35(9)
N7 C2 C1	110.27(8)
C3 C2 C1	130.37(9)
C2 C3 C4	118.51(10)
C3 C4 C5	120.41(10)
C6 C5 C4	119.27(10)
N7 C6 C5	118.94(10)
C2 N7 C6	123.47(9)
C2 N7 C8	113.22(8)
C6 N7 C8	123.31(9)
N7 C8 C31	109.34(8)
N7 C8 C9	99.58(7)
C31 C8 C9	117.31(9)
C10 C9 C14	111.61(8)
C10 C9 C8	116.16(8)
C14 C9 C8	108.64(8)
C10 C9 C1	108.61(8)
C14 C9 C1	109.21(8)
C8 C9 C1	102.05(7)
O21 C10 N11	121.71(9)
O21 C10 C9	124.43(9)
N11 C10 C9	113.74(8)
C10 N11 C12	123.74(9)
C10 N11 C22	117.91(9)
C12 N11 C22	118.04(9)
O23 C12 N13	121.75(10)
O23 C12 N11	121.27(10)
N13 C12 N11	116.66(9)
C14 N13 C12	123.38(9)
C14 N13 C24	118.96(9)
C12 N13 C24	117.65(9)
O25 C14 N13	122.72(10)
O25 C14 C9	122.65(9)
N13 C14 C9	114.59(9)
C20 C15 C16	121.87(9)
C20 C15 C1	116.86(9)
C16 C15 C1	121.27(9)
O26 C16 C15	125.07(9)
O26 C16 N17	118.52(9)
C15 C16 N17	116.40(9)

Table 18 (F1) cont.

C18 N17 C16	124.19(9)
C18 N17 C27	117.31(9)
C16 N17 C27	118.50(9)
O28 C18 N19	121.43(10)
O28 C18 N17	121.86(10)
N19 C18 N17	116.71(9)
C18 N19 C20	124.21(9)
C18 N19 C29	117.18(9)
C20 N19 C29	118.59(9)
O30 C20 C15	125.08(9)
O30 C20 N19	118.42(9)
C15 C20 N19	116.50(9)
N32 C31 C36	123.40(10)
N32 C31 C8	116.17(9)
C36 C31 C8	120.43(10)
C31 N32 C33	117.33(10)
N32 C33 C34	123.37(12)
C35 C34 C33	118.62(11)
C34 C35 C36	119.01(11)
C31 C36 C35	118.19(11)
C15 C1 C2 N7	152.38(9)
C9 C1 C2 N7	21.12(10)
C15 C1 C2 C3	-28.54(16)
C9 C1 C2 C3	-159.80(11)
N7 C2 C3 C4	-1.82(16)
C1 C2 C3 C4	179.16(10)
C2 C3 C4 C5	-0.28(17)
C3 C4 C5 C6	1.76(17)
C4 C5 C6 N7	-1.12(16)
C3 C2 N7 C6	2.57(16)
C1 C2 N7 C6	-178.24(9)
C3 C2 N7 C8	-176.54(9)
C1 C2 N7 C8	2.66(12)
C5 C6 N7 C2	-1.06(16)
C5 C6 N7 C8	177.96(10)
C2 N7 C8 C31	97.38(10)
C6 N7 C8 C31	-81.72(12)
C2 N7 C8 C9	-26.14(11)
C6 N7 C8 C9	154.75(9)
N7 C8 C9 C10	154.65(9)
C31 C8 C9 C10	36.94(13)
N7 C8 C9 C14	-78.56(9)

Table 18 (F1) cont.

C31 C8 C9 C14	163.72(9)
N7 C8 C9 C1	36.72(9)
C31 C8 C9 C1	-80.99(10)
C15 C1 C9 C10	71.12(11)
C2 C1 C9 C10	-158.91(8)
C15 C1 C9 C14	-50.81(11)
C2 C1 C9 C14	79.16(9)
C15 C1 C9 C8	-165.67(9)
C2 C1 C9 C8	-35.70(9)
C14 C9 C10 O21	-143.23(10)
C8 C9 C10 O21	-17.94(15)
C1 C9 C10 O21	96.32(12)
C14 C9 C10 N11	40.87(12)
C8 C9 C10 N11	166.16(9)
C1 C9 C10 N11	-79.59(10)
O21 C10 N11 C12	170.06(10)
C9 C10 N11 C12	-13.91(14)
O21 C10 N11 C22	-16.38(15)
C9 C10 N11 C22	159.65(9)
C10 N11 C12 O23	170.68(10)
C22 N11 C12 O23	-2.88(16)
C10 N11 C12 N13	-15.62(15)
C22 N11 C12 N13	170.82(9)
O23 C12 N13 C14	-170.11(10)
N11 C12 N13 C14	16.22(15)
O23 C12 N13 C24	8.85(16)
N11 C12 N13 C24	-164.83(10)
C12 N13 C14 O25	-169.75(10)
C24 N13 C14 O25	11.32(16)
C12 N13 C14 C9	12.61(14)
C24 N13 C14 C9	-166.33(10)
C10 C9 C14 O25	141.71(10)
C8 C9 C14 O25	12.35(13)
C1 C9 C14 O25	-98.19(11)
C10 C9 C14 N13	-40.64(12)
C8 C9 C14 N13	-170.00(8)
C1 C9 C14 N13	79.46(10)
C2 C1 C15 C20	141.54(10)
C9 C1 C15 C20	-97.15(11)
C2 C1 C15 C16	-39.24(14)
C9 C1 C15 C16	82.06(12)
C20 C15 C16 O26	175.71(10)
C1 C15 C16 O26	-3.46(16)

Table 18 (F1) cont.

C20 C15 C16 N17	-3.90(15)
C1 C15 C16 N17	176.92(9)
O26 C16 N17 C18	-177.66(10)
C15 C16 N17 C18	1.98(15)
O26 C16 N17 C27	2.61(15)
C15 C16 N17 C27	-177.75(10)
C16 N17 C18 O28	179.37(10)
C27 N17 C18 O28	-0.89(16)
C16 N17 C18 N19	-0.22(15)
C27 N17 C18 N19	179.52(10)
O28 C18 N19 C20	-179.32(10)
N17 C18 N19 C20	0.27(15)
O28 C18 N19 C29	-0.78(16)
N17 C18 N19 C29	178.81(10)
C16 C15 C20 O30	-175.99(10)
C1 C15 C20 O30	3.22(15)
C16 C15 C20 N19	3.95(15)
C1 C15 C20 N19	-176.84(9)
C18 N19 C20 O30	177.86(10)
C29 N19 C20 O30	-0.66(15)
C18 N19 C20 C15	-2.09(15)
C29 N19 C20 C15	179.39(10)
N7 C8 C31 N32	-48.07(12)
C9 C8 C31 N32	64.24(12)
N7 C8 C31 C36	131.94(10)
C9 C8 C31 C36	-115.76(11)
C36 C31 N32 C33	2.79(16)
C8 C31 N32 C33	-177.21(9)
C31 N32 C33 C34	-0.83(17)
N32 C33 C34 C35	-1.26(19)
C33 C34 C35 C36	1.45(19)
N32 C31 C36 C35	-2.57(17)
C8 C31 C36 C35	177.43(10)
C34 C35 C36 C31	0.33(18)

X-ray crystallographic Data- Compound G37

(1,3-dimethyl-5-[(2,4,6-trioxohexahydropyrimidin-5-yl)(quinolin-4-yl)methyl]pyrimidine-2,4,6(1H,3H,5H)-trione morpholinium salt)

Table 19. Crystal data and structure refinement for compound

Empirical formula	$C_{26}\ H_{34}\ N_6\ O_9\ S_2$
Formula weight	638.71
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system, space group	Monoclinic, P2(1)
Unit cell dimensions	a=8.5679(2) Å, alpha = 90.00 deg. b=15.5485(4) Å, beta = 93.1700(10) deg c=11.1461(3) Å, gamma = 90.00 deg
Volume	1482.59(7) $Å^3$
Z, calculated density	2, 1.431 Mg/m^3
Absorption coefficient	0.242 mm^{-1}
F(000)	672
Crystal size	0.20 x 0.35 x 0.45 mm
Theta range for data collection	2.250 to 29.00 deg.
Limiting indices	-12<=h<=12, -22<=k<=22, -15<=l<=15
Reflections collected / unique	24322 / 7431 [R(int) = 0.0453]
Completeness to theta = 29.00	100.0%
Absorption correction	empirical
Max. and min. transmission	30.55 and 1.83
Refinement method	Full matrix least squares on F^2
Data / restraints/ parameters	7431 / 262 / 465
Goodness of fit on F^2	0.691
Final R indices [I>2sigma(I)]	R1=0.0773, wR2=0.0534
Largest diff. peak and hole	0.408 and -0.437 $e.A^3$

Table 20: Atomic coordinates and equivalent isotropic displacement parameters (A^2) for **G37.** U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)	
C1	0.9958(2)	1.07946(11)	0.80317(15)	0.0160(4)	
C2	0.8605(2)	1.04557(12)	0.84230(18)	0.0231(5)	
C3	0.8608(2)	0.99872(14)	0.94918(19)	0.0295(5)	
N4	0.98553(19)	0.98252(10)	1.01896(14)	0.0266(4)	
C5	1.1243(2)	1.01517(12)	0.98316(17)	0.0220(4)	
C6	1.2597(2)	0.99875(13)	1.05799(18)	0.0275(5)	
C7	1.4027(3)	1.02771(13)	1.02718(19)	0.0286(5)	
C8	1.4157(2)	1.07103(13)	0.91878(18)	0.0258(5)	
C9	1.2872(2)	1.08913(12)	0.84473(17)	0.0189(4)	
C10	1.1361(2)	1.06270(11)	0.87514(15)	0.0169(4)	
C11	1.0012(2)	1.13043(11)	0.68623(16)	0.0144(4)	
C12	1.0658(2)	1.22049(11)	0.70650(15)	0.0150(4)	
C13	.1992(2)	1.24491(11)	0.64306(16)	0.0169(4)	
N14	1.26397(18)	1.32472(10)	0.66855(13)	0.0179(3)	
C15	1.2160(2)	1.38107(12)	0.75321(15)	0.0179(4)	
N16	1.08894(17)	1.35404(10)	.81203(13)	0.0174(4)	
C17	1.0126(2)	1.27742(12)	0.79067(16)	0.0176(4)	
O18	1.26202(13)	1.19902(8)	0.56667(11)	0.0196(3)	
O19	1.28122(14)	1.45014(8)	0.77497(10)	0.0211(3)	
O20	0.89068(14)	1.26498(8)	0.85227(10)	0.0203(3)	
C21	0.85373(19)	1.12358(11)	.60455(15)	0.0144(4)	
C22	0.7153(2)	1.16403(12)	0.62423(16)	0.0185(4)	
N23	0.59001(18)	1.15600(11)	0.54215(14)	0.0190(4)	
C24	0.5919(2)	1.11117(12)	0.43690(16)	0.0182(4)	
N25	0.72723(18)	1.06670(11)	0.42348(15)	0.0197(4)	
C26	0.8576(2)	1.06604(11)	0.50437(16)	0.0185(4)	
O27	0.68251(14)	1.21154(8)	0.71602(12)	0.0228(3)	
O28	0.48105(14)	1.11032(8)	0.36287(11)	0.0261(3)	
O29	0.96645(14)	1.01698(8)	0.48339(11)	0.0271(3)	
N30	0.7226(4)	0.7629(2)	0.6817(4)	0.0251(8)	
N30B	0.7549(11)	0.7482(6)	0.6678(11)	0.023(3)	Uiso 0.266(3)
C31	0.8188(4)	0.8414(2)	0.6758(3)	0.0372(9)	Uani 0.734(3)
C31B	0.8653(11)	0.8194(6)	0.6439(7)	0.025(2)	Uiso 0.266(3)
C32	0.9803(4)	0.8175(3)	0.6437(3)	0.0568(11)	0.734(3)
C32B	0.9564(10)	0.8435(5)	0.7584(7)	0.046(2)	Uiso 0.266(3)
O33	1.0515(2)	0.75667(16)	0.7250(3)	0.0516(7)	Uani 0.734(3)
O33B	1.0363(7)	0.7721(4)	0.8089(7)	0.0484(19)	Uiso 0.266(3)
C34	0.9604(4)	0.6810(2)	0.7239(3)	0.0512(10)	0.734(3)
C34B	0.9244(10)	0.7082(6)	0.8368(8)	0.053(3)	Uiso 0.266(3)
C35	0.7997(3)	0.6977(2)	0.7639(3)	0.0313(8)	0.734(3)

Table 20 (G37) cont.

C35B	0.8398(13)	0.6744(6)	0.7255(8)	0.038(3)	Uiso 0.266(3)
S36	0.34706(6)	0.87188(3)	0.50932(4)	0.02501(12)	
O36	0.51865(14)	0.85421(9)	0.50005(11)	0.0317(4)	
C37	0.2812(2)	0.92138(13)	0.37130(17)	0.0299(5)	
C38	0.3353(2)	0.96397(12)	0.60254(17)	0.0307(5)	
S39	0.39083(7)	0.81411(4)	0.90142(5)	0.04240(16)	
O39	0.5092(2)	0.83465(11)	0.81213(14)	0.0698(6)	
C40	0.3435(3)	0.70381(14)	0.8803(2)	0.0508(7)	
C41	0.4979(2)	0.80405(15)	1.04116(16)	0.0370(5)	

Table 21: Bond lengths [Å] and angles [deg] for **G37**

C1 C2	1.367(2)
C1 C10	1.432(2)
C1 C11	1.528(2)
C2 C3	1.396(3)
C3 N4	1.311(2)
N4 C5	1.372(2)
C5 C6	1.414(3)
C5 C10	1.421(2)
C6 C7	1.367(3)
C7 C8	1.393(3)
C8 C9	1.368(3)
C9 C10	1.417(2)
C11 C12	1.518(2)
C11 C21	1.520(2)
C12 C17	1.385(2)
C12 C13	1.428(2)
C13 O18	1.2548(19)
C13 N14	1.383(2)
N14 C15	1.367(2)
C15 O19	1.229(2)
C15 N16	1.367(2)
N16 C17	1.374(2)
C17 O20	1.296(2)
C21 C22	1.371(2)
C21 C26	1.433(2)
C22 O27	1.305(2)
C22 N23	1.377(2)
N23 C24	1.365(2)
C24 O28	1.223(2)
C24 N25	1.365(2)
N25 C26	1.396(2)
C26 O29	1.237(2)
N30 C31	1.477(3)
N30 C35	1.495(4)
N30B C35B	1.486(7)
N30B C31B	1.491(7)
C31 C32	1.496(4)
C31B C32B	1.506(7)
C32 O33	1.423(3)
C32B O33B	1.405(6)
O33 C34	1.412(4)
O33B C34B	1.427(7)
C34 C35	1.494(4)
C34B C35B	1.497(7)

Table 21 (G37) cont.

S36 O36	1.5048(13)
S36 C38	1.7752(19)
S36 C37	1.7836(18)
S39 O39	1.4940(17)
S39 C41	1.7703(18)
S39 C40	1.775(2)

Symmetry transformations used to generate equivalent atoms: #1 -x+2,-y+1,-z+1

Table 22: Anisotropic displacement parameters (A^2) for **G37.** The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U11 + \ldots + h k a^* b^* U12]$

	U11	U22	U33	U23	U13	U12
C1	0.0180(10)	0.0140(10)	0.0158(9)	-0.0020(8)	0.0007(8)	0.0007(8)
C2	0.0135(10)	0.0273(12)	0.0288(12)	0.0055(9)	0.0024(9)	0.0008(9)
C3	0.0213(12)	0.0315(13)	0.0365(13)	0.0142(10)	0.0089(10)	-0.0018(10)
N4	0.0284(10)	0.0278(10)	0.0242(9)	0.0080(8)	0.0072(8)	0.0027(8)
C5	0.0249(11)	0.0193(10)	0.0218(10)	0.0009(9)	0.0028(9)	0.0035(9)
C6	0.0361(13)	0.0273(12)	0.0187(11)	0.0034(10)	-0.0034(10)	0.0040(1)
C7	0.0277(12)	0.0274(12)	0.0293(12)	0.0007(10)	-0.0118(10)	0.0048(1)
C8	0.0206(11)	0.0260(12)	0.0304(12)	-0.0019(10)	-0.0010(10)	-0.0012(1)
C9	0.0222(11)	0.0163(11)	0.0180(10)	0.0010(9)	0.0007(9)	0.0017(8)
C10	0.0203(10)	0.0143(10)	0.0159(10)	-0.0032(8)	-0.0003(8)	0.0028(8)
C11	0.0126(9)	0.0148(10)	0.0160(9)	0.0002(8)	0.0025(8)	0.0032(8)
C12	0.0144(9)	0.0163(9)	0.0143(9)	0.0012(8)	0.0017(7)	-0.0004(8)
C13	0.0171(10)	0.0184(10)	0.0149(10)	0.0013(8)	-0.0012(8)	0.0011(8)
N14	0.0147(8)	0.0196(9)	0.0197(8)	0.0001(7)	0.0051(7)	-0.0037(7)
C15	0.0179(10)	0.0187(10)	0.0163(9)	0.0014(9)	-0.0064(8)	0.0011(9)
N16	0.0182(9)	0.0174(9)	0.0170(9)	-0.0062(7)	0.0039(7)	-0.0009(7)
C17	0.0160(10)	0.0200(10)	0.0167(10)	0.0018(8)	-0.0002(8)	0.0007(8)
O18	0.0169(7)	0.0192(7)	0.0234(7)	-0.0041(6)	0.0086(6)	-0.0008(6)
O19	0.0236(7)	0.0182(7)	0.0215(7)	-0.0007(6)	-0.0001(6)	-0.0052(6)
O20	0.0178(7)	0.0248(7)	0.0190(7)	-0.0056(6)	0.0065(6)	-0.0051(6)
C21	0.0132(9)	0.0143(9)	0.0158(9)	-0.0002(8)	0.0025(8)	-0.0001(7)
C22	0.0222(11)	0.0152(10)	0.0182(10)	0.0016(8)	0.0021(8)	-0.0010(8)
N23	0.0122(9)	0.0225(9)	0.0223(9)	-0.0034(7)	0.0005(7)	0.0059(7)
C24	0.0195(10)	0.0170(10)	0.0183(10)	0.0010(8)	0.0022(8)	-0.0003(8)
N25	0.0186(9)	0.0232(9)	0.0172(9)	-0.0072(8)	-0.0017(7)	0.0022(7)
C26	0.0180(10)	0.0161(10)	0.0213(10)	0.0028(9)	-0.0009(8)	-0.0004(9)
O27	0.0177(7)	0.0288(8)	0.0219(7)	-0.0105(6)	0.0016(6)	0.0024(6)
O28	0.0201(7)	0.0321(8)	0.0254(7)	-0.0039(7)	-0.0060(6)	0.0044(6)
O29	0.0193(7)	0.0299(8)	0.0319(8)	-0.0125(7)	-0.0015(6)	0.0094(6)
N30	0.0181(16)	0.0282(16)	0.0291(16)	-0.0044(14)	0.0013(14)	0.0003(1)
C31	0.038(2)	0.032(2)	0.040(2)	0.0045(16)	-0.0071(17)	-0.0094(15)
C32	0.0345(19)	0.082(3)	0.053(2)	0.025(2)	-0.0050(16)	-0.0193(19)
O33	0.0170(12)	0.0768(17)	0.0601(19)	0.0120(15)	-0.0049(11)	-0.0056(11)
C34	0.0343(19)	0.053(2)	0.065(3)	-0.0040(19)	-0.0082(17)	0.0174(17)
C35	0.0285(17)	0.0326(19)	0.0318(19)	0.0059(16)	-0.0071(15)	-0.0084(15)
S36	0.0245(3)	0.0231(3)	0.0284(3)	-0.0006(3)	0.0094(2)	0.0043(2)
O36	0.0244(8)	0.0459(10)	0.0253(7)	0.0005(7)	0.0076(6)	0.0157(7)
C37	0.0295(12)	0.0318(13)	0.0277(12)	-0.0024(10)	-0.0060(10)	0.0045(10)
C38	0.0349(12)	0.0262(12)	0.0317(12)	-0.0004(10)	0.0087(10)	0.0052(10)
S39	0.0516(4)	0.0426(4)	0.0322(3)	-0.0017(3)	-0.0043(3)	0.0172(3)
O39	0.1248(17)	0.0484(12)	0.0395(10)	0.0117(9)	0.0343(10)	0.0157(11)

Table 22 (G37) cont.

C40	0.0461(15)	0.0528(16)	.0516(16)	-0.0150(13)	-0.0134(12)	0.0081(13)
C41	0.0357(13)	0.0437(14)	0.0315(12)	0.0070(11)	0.0006(10)	-0.0069(11)

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Table 23: Hydrogen coordinates and isotropic displacement parameters (A^2) for **G37**

	x	y	z	U(eq)
H2 H	0.765(2)	1.0508(10)	0.7986(14)	0.016(5) Uiso 1 1 d
H3 H	0.769(2)	0.9769(13)	0.9725(17)	0.037(6) Uiso 1 1 d
H6 H	1.2483(19)	0.9680(11)	1.1337(16)	0.022(5) Uiso 1 1 d
H7 H	1.4889(19)	1.0197(10)	1.0785(15)	0.012(5) Uiso 1 1 d
H8 H	1.509(2)	1.0946(12)	0.8922(15)	0.023(5) Uiso 1 1 d
H9 H	1.2946(17)	1.1154(10)	0.7728(13)	0.002(4) Uiso 1 1 d
H11 H	1.0720(17)	.0997(10)	0.6462(13)	0.004(4) Uiso 1 1 d .
H14 H	1.346(2)	1.3429(13)	0.6242(18)	0.053(7) Uiso 1 1 d
H16 H	1.048(2)	1.3894(13)	0.8624(17)	0.034(6) Uiso 1 1 d
H23 H	0.509(2)	1.1866(14)	0.5502(18)	0.047(7) Uiso 1 1 d
H25 H	0.724(2)	1.0347(12)	0.3643(17)	0.028(6) Uiso 1 1 d .
H27 H	0.772(3)	1.2330(16)	0.782(2)	0.083(9) Uiso 1 1 d
H30A H	0.7076	0.7397	0.6060	0.030 Uiso 0.734(3)
H30B H	0.6263	0.7768	0.7087	0.030 Uiso 0.734(3)
H30C H	0.6800	0.7675	0.7173	0.027 Uiso 0.266(3)
H30D H	0.7053	0.7305	0.5967	0.027 Uiso 0.266(3)
H31A H	0.8230	0.8711	0.7545	0.045 Uiso 0.734(3)
H31B H	0.7716	0.8812	0.6146	0.045 Uiso 0.734(3)
H31C H	0.8063	0.8700	0.6120	0.030 Uiso 0.266(3)
H31D H	0.9381	0.8009	0.5829	0.030 Uiso 0.266(3)
H32A H	0.9758	0.7930	0.5616	0.068 Uiso 0.734(3)
H32B H	1.0457	0.8699	0.6434	0.068 Uiso 0.734(3)
H32C H	1.0325	0.8892	0.7415	0.055 Uiso 0.266(3)
H32D H	0.8839	0.8665	0.8167	0.055 Uiso 0.266(3)
H34A H	1.0125	0.6378	0.7777	0.061 Uiso 0.734(3)
H34B H	0.9530	0.6569	0.6416	0.061 Uiso 0.734(3)
H34C H	0.8479	0.7333	0.8903	0.064 Uiso 0.266(3)
H34D H	0.9782	0.6602	0.8802	0.064 Uiso 0.266(3)
H35A H	0.8054	0.7196	0.8475	0.038 Uiso 0.734(3)
H35B H	0.7382	0.6437	0.7615	0.038 Uiso 0.734(3)
H35C H	0.9149	0.6499	0.6704	0.045 Uiso 0.266(3)
H35D H	0.7653	0.6287	0.7461	0.045 Uiso 0.266(3)
H37A H	0.3500	0.9697	0.3543	0.045 Uiso
H37B H	0.1742	0.9424	0.3777	0.045 Uiso 1 1 calc R . .
H37C H	0.2834	0.8792	0.3061	0.045 Uiso 1 1 calc R
H38A H	0.3726	0.9493	0.6847	0.046 Uiso 1 1 calc R . .
H38B H	0.2265	0.9834	0.6025	0.046 Uiso 1 1 calc R . .
H38C H	0.4003	1.0100	0.5719	0.046 Uiso 1 1 calc R
H40A H	0.2901	0.6959	0.8010	0.076 Uiso 1 1 calc R . .
H40B H	0.2747	0.6852	0.9427	0.076 Uiso 1 1 calc R . .
H40C H	.4396	0.6695	0.8855	0.076 Uiso 1 1 calc R . .
H41A H	0.5816	0.7617	1.0340	0.056 Uiso 1 1 calc R . .

Table 23 (G37) cont.

H41B H	0.4279	0.7850	1.1025	0.056 Uiso 1 1 calc R . .
H41C H	0.5435	0.8598	1.0643	0.056 Uiso 1 1 calc R .

Table 24: Torsion angles [deg] for **G37**

C2 C1 C10	116.85(17)
C2 C1 C11	122.58(16)
C10 C1 C11	120.54(15)
C1 C2 C3	120.79(19)
N4 C3 C2	124.7(2)
C3 N4 C5	116.57(17)
N4 C5 C6	117.22(18)
N4 C5 C10	122.85(16)
C6 C5 C10	119.92(18)
C7 C6 C5	120.7(2)
C6 C7 C8	119.5(2)
C9 C8 C7	121.5(2)
C8 C9 C10	120.75(18)
C9 C10 C5	117.56(16)
C9 C10 C1	124.25(16)
C5 C10 C1	118.18(17)
C12 C11 C21	115.98(15)
C12 C11 C1	112.30(15)
C21 C11 C1	114.27(14)
C17 C12 C13	117.90(16)
C17 C12 C11	124.00(16)
C13 C12 C11	117.82(16)
O18 C13 N14	117.87(16)
O18 C13 C12	124.74(16)
N14 C13 C12	117.39(16)
C15 N14 C13	125.75(16)
O19 C15 N14	123.05(17)
O19 C15 N16	122.64(17)
N14 C15 N16	114.31(17)
C15 N16 C17	124.58(17)
O20 C17 N16	115.33(16)
O20 C17 C12	124.66(16)
N16 C17 C12	119.99(17)
C22 C21 C26	117.93(16)
C22 C21 C11	124.76(16)
C26 C21 C11	117.17(15)
O27 C22 C21	127.64(17)
O27 C22 N23	112.25(16)
C21 C22 N23	120.11(17)
C24 N23 C22	124.84(16)
O28 C24 N25	123.58(17)
O28 C24 N23	122.63(17)
N25 C24 N23	113.78(16)
C24 N25 C26	125.94(17)

Table 24 (G37) cont.

O29 C26 N25	117.84(17)
O29 C26 C21	125.61(16)
N25 C26 C21	116.54(16)
C31 N30 C35	111.1(3)
C35B N30B C31B	110.5(9)
N30 C31 C32	109.3(3)
N30B C31B C32B	109.7(8)
O33 C32 C31	112.5(2)
O33B C32B C31B	111.2(7)
C34 O33 C32	109.3(3)
C32B O33B C34B	108.6(7)
O33 C34 C35	111.8(3)
O33B C34B C35B	111.4(8)
C34 C35 N30	108.5(3)
N30B C35B C34B	106.9(9)
O36 S36 C38	105.94(9)
O36 S36 C37	106.45(9)
C38 S36 C37	97.55(9)
O39 S39 C41	105.50(10)
O39 S39 C40	106.05(11)
C41 S39 C40	97.76(11)
C10 C1 C2 C3	1.5(3)
C11 C1 C2 C3	179.42(18)
C1 C2 C3 N4	-0.7(3)
C2 C3 N4 C5	0.6(3)
C3 N4 C5 C6	179.56(19)
C3 N4 C5 C10	-1.3(3)
N4 C5 C6 C7	178.72(19)
C10 C5 C6 C7	-0.4(3)
C5 C6 C7 C8	-2.4(3)
C6 C7 C8 C9	3.3(3)
C7 C8 C9 C10	-1.2(3)
C8 C9 C10 C5	-1.6(3)
C8 C9 C10 C1	179.61(18)
N4 C5 C10 C9	-176.72(17)
C6 C5 C10 C9	2.4(3)
N4 C5 C10 C1	2.2(3)
C6 C5 C10 C1	-178.73(17)
C2 C1 C10 C9	176.66(17)
C11 C1 C10 C9	-1.3(3)
C2 C1 C10 C5	-2.2(2)
C11 C1 C10 C5	179.84(16)
C2 C1 C11 C12	121.94(19)

Table 24 (G37) cont.

C10 C1 C11 C12	-60.2(2)
C2 C1 C11 C21	-12.8(2)
C10 C1 C11 C21	165.04(15)
C21 C11 C12 C17	83.2(2)
C1 C11 C12 C17	-50.8(2)
C21 C11 C12 C13	-103.03(19)
C1 C11 C12 C13	123.02(17)
C17 C12 C13 O18	178.26(17)
C11 C12 C13 O18	4.1(3)
C17 C12 C13 N14	-1.3(2)
C11 C12 C13 N14	-175.46(15)
O18 C13 N14 C15	-176.46(16)
C12 C13 N14 C15	3.1(3)
C13 N14 C15 O19	177.50(16)
C13 N14 C15 N16	-2.4(2)
O19 C15 N16 C17	-179.96(16)
N14 C15 N16 C17	0.0(2)
C15 N16 C17 O20	-177.30(15)
C15 N16 C17 C12	1.6(3)
C13 C12 C17 O20	177.93(16)
C11 C12 C17 O20	-8.3(3)
C13 C12 C17 N16	-0.9(2)
C11 C12 C17 N16	172.91(16)
C12 C11 C21 C22	-58.6(2)
C1 C11 C21 C22	74.5(2)
C12 C11 C21 C26	125.83(18)
C1 C11 C21 C26	-101.11(18)
C26 C21 C22 O27	172.53(17)
C11 C21 C22 O27	-3.0(3)
C26 C21 C22 N23	-6.8(3)
C11 C21 C22 N23	177.64(16)
O27 C22 N23 C24	178.90(16)
C21 C22 N23 C24	-1.7(3)
C22 N23 C24 O28	-175.12(18)
C22 N23 C24 N25	5.9(3)
O28 C24 N25 C26	179.36(17)
N23 C24 N25 C26	-1.7(3)
C24 N25 C26 O29	174.43(17)
C24 N25 C26 C21	-6.2(3)
C22 C21 C26 O29	-170.47(18)
C11 C21 C26 O29	5.4(3)
C22 C21 C26 N25	10.3(2)
C11 C21 C26 N25	-173.82(15)

Table 24 (G37) cont.

C35 N30 C31 C32	53.5(4)
C35B N30B C31B C32B	-54.5(11)
N30 C31 C32 O33	56.3(4) .
N30B C31B C32B O33B	56.8(11)
C31 C32 O33 C34	60.0(4)
C31B C32B O33B C34B	-61.2(10)
C32 O33 C34 C35	-61.5(4)
C32B O33B C34B C35B	65.0(10)
O33 C34 C35 N30	59.1(4)
C31 N30 C35 C34	-54.9(4)
C31B N30B C35B C34B	56.3(11)
O33B C34B C35B N30B	-62.0(11)

X-ray crystallographic Data- Compound I-1
(5,5'-(2-pyrilidene)bis(1,3-dimethylbarbituric acid))

Table 25. Crystal data and structure refinement for compound **I-1**

Empirical formula	$C_{18}\ H_{21}\ N_5\ O_7$
Formula weight	419.40
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system, space group	Monoclinic, P2(1)/n
Unit cell dimensions	a=8.9107(19) Å, alpha = 90.00 deg. b=10.457(2) Å, beta = 93.098(5) deg c=20.387(4) Å, gamma = 90.00 deg
Volume	1896.9(7) $Å^3$
Z, calculated density	4, 1.469 Mg/m^3
Absorption coefficient	0.115 mm^{-1}
F(000)	880
Crystal size	0.50 x 0.50 x 0.30 mm
Theta range for data collection	2.1895 to 30.498 deg.
Limiting indices	-12<=h<=12, -14<=k<=14, -29<=l<=29
Reflections collected / unique	34737 / 5827 [R(int) = 0.0384]
Completeness to theta =30.498	100.0%
Absorption correction	empirical
Max. and min. transmission	1.000000 and 0.761887
Refinement method	Full matrix least squares on F^2
Data / restraints/ parameters	5827 / 89 / 310
Goodness of fit on F^2	0.699
Final R indices [I>2sigma(I)]	R1=0.0383, wR2=0.0987
R indices (all data)	R1=0.0763, wR2=0.1032
Largest diff. peak and hole	0.209 to -0.211 $e.A^3$

Table 26: Atomic coordinates and equivalent isotropic displacement parameters (A^2) for **I-1.** U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
C1 C	0.00074(13)	0.35018(11)	0.10837(6)	0.0301(3)
N1 N	-0.00765(12)	0.12161(10)	0.10799(5)	0.0405(3)
O1 O	-0.16289(12)	0.01743(9)	0.03357(6)	0.0656(3)
N2 N	-0.15615(12)	0.23353(10)	0.03006(5)	0.0405(3)
C2 C	-0.10899(14)	0.35304(12)	0.05472(6)	0.0339(3)
O2 O	-0.16226(11)	0.45059(9)	0.02920(5)	0.0470(2)
O3 O	0.14573(11)	0.22187(9)	0.18332(5)	0.0478(3)
N3 N	-0.13634(12)	0.69623(10)	0.24788(5)	0.0400(3)
C3 C	-0.11202(16)	0.11818(13)	0.05580(7)	0.0437(3)
C4 C	0.04728(14)	0.23553(11)	0.13428(6)	0.0345(3)
O4 O	-0.12521(13)	0.69851(9)	0.13728(5)	0.0578(3)
N4 N	-0.01165(12)	0.54020(10)	0.31164(5)	0.0415(3)
N5 N	0.30302(13)	0.41658(10)	0.08727(5)	0.0364(3)
O5 O	-0.14185(13)	0.69880(10)	0.35886(5)	0.0636(3)
C5 C	0.0376(2)	-0.00107(13)	0.13818(9)	0.0655(5)
O6 O	0.12712(11)	0.38474(9)	0.26720(4)	0.0475(3)
C6 C	-0.27107(19)	0.23070(15)	-0.02365(8)	0.0616(4)
O7 O	0.23413(16)	0.24469(11)	-0.01023(6)	0.0660(4)
C7 C	0.06328(13)	0.47835(11)	0.13205(6)	0.0300(3)
C8 C	0.00400(13)	0.53311(11)	0.19488(6)	0.0305(3)
C9 C	-0.08711(14)	0.64418(12)	0.18923(6)	0.0364(3)
C10 C	-0.09947(15)	0.64812(13)	0.30917(7)	0.0419(3)
C11 C	0.04209(14)	0.48342(12)	0.25590(6)	0.0349(3)
C12 C	-0.23013(18)	0.81121(14)	0.24477(8)	0.0559(4)
C13 C	0.0225(2)	0.48613(16)	0.37711(7)	0.0682(5)
C14 C	0.23319(14)	0.48678(11)	0.13125(6)	0.0322(3)
C15 C	0.32013(16)	0.57057(14)	0.16933(7)	0.0452(3)
C16 C	0.47168(17)	0.58118(16)	0.16045(8)	0.0560(4)
C17 C	0.53801(17)	0.50885(15)	0.11395(8)	0.0538(4)
C18 C	0.45060(16)	0.42533(14)	0.07768(8)	0.0457(3)

Table 27: Bond lengths [Å] and angles [deg] for **I-1.**

C1 C4	1.3656(17)
C1 C2	1.4275(17)
C1 C7	1.5201(16)
N1 C3	1.3752(17)
N1 C4	1.3848(16)
N1 C5	1.4698(18)
O1 C3	1.2242(15)
N2 C3	1.3648(17)
N2 C2	1.4030(16)
N2 C6	1.4585(18)
C2 O2	1.2288(15)
O3 C4	1.3018(15)
N3 C10	1.3704(17)
N3 C9	1.4055(16)
N3 C12	1.4637(17)
O4 C9	1.2332(15)
N4 C10	1.3727(17)
N4 C11	1.3900(16)
N4 C13	1.4662(18)
N5 C14	1.3381(15)
N5 C18	1.3431(17)
O5 C10	1.2211(16)
O6 C11	1.2935(15)
C7 C14	1.5175(17)
C7 C8	1.5236(17)
C8 C11	1.3736(17)
C8 C9	1.4182(17)
C14 C15	1.3804(18)
C15 C16	1.377(2)
C16 C17	1.372(2)
C17 C18	1.362(2)

Table 28: Anisotropic displacement parameters (A^2) for **G37.** The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U11 + \ldots + h k a^* b^* U12]$

	U11	U22	U33	U23	U13	U12
C1	0.0324(7)	0.0285(6)	0.0294(6)	-0.0034(5)	0.0027(5)	-0.0020(5)
N1	0.0479(7)	0.0271(5)	0.0470(7)	-0.0024(5)	0.0075(6)	-0.0029(5)
O1	0.0743(8)	0.0415(6)	0.0809(8)	-0.0224(6)	0.0031(6)	-0.0161(5)
N2	0.0414(6)	0.0416(6)	0.0382(6)	-0.0104(5)	-0.0010(5)	-0.0082(5)
C2	0.0328(7)	0.0358(7)	0.0335(7)	-0.0055(6)	0.0060(6)	-0.0042(6)
O2	0.0498(6)	0.0435(5)	0.0460(6)	0.0008(4)	-0.0129(5)	0.0028(4)
O3	0.0596(6)	0.0364(5)	0.0459(6)	0.0014(4)	-0.0096(5)	0.0071(5)
N3	0.0402(6)	0.0358(6)	0.0441(7)	-0.0061(5)	0.0042(5)	0.0061(5)
C3	0.0454(8)	0.0386(8)	0.0483(8)	-0.0128(6)	0.0122(7)	-0.0084(6)
C4	0.0374(7)	0.0312(6)	0.0352(7)	-0.0029(5)	0.0044(6)	-0.0019(6)
O4	0.0889(8)	0.0414(5)	0.0417(6)	0.0003(5)	-0.0102(5)	0.0212(5)
N4	0.0467(7)	0.0462(7)	0.0317(6)	-0.0005(5)	0.0030(5)	0.0059(5)
N5	0.0401(7)	0.0342(6)	0.0352(6)	-0.0020(5)	0.0043(5)	-0.0001(5)
O5	0.0771(8)	0.0674(7)	0.0483(7)	-0.0127(5)	0.0208(6)	0.0127(6)
C5	0.0878(13)	0.0295(8)	0.0795(12)	0.0036(7)	0.0087(10)	0.0040(8)
O6	0.0576(6)	0.0460(6)	0.0380(5)	0.0006(4)	-0.0053(5)	0.0181(5)
C6	0.0632(11)	0.0663(10)	0.0533(10)	-0.0195(8)	-0.0150(8)	-0.0098(8)
O7	0.1120(11)	0.0432(7)	0.0415(7)	-0.0061(5)	-0.0079(7)	-0.0067(7)
C7	0.0332(7)	0.0278(6)	0.0286(7)	0.0005(5)	-0.0012(5)	-0.0005(5)
C8	0.0327(7)	0.0275(6)	0.0312(7)	-0.0016(5)	0.0001(5)	-0.0003(5)
C9	0.0395(7)	0.0302(6)	0.0391(7)	-0.0028(6)	-0.0015(6)	-0.0006(6)
C10	0.0409(8)	0.0456(8)	0.0399(8)	-0.0058(6)	0.0089(6)	-0.0012(6)
C11	0.0336(7)	0.0366(7)	0.0343(7)	-0.0029(6)	0.0009(6)	-0.0011(6)
C12	0.0554(10)	0.0446(8)	0.0682(11)	-0.0092(8)	0.0066(8)	0.0157(7)
C13	0.0896(13)	0.0839(12)	0.0310(8)	0.0046(8)	0.0030(8)	0.0233(10)
C14	0.0392(7)	0.0290(6)	0.0286(7)	0.0016(5)	0.0030(5)	-0.0023(5)
C15	0.0412(8)	0.0481(8)	0.0465(9)	-0.0138(7)	0.0032(7)	-0.0093(7)
C16	0.0436(9)	0.0623(10)	0.0613(10)	-0.0099(8)	-0.0031(8)	-0.0146(8)
C17	0.0334(8)	0.0639(10)	0.0645(11)	0.0038(8)	0.0074(7)	-0.0031(8)
C18	0.0391(8)	0.0485(8)	0.0503(9)	0.0002(7)	0.0101(7)	0.0046(7)

Table 29: Hydrogen coordinates and isotropic displacement parameters (A^2) for **I-1**

	x	y	z	U(eq)
H3 H	0.143(2)	0.3011(19)	0.2212(11)	0.104(6)
H5 H	0.2501(17)	0.3583(15)	0.0624(7)	0.060(5)
H5A H	0.0428	0.0077	0.1861	0.098
H5B H	0.1364	-0.0258	0.1235	0.098
H5C H	-0.0363	-0.0669	0.1250	0.098
H6A H	-0.3107	0.3172	-0.0313	0.092
H6B H	-0.3529	0.1737	-0.0121	0.092
H6C H	-0.2269	0.1994	-0.0636	0.092
H7B H	0.204(2)	0.2770(16)	-0.0469(7)	0.082(6)
H7C H	0.213(2)	0.1657(12)	-0.0135(10)	0.100(7)
H7 H	0.0276(12)	0.5374(9)	0.0994(4)	0.024(3)
H12B H	-0.3183	0.7980	0.2707	0.084
H12A H	-0.2629	0.8286	0.1990	0.084
H12C H	-0.1720	0.8841	0.2626	0.084
H13B H	-0.0691	0.4844	0.4016	0.102
H13C H	0.0986	0.5390	0.4007	0.102
H13A H	0.0609	0.3989	0.3728	0.102
H15 H	0.2695(13)	0.6202(11)	0.2003(5)	0.046(4)
H16 H	0.5255(16)	0.6421(12)	0.1871(6)	0.069(5)
H17 H	0.6415(8)	0.5216(14)	0.1071(8)	0.070(5)
H18 H	0.4831(14)	0.3706(11)	0.0441(5)	0.040(4)

Table 30. Torsion angles [deg] for **I-1**.

C4 C1 C2	119.73(11)
C4 C1 C7	123.56(11)
C2 C1 C7	116.68(10)
C3 N1 C4	122.14(11)
C3 N1 C5	117.38(12)
C4 N1 C5	120.36(12)
C3 N2 C2	125.10(11)
C3 N2 C6	116.54(11)
C2 N2 C6	118.14(12)
O2 C2 N2	119.10(11)
O2 C2 C1	125.08(11)
N2 C2 C1	115.81(11)
C10 N3 C9	124.27(11)
C10 N3 C12	116.70(11)
C9 N3 C12	119.01(11)
O1 C3 N2	121.67(14)
O1 C3 N1	122.02(13)
N2 C3 N1	116.31(11)
O3 C4 C1	124.84(11)
O3 C4 N1	114.35(11)
C1 C4 N1	120.79(11)
C10 N4 C11	122.83(11)
C10 N4 C13	116.12(11)
C11 N4 C13	121.05(12)
C14 N5 C18	123.68(12)
C14 C7 C1	113.37(10)
C14 C7 C8	112.25(10)
C1 C7 C8	117.42(10)
C11 C8 C9	119.73(11)
C11 C8 C7	122.64(11)
C9 C8 C7	117.54(11)
O4 C9 N3	117.91(11)
O4 C9 C8	125.24(12)
N3 C9 C8	116.84(11)
O5 C10 N3	121.84(13)
O5 C10 N4	121.85(13)
N3 C10 N4	116.32(11)
O6 C11 C8	125.22(11)
O6 C11 N4	114.80(11)
C8 C11 N4	119.97(12)
N5 C14 C15	117.26(12)
N5 C14 C7	118.40(11)
C15 C14 C7	124.11(11)
C16 C15 C14	120.13(13)

Table 30 **(I-1)** cont.

C17 C16 C15	120.59(14)
C18 C17 C16	118.29(14)
N5 C18 C17	120.04(14)

VITA

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