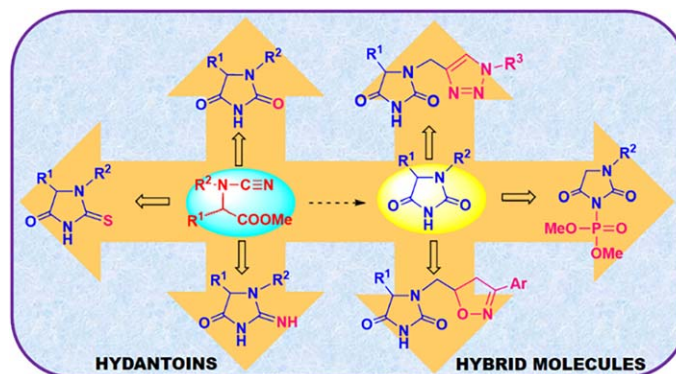


Designed Synthesis of Diversely Substituted Hydantoins and Hydantoin-Based Hybrid Molecules: A Personal Account

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Abstract Hydantoin and its analogues such as thiohydantoin and iminohydantoin have received substantial attention from both a chemical and a biological point of view. Several compounds of this class have shown useful pharmacological activities such as anticonvulsant, antitumor, antiarrhythmic, and herbicidal properties that have led, in some cases, to clinical applications. Because of these broad-spectrum activities, intensive research efforts have been dedicated in industry and academia to the synthesis and structural modifications of hydantoin and its derivatives. Realizing the importance of hydantoin in organic and medicinal chemistry, we also initiated a research program that successfully designed and developed new routes and methods for the formation of hydantoin, thiohydantoin, and iminohydantoin substituted at various positions, particularly at the N-1 position without following a protection-deprotection strategy. Because combinations of two or more pharmacophoric groups can lead to hybrid molecules that display a mixed mechanism of action on biological targets, we extended our developed strategy to the syntheses of new types of hydantoin-based hybrid molecules by combining hydantoin with a triazole, isoxazoline, or phosphate scaffold as a second pharmacophore to exploit their diverse biological functions.

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Key words hydantoins, thiohydantoins, iminohydantoins, hybrid molecules, pharmaceutical chemistry

1 Introduction

The chemistry and properties of hydantoin and its derivatives have been investigated for more than 150 years.¹ This scaffold is of considerable interest because of its diverse chemical and biological activities.² The basic ring is rarely found in nature, although hydantoin substructures are known to occur in some natural products such as allantoin (a component of urine). Allantoin (**1**) was first isolated in 1861 during a metabolic study of uric acid by Adolf von Baeyer; the product of hydrogenation of allantoin was named hydantoin (Figure 1A).³ Later, von Baeyer prepared it by the reduction of alloxanic acid with hydrogen iodide.⁴ Closely allied to hydantoin (**2**) are thiohydantoin (**3**), selenohydantoin (**4**), and iminohydantoin (**5**) which are considered to be the sulfur, selenium, and nitrogen analogues, respectively, of hydantoin (Figure 1B). These analogues show some similar and some dissimilar physical, chemical, and biological properties. The development of hydantoin chemistry was exhaustively reviewed by Ware⁵ in 1950 and, more recently, by Konnert⁶ (2017) and Shin² (2019). Therefore, in this account, I will briefly introduce the chemistry and applications of hydantoin and its analogues and I will comprehensively summarize the research conducted in our laboratory in this field.

Interestingly, all the substituent positions in the core unit are interactive sites, as the molecule contains two hydrogen-bond acceptors and two hydrogen-bond donors that can interact physically as well as chemically with various substrates. Because of these features, many hydantoin derivatives with different substituents have been designed and synthesized to exhibit a broad spectrum of biological and pharmaceutical activities, such as anticonvulsant, antitumor, antiarrhythmic, and herbicidal activities, that have led, in some cases, to clinical applications.^{2,6} There are also various natural products that possess a hydantoin moiety

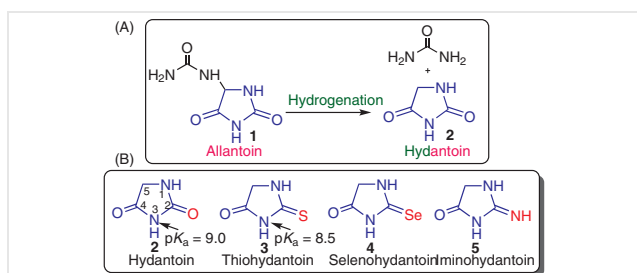


Figure 1 (A) Scheme for the hydrogenation of allantoin to hydantoin, (B) Chemical structures of hydantoin, thiohydantoin, selenohydantoin, and iminohydantoin.

and exhibit a broad range of biological activities. Hydantoin derivatives have also been used as synthons for supramolecular chemistry,⁷ in agrochemicals,⁸ and for β -strand mimetics.⁹ In recent decades, intensive research efforts in industry and academia have been dedicated to the structural modification of hydantoin and its derivatives. Various groups have focused their research interests on developing simple, rapid, convenient, and ecofriendly methods for producing diversely substituted hydantoins and thiohydantoins. Hydantoins can be viewed as cyclic ureides of α -amino acids and, due to this close relationship, they are primarily prepared from the corresponding α -amino acids.¹⁰

Along with hydantoin, comprehensive studies on the chemistry and biology of thiohydantoins have also been conducted.¹¹ Thiohydantoins are more reactive than their oxygen analogues and are, therefore, easily converted into hydantoins. Apart from 2-thiohydantoin, 4-thiohydantoin and 2,4-thiohydantoin also exist. In contrast, there are generally fewer reports in the literature on selenohydantoins, although some reports have recently appeared.^{12,13}

2 Chemistry and Properties

2.1 Physical Properties

Unsubstituted hydantoin is a crystalline solid with a high melting point; substitution reduces hydrogen-bonding interactions with the N–H group, thereby lowering the melting point. Owing to the presence of two carbonyl groups, the NH at the N-3 position is more acidic ($pK_a = 9.0$) than that at N-1.¹⁴ This results in base-promoted alkylation occurring initially at the N-3 position and secondly at the N-1 position. Functionalization at N-1 and C-5 with alkyl groups does not affect the pK_a value, whereas arylation enhances the acidity of the N-3 position. For instance, the pK_a values of 5,5-diphenylhydantoin and 1-methylhydantoin are 8.1 and 9.1, respectively.¹⁵ Studies have also shown that hydantoin is more acidic in water than in any other solvent. For example, in the case of DMSO, hydantoin has a high pK_a of 15,¹⁶ because water provides better stabilization of the hydantoin anion, and hence increases its acidity when compared with that in DMSO. 2-Thiohydantoin with a pK_a of 8.5 is slightly more acidic than hydantoin (Figure 1).¹⁷

Hydantoins substituted at the C-5 position are known to possess stereogenic centers and to show optical activity when prepared from optically active α -amino acids. Furthermore, the existence of geometrical isomerism has also been demonstrated in many alkylidene hydantoins **7** (Figure 2).

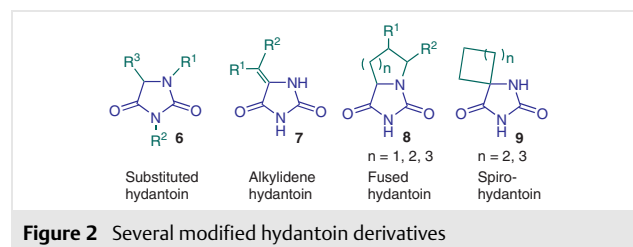


Figure 2 Several modified hydantoin derivatives

Biographical Sketch



Vinod Kumar completed his bachelor's and master's degrees from Chaudhary Charan Singh University, Meerut, India. He joined DRDE, Gwalior as a scientist in 2002. In 2007, he completed his doctoral studies with

his parent organization under the guidance of Professor M. P. Kaushik. In 2011, he moved to the University of Texas at Austin, USA, and worked with Professor Eric V. Anslyn in the field of chromofluorogenic detection

of sulfur mustard and explosives. Currently, he is working on the synthesis of bioactive molecules and on the development of a chemical sensor/detection system for toxicants.

2.2 Chemical Properties

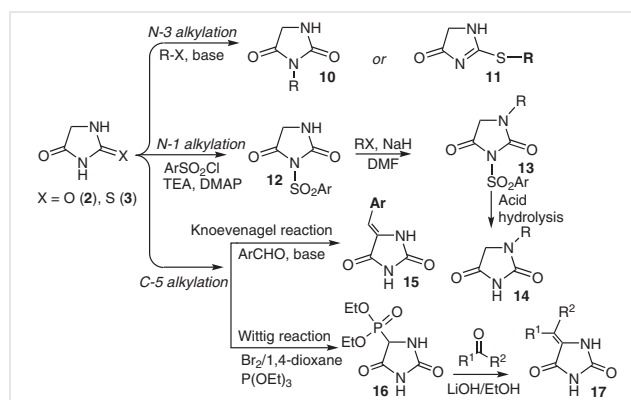
Amazingly, all the positions in the hydantoin ring system are chemically reactive and can therefore react with or be functionalized by various nucleophiles or electrophiles. These chemical reactions can produce substituted hydantoin **6**, alkylidene hydantoin **7**, fused hydantoin **8**, or spiro hydantoin **9** (Figure 2). The carbonyl groups can be also attacked by nucleophiles, leading to hydrolysis of the ring or to partial or total reduction of the carbonyl system. In the case of hydantoin, photochemical cleavage of the ring has also been observed.¹⁸

2.2.1 Substitution of Hydantoin at the N-1 and N-3 Positions

Due to the presence of the two carbonyl groups, the imidic NH at the N-3 position of hydantoin is more acidic than that at N-1 (pK_a 9). Hence, the first alkylation with an alkyl halide in the presence of a mild base (usually potassium carbonate) generally takes place at the N-3 position (Scheme 1).¹⁹ Alkylation at the N-1 position requires harsher conditions involving the use of sodium hydride in *N,N*-dimethylformamide to give N-1 and N-3 disubstituted products.¹⁹ The exclusive formation of N-1 alkylated hydantoin necessitates a laborious, time-consuming, and lengthy process that normally involves a protection–deprotection strategy.²⁰ The first step involves protection of the N-3 position by treatment with an arylsulfonyl chloride in the presence of triethylamine and DMAP (Scheme 1). The next step leads to alkylation at N-1 position by the above method; this is followed by deprotection of arylsulfonylhydantoin **12** under acidic conditions. Other methods for the alkylation of the hydantoin ring include the Mannich reaction,²¹ the Mitsunobu reaction,²² or the use of dimethyl sulfate,²³ diazomethane,²⁴ or *p*-tolyllead triacetate in the presence of sodium hydride and a catalytic amount of copper(II) acetate.²⁵ In contrast, the alkylation in thiohydantoin is kinetically controlled and produces less-stable S-alkylated thiohydantoin.²⁶

2.2.2 Substitution of Hydantoin at the C-5 Position

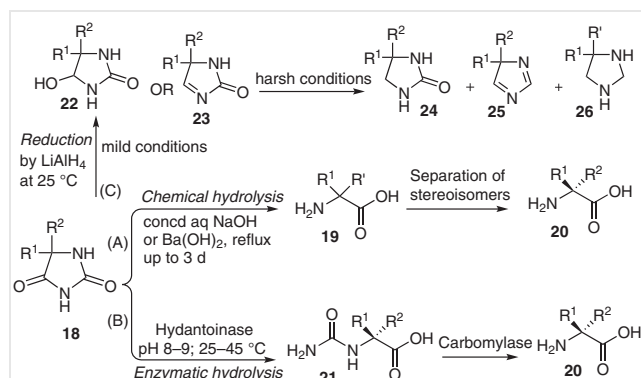
The C-5 position in hydantoin behaves like a reactive methylene group. Therefore, it is considered to be a suitable position for base-catalyzed Knoevenagel condensation reactions with aldehydes to form 5-alkylidenehydantoin **15** (Scheme 1).²⁷ These products can also be prepared by Wittig-type reactions via 5-phosphorylated hydantoin **16** (Scheme 1). The introduction of an arylmethylene group at C-5 enhances the acidity of the N-1 hydrogen, making it quantifiable.²⁸ This is due to the delocalization of the negative charge at N-1 into the C-5 substituent. 2-Thiohydantoin undergoes this reaction more readily than their oxygen counterparts.²⁹



Scheme 1 Various types of substitution of the hydantoin ring

2.2.3 Hydrolysis

The final product of hydrolysis of hydantoin and thiohydantoin are α -amino acids, which are formed via ureido or thioureido acid intermediates, respectively. Hydrolysis is normally achieved by chemical or enzymatic methods. The chemical hydrolysis of hydantoin is generally accomplished under strongly basic conditions (Scheme 2; Pathway A) or, sometimes, under acidic conditions. Concentrated aqueous sodium hydroxide or aqueous barium hydroxide is used to hydrolyze hydantoin and thiohydantoin at high temperatures over a few days.³⁰ Acidic hydrolyses are generally carried out by using halo acids.³¹ To make the hydrolysis easier, the use of microwave radiation was initially suggested by Pham et al., who used 10% aqueous HCl at 100 °C for 30 minutes to perform the reaction,³² and later by Chen et al., who employed aqueous NaOH in 1,2-dimethoxyethane for ten minutes at 150 °C.³³



Scheme 2 Hydrolysis and reduction reactions of hydantoin

Considerable efforts have been directed toward the development of enzymatic methods for the stereoselective hydrolysis of hydantoin to yield optically pure α -amino acids. Enzymatic hydrolysis of hydantoin is usually per-

formed by using D-hydantoinase and D-N-carbamoylase sequentially (Scheme 2; Pathway B).³⁴ First, D-hydantoinase selectively cleaves D-hydantoin to afford N-carbamoyl D-amino acids **21**, which, in the presence of D-N-carbamoylase, are converted into the corresponding free D-amino acids **20**. D-(*p*-hydroxyphenyl)glycine, a valuable precursor for penicillins and cephalosporins, is produced commercially by this technique.³⁵

2.2.4 Reduction

Hydantoin can be reduced by lithium aluminum hydride under mild or harsh conditions to produce a variety of products, depending on the C-5, N-1, and N-3 substituents. Under mild conditions, 4-hydroxy-2-imidazolidinones **22**³⁶ or their dehydration products³⁷ are usually obtained (Scheme 2; Pathway C), whereas under harsh conditions, 2-imidazolidinones **23**, imidazoles **24**, or imidazolidines **25** are formed.^{38,39} In some cases, reduction has also been realized by treatment with an excess of lithium-liquid ammonia in *tert*-butyl alcohol to give imidazolidines **26**.¹⁸ Because the thiocarbonyl group is more polarized than the carbonyl group, it would be expected that thiohydantoin should be more easily reduced than hydantoin. This is evidenced by the fact that reduction of thiohydantoin by sodium in ethanol or with Raney nickel gives 4-imidazolidinones under conditions that do not affect hydantoin.⁴⁰

2.2.5 Hydantoin as Ligands in Organometallic Complexes

Hydantoin, through their nitrogen atoms, have the ability to coordinate with various transition metals such as platinum(II), copper(II), nickel, iron(II), gold(III), cobalt(II), mercury(II), or silver(I) to give organometallic complexes in which hydantoin can adopt mono- or bidentate behavior.^{41,42} Some of these complexes (Figure 3; **27** and **28**) have been tested and found to be strong cytotoxic agents.

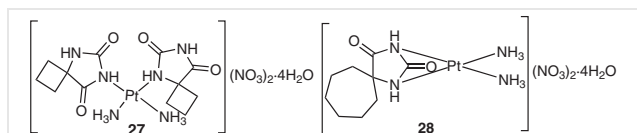


Figure 3 Hydantoin in organometallic complexes

2.2.6 N-Halogenation of Hydantoin

N-Halogenated hydantoin, e.g. 1,3-dihalo-5,5-dimethylhydantoin (**29–31**) (Figure 4)⁴³ are important and versatile oxidizing and halogenating agents in organic syntheses; the dichloro derivatives have been employed as chlorine sources and shown to be useful in a range of synthetic transformations.^{44,45} These reagents have significant operational

advantages, including commercial availability, air and moisture stability, generally high reactivity, and easy product-purification processes. N-Halogenated hydantoin have a low solubility in water, but parts-per-million levels are enough to serve as bleaching agents, antiseptics, or fungicides, as they slowly decompose to produce the free halogen in water. They have also been used in sanitizing and bleaching of toilet bowls, as disinfectants for dental appliances and automatic dishwashers, and as resin stabilizers, among other applications. N-Chloro and N-bromo derivatives of hydantoin are generally prepared by reaction with chlorine or bromine, respectively, in alkaline solution;⁵ however, their N-iodo counterparts are obtained by treatment with iodine monochloride.⁴⁶

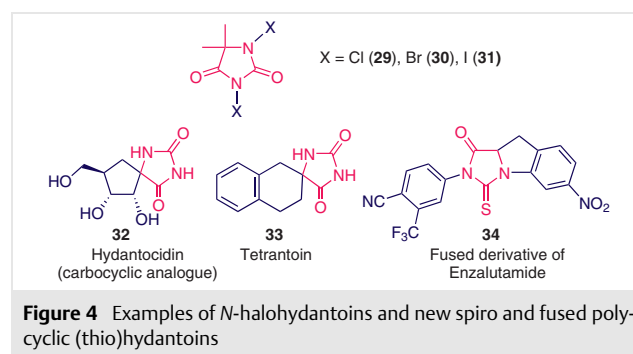


Figure 4 Examples of N-halohydantoin and new spiro and fused polycyclic (thio)hydantoin

2.3 Biological Properties

The presence of a hydantoin ring alone does not signify any biological activity; however, substituted hydantoin have found a wide range of applications in medicinal chemistry, where amazing progress has been made during the last few decades. Many hydantoin exhibit strong bioactivities, which has led to clinical trials and to commercialized drugs. Some of these potent drugs include phenytoin (**35**), fosphenytoin (**36**), and ethotoin (**37**), as anticonvulsants; nitrofurantoin (**38**) and dantrium (**39**) as muscle relaxants; and nilutamide (**40**) and enzalutamide (**41**) as androgen receptor antagonists (Figure 5). The medicinal applications of hydantoin and thiohydantoin have recently been exhaustively reviewed by Shin;⁷ therefore, we will only briefly introduce their biological properties.

2.3.1 Hydantoin in Medicinal Chemistry

Among the hydantoin derivatives, 5,5-diphenylhydantoin (phenytoin) has received the greatest attention in the field of medicinal chemistry. It was first synthesized in the early 1900s by Biltz,⁴⁷ and was recommended for the treatment of epilepsy in 1938 by Merrit and Putman.⁴⁸ The sodium salt of phenytoin was commercialized under the name of Dilantin by Pfizer in 1951 for its anticonvulsant and antiarrhythmic properties. Fosphenytoin, a water-soluble prod-

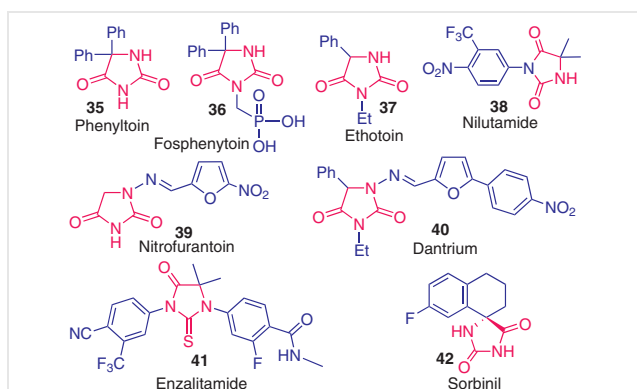


Figure 5 Hydantoin-based marketed drugs

rug, was marketed in its sodic form by Erfa in 2000 and later by Pfizer in 2013 under the name of Cerebyx. Ethotoin (3-ethyl-5-phenyl hydantoin) is another prominent commercialized drug used as an antiepileptic. Nilutamide and enzalutamide are nonsteroidal antiandrogenic drug used in the treatment of prostate cancer, whereas structurally related nitrofurantoin and dantrium are an antibacterial and a muscle relaxant, respectively. Spiro hydantoin-based sorbinil⁴⁹ (**36**) is being investigated for the treatment of diabetic complications. In recent years, spiro hydantoin and fused or bicyclic hydantoin have attracted much attention and are being explored for various biological activities (Figure 5).^{50,51} Examples of these, including the carbocyclic analogue of hydantocidin (**40**),³² palauamine,⁵² axinellamines,⁵³ tetrantoin (**41**),⁵⁴ and the fused derivative enzalutamide (**42**), are shown in Figure 5.⁵⁵

2.3.2 The Hydantoin Moiety in Natural Products

Hydantoin-ring-based natural products have been isolated from various genera of marine sponges, as well as from some bacterial species (Figure 6). For example, (*E*)-axinohydantoin (**44**) was isolated from the *Axinella* genus of sponges. Axinohydantoin has been shown to inhibit protein kinase C.⁵⁶ Hydantocidin (**45**) is a spiro nucleoside isolated from *Streptomyces hygroscopicus* that shows herbicidal activity.⁵⁷ Mukanadin B (**46**) is a bromopyrrole-based alkaloid from marine sponges of the genus *Agelas* or *Hymeniacidon*, such as *Agelas nakamurai*.⁵⁸

3 General Synthetic Methods

Because of the biological significance of hydantoin and thiohydantoin, both solution-phase and solid-phase methods for their synthesis have been extensively explored. Konert et al.⁶ and Meusel and Gütschow⁵⁹ have recently published detailed reviews on synthetic methods for hydantoin. Solution-phase syntheses include (i) the Read synthesis, in which amino acids or related compounds react

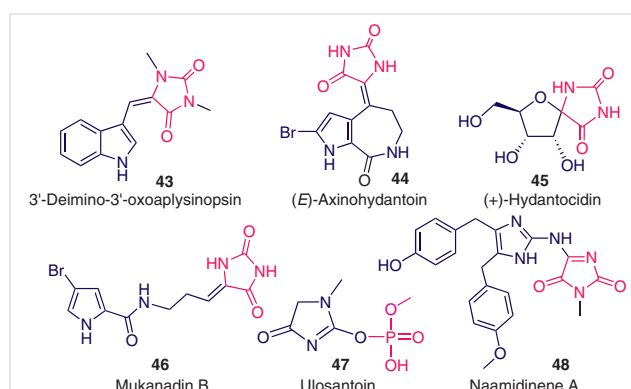


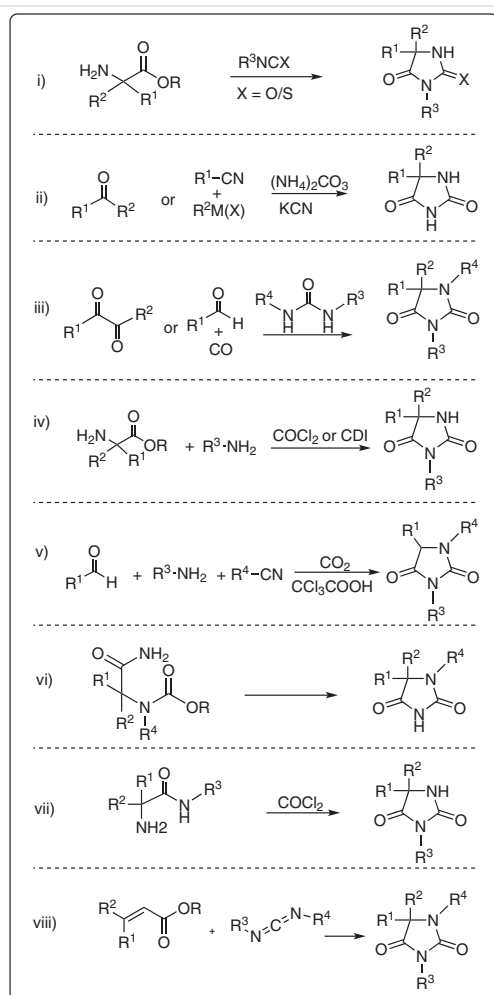
Figure 6 Natural products containing a hydantoin moiety

with cyanates, isocyanates, thiocyanates, or urea derivatives;^{60–62} (ii) the Bucherer–Bergs reaction, in which aldehydes and ketones are treated with potassium cyanide and ammonium carbonates;^{63,64} and (iii) the condensation of α -dicarbonyl compounds with ureas or thioureas.⁶⁸ The last strategy was followed by Blitz in an efficient synthesis of phenytoin through a benzil rearrangement.⁴⁷ Other methods for synthesizing hydantoin include (iv) the sequential reaction of α -amino esters with phosgene, triphosgene, or CDI, and a primary amine;⁶⁶ (v) the Ugi reaction;⁶⁷ (vi) cyclization of activated carbamates;⁶⁸ (vii) the reaction of amino acids amides with triphosgene;⁶⁹ and (viii) the condensation of α,β -unsaturated acid esters with carbodiimides.⁷⁰ Of these methods, the Read synthesis and the Bucherer–Bergs synthesis are the most frequently used protocols. These synthetic routes are shown schematically in Scheme 3.

The major limitations in using these methods are associated with problems of solubility of the substrates and difficult reaction conditions; moreover, the resulting hydantoin rings are invariably substituted at the C-5 position. To overcome the limitations associated with these methods, new methods and techniques have been developed that include the use of solid-phase synthesis,⁷¹ microwave synthesis,⁷² and catalysis.⁷³ The use of solid supports involves similar chemistry to that used in the solution-phase synthesis.

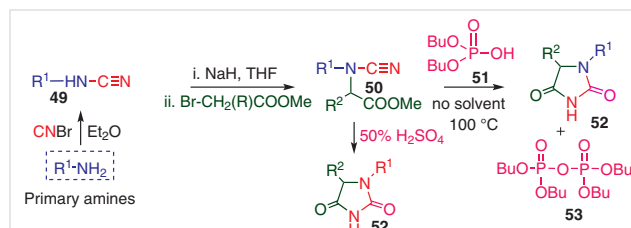
4 Synthesis of Diversely Substituted Hydantoin

A retrosynthetic analysis of hydantoin suggests that this moiety might be created from an N–C–N building block, as found in ureas, (iso)cyanates, carbodiimides, and cyanamides. On the basis of our previous research interest in cyanamide chemistry,⁷⁴ we proposed to synthesize the hydantoin moiety from cyanamide (NH_2CN). The chemistry and applications of cyanamide are well reported in the literature.⁷⁵ The cyanamide moiety can easily be prepared and modified as required. From our retrosynthetic analysis,



Scheme 3 General synthetic methods for hydantoin synthesis

we developed the complete synthetic scheme shown in Scheme 4, which starts from an alkyl or aryl amine. In the first step, a mono(alkyl/aryl)cyanamide **49** is prepared by the reaction of the appropriate amine with cyanogen bromide. This product is treated with methyl bromoacetate in the presence of sodium hydride to give a methyl *N*-cyano-*N*-(alkyl/aryl)aminoacetate **50**, which, on treatment with H_2SO_4 (50%) undergoes hydrolysis and cyclization to afford an *N*-1 (alkyl/aryl)hydantoin in good yields.⁷⁶ Due to the ease and convenience of this method, many hydantoin **52** substituted at the *N*-1 and *C*-5 positions with various substituents, such as primary, secondary, or tertiary alkyl, cycloalkyl, or aryl groups were successfully prepared (Table 1). Hydantoin **50** having aromatic or sterically hindered (tertiary alkyl) substituents at the *N*-1 position are difficult to prepare by other methods, but our strategy permits the synthesis of these hydantoin and their analogues conveniently and in good yields without protection and deprotection steps.



Scheme 4 Novel route for the synthesis of hydantoin

After reviewing our method, we attempted to bypass the use of concentrated sulfuric acid in the final step, as this reagent is highly dangerous and corrosive. Furthermore, acid-sensitive groups (halides, nitriles, ethers, alcohols, or double or triple bonds) tend not to survive such harsh acidic conditions. Consequently, hydantoin containing these functionalities could not be synthesized. In an attempt to overcome this weakness, we employed dibutyl phosphate (DBP) as a mild reagent to hydrolyze and cyclize the substrate in one step, giving quantitative yields of the desired products without affecting acid-sensitive moieties.⁷⁷ The reaction conditions and various substituted products are described in Scheme 4 and Table 1, respectively. The wide varieties of substituted hydantoin **54–71** were successfully prepared in one to two hours.

The chemical structures of these products were analyzed by spectroscopic techniques, and that of the representative hydantoin **59** was confirmed by X-ray crystallography (Figure 7).

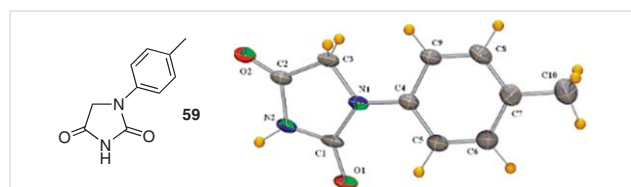




Figure 7 Crystal structure of **59**. (Reprinted with permission from ref. 79. © 2011, Elsevier Ltd.)

The reaction between **50** and H_2SO_4 or DBP is thought to proceed via the proposed path shown in Scheme 5. The first step leads to activation of the cyanamide group of **50** by transfer of a proton from H_2SO_4 or DBP. In the next step, nucleophilic attack on the activated cyanamide results in an unstable intermediate **72**, which undergoes cyclization under the influence of heat to form the product.

5 Synthesis of Diversely Substituted Thiohydantoin

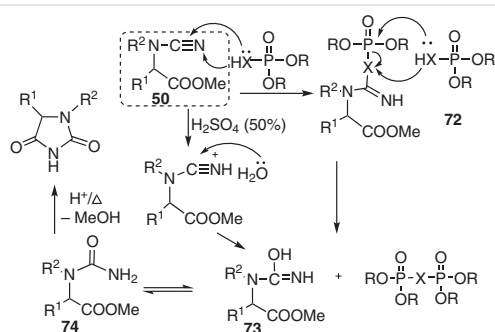
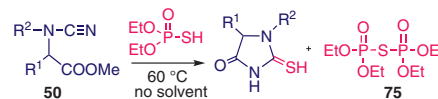
Thiohydantoin also have interesting features in structural chemistry. 2-Thiohydantoin are well known to have a wide range of applications, for example, as hypolipidemic,⁷⁸ anticarcinogenic,⁷⁹ antimutagenic,⁸⁰ antithyroidal,⁸¹ anti-

Table 1 Various Hydantoin from Methyl (Cyanoamino)acetates **50**

Product	R ¹	R ²	Time (h)	Yield (%)
54	cyclohexyl	H	1	92
55	cyclooctyl	H	1	92
56	<i>n</i> -octyl	H	1.5	88
57	<i>t</i> -Bu	H	1	90
58	Ph	H	1	88
59	Tol	H	2	85
60	4-MeOC ₆ H ₄	H	2	82
61	Ph	Me	2	80
62	All	H	1.5	84
63		H	1.5	80
64	CH ₂ =CH	H	1.5	83
65	4-FC ₆ H ₄	H	2	90
66	4-FC ₆ H ₄	Me	2	91
67	4-FC ₆ H ₄	Ph	2	88
68	4-ClC ₆ H ₄	H	2	85
69	4-BrC ₆ H ₄	H	2	86
70		Ph	2	75
71	Bn	H	1	89

ral,⁸² anti-HIV,⁸³ antitubercular,⁸⁴ antimicrobial,⁸⁵ anti-inflammatory, or antiulcer agents,⁸⁶ or as pesticides.⁸⁷ Moreover, they have also found applications as reference standards for C-terminal protein sequencing,⁸⁸ in textile printing,⁸⁹ in the complexation of metal cations, and as polymerization catalysis.⁹⁰

The various applications of the sulfur analogues of hydantoin have encouraged researchers to develop convenient methods for synthesizing thiohydantoin extensively substituted at various positions.⁹¹ Although, several synthetic routes to hydantoin have been reported, few yield thiohy-

**Scheme 5** Mechanism for the formation of hydantoin from methyl (cyanoamino)acetates **50****Scheme 6** Synthesis of 2-thiohydantoin from methyl (cyanoamino)acetates **50**

dantoin, particularly substituted thiohydantoin.¹¹ Substitution at the N-1 position in hydantoin generally involves the following three steps: (i) protection of the N-3 position, (ii) alkylation of the N-1 position and, (iii) removal of the protecting group (Scheme 1). However, this procedure cannot be followed in the case of thiohydantoin because of the inevitable formation of the S-alkylated thiohydantoin.²⁵ Therefore, a new approach is necessary for providing the desired thiohydantoin derivatives.

In view of this, we extended our approach to a clean, green, practical, and high-yielding method for the synthesis of thiohydantoin. The method is based on the reaction of intermediates **50** with diethyl thiophosphate (DETP). The reaction takes place under solvent-free conditions at 60 °C to give the desired products in good to excellent yields (Scheme 6).⁹² It is interesting to note that DETP, being more acidic and a better nucleophile than DBP, reacts faster with intermediates **50**. A library of thiohydantoin with various substituents such as alkyl, cycloalkyl, or aryl groups was generated by this route. A plausible mechanism is believed to follow the same mechanistic path as in the case of the previous method using DBP, which also explains the formation of ethyl thiopyrophosphate as a byproduct that can be easily be removed by the use of a solvent. The reaction conditions and results are briefly summarized in Table 2. Tables 1 and 2 also show that the formation of products with alkyl substituents is faster than that of products with aryl substituents. This is probably due to the donation of aromatic electron density to the cyanamide moiety, which decreases its reactivity toward nucleophilic attack by DBP and DETP.

All the products were characterized by spectroscopic techniques. To substantiate our spectroscopic data, recrystallization of the representative product **82** in CHCl₃ was carried out to obtain single crystals that provided an X-ray crystallographic structure (Figure 8).

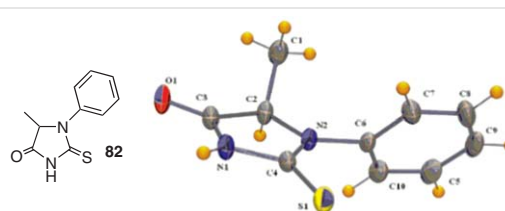

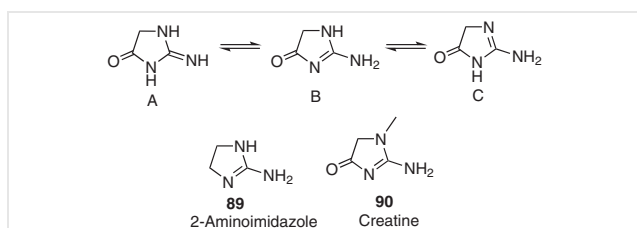
**Figure 8** Crystal structure of **82**. (Reprinted with permission from ref. 95. © 2012 Elsevier Ltd.)

Table 2 Various 2-Thiohydantoin from Methyl (Cyanoamino)acetates **50**

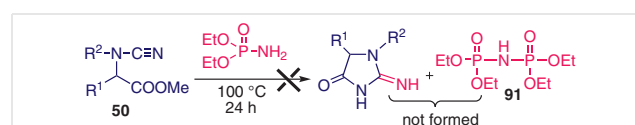
Product	R ¹	R ²	Time (h)	Yield (%)
76	cyclohexyl	H	0.5	90
77	cyclooctyl	H	0.5	88
78	<i>n</i> -octyl	H	1	82
79	Ph	H	1	90
80	Tol	H	1.5	89
81	4-MeOC ₆ H ₄	H	1.5	90
82	Ph	Me	2	84
83	All	H	2	85
84		H	2	83
85	4-FC ₆ H ₄	H	1.5	88
86	4-FC ₆ H ₄	Me	1.5	90
87	4-ClC ₆ H ₄	H	2	75
88	4-BrC ₆ H ₄	H	2	90

6 Synthesis of Diversely Substituted Imino-hydantoin

2-Imino-hydantoin is a nitrogenous analogue of hydantoin, and along with hydantoin and thiohydantoin, forms a widespread and close-knit group of derivatives that exhibit varied chemical and biological activities.^{93–95} This analogue contains amide and guanidine moieties in a five-membered ring, and exists in various tautomeric forms (Figure 9). Aminoimidazoles⁹⁶ and creatine⁹⁷ are heterocycles that are well known also to contain this ring system (Figure 9). The presence of 2-imino-hydantoin in pharmacophores covers a wide range of pharmaceutical activities, such as β -secretase (BACE1) inhibitory activity,⁹⁸ protein kinase inhibitory activity,⁹⁹ anticonvulsant activity,⁹⁴ antimalarial activity,¹⁰⁰ and inhibition of NF- κ B activation¹⁰¹ Moreover, imino-hydantoin intrinsically possess a guanidine moiety that has been exploited as an efficient binding site in supramolecular chemistry.¹⁰²

**Figure 9** Tautomeric forms of 2-imino-hydantoin

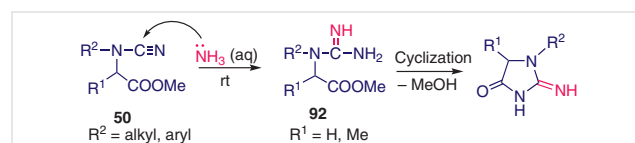
Encouraged by these chemical and biological properties of imino-hydantoin, we extended our synthetic strategy to the preparation of imino-hydantoin. Following the previous strategy, we intended to use diethyl phosphoramidate (DEPA), so we allowed it to react with **50**, but even at a high temperature (100 °C) and with a prolonged reaction time (Scheme 7), we did not get the desired product. This was possibly due to $d\pi$ - $p\pi$ bonding in the P-N bond of DEPA, which prevents it from reacting with **50**. Besides this, the basic amino group might also fail to activate the cyanamide functionality of **50** as in the case of hydantoin and thio-hydantoin.

**Scheme 7** Unsuccessful attempt to prepare 2-imino-hydantoin

We therefore redesigned our reaction conditions and used aqueous ammonia instead of DEPA. The reaction of **50** with aqueous ammonia took place to yield 2-imino-hydantoin at room temperature in 10–30 minutes (Scheme 8).¹⁰³ Interestingly, the developed method meets several criteria for green chemistry. The distinctive attributes of this reaction pertaining to green chemistry are its solvent-free nature, no requirement for extra heating, the use of water as the reaction medium, no formation of any byproducts, and no workup for the isolation or purification of the products, as simple filtration leads to the pure products. A series of N-1- and C-5-substituted 2-imino-hydantoin were prepared by this method in good to excellent yields (Table 3). All the products were characterized by means of IR and NMR spectroscopy, and mass spectrometry.

7 Fused or Bicyclo(thio)hydantoin

Bicyclohydantoin does not display any remarkable affinity toward the 5-HT1AR receptor,¹⁰⁴ whereas variations in the aryl substituent on the piperazine moiety might produce marked changes in the affinity and selectivity of the ligand. Therefore, structural diversity in bicyclo(thio)hydantoin could become an attractive tool for medicinal chemists.^{105,106} This stimulated us to explore a strategy for the synthesis of bicyclo(thio)hydantoin. These are generally prepared by the reaction of proline with an isocyanate or

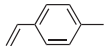
**Scheme 8** Synthesis of 2-imino-hydantoin from methyl (cyanoamino)acetates **50**

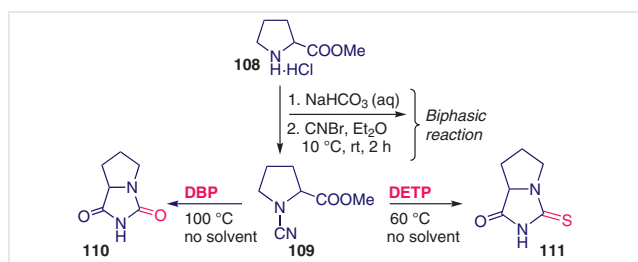
urea. By following our earlier approach, we successfully synthesized the bicyclohydantoin **110** and the bicyclothiohydantoin **111** from methyl *N*-cyanoprolinate (**109**) (Scheme 9). The precursor **109** was conveniently prepared by the reaction of methyl proline hydrochloride (**108**) with cyanogen bromide in a biphasic reaction setup. In this modified method, the self-condensation of the free proline methyl ester to form dioxopiperazines and polycondensation products was avoided by conversion of **108** into **109** in situ, without isolation.

8 Di- or Multivalent (Thio)hydantoins

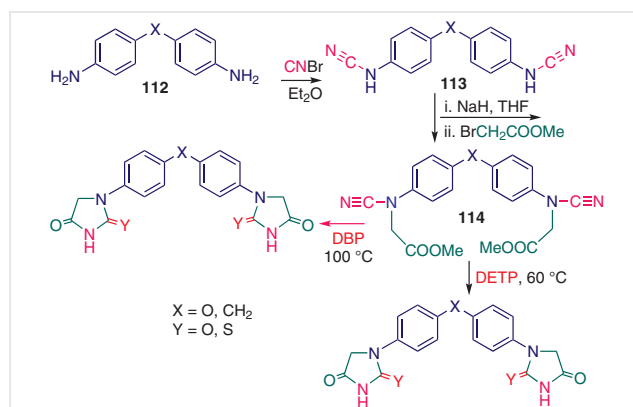
The creation of multiple hydrogen-bond donor and acceptor sites in a new molecular receptor is keenly sought after because this can open up a range of supramolecular chemistry.^{102,107} Encouraged by our recent efforts to incorporate urea/thiourea functionality in ditopic receptors,¹⁰⁸ we became interested in preparing hydantoin-based ditopic

Table 3 Various 2-Iminohydantoins from Methyl (Cyanoamino)acetates **50**

Product	R ¹	R ²	Time (min)	Yield (%)
93	Me	H	30	90
94	cyclohexyl	H	10	90
95	cyclooctyl	H	10	88
96	Ph	H	30	90
97	4-MeOC ₆ H ₄	H	30	90
98	4-FC ₆ H ₄	Me	30	85
99		H	30	83
100	4-ClC ₆ H ₄	H	25	90
101	4-BrC ₆ H ₄	H	30	90
102	4-NCC ₆ H ₄	H	30	90
103	3-NCC ₆ H ₄	H	30	90
104	CH ₂ C=CH	H	25	90
105	All	H	20	85
106	Tol	H	30	91
107	Bn	H	30	90



Scheme 9 Synthesis of bicyclo(thio)hydantoins



Scheme 10 Synthesis of bis(thio)hydantoins

receptors and in evaluating them for the detection of toxic analytes. We therefore effectively adapted our developed strategy to the synthesis of bishydantoins and bisthiohydantoins with various spacers (Scheme 10). The reaction between diamines **112** and cyanogen bromide (2 equiv) afforded the corresponding dicyanamides **113**. These cyanamide derivatives were allowed to react further with methyl bromoacetate (2 equiv) in the presence of sodium hydride to form intermediates **114**. Finally, treatment of **114** with DBP or DETP was carried out to afford the corresponding bishydantoins and bisthiohydantoins, respectively. Numerous derivatives **115–118** of these multivalent hydantoins with methylene or ether pivots were synthesized under the reaction conditions listed in Table 4.

Table 4 Reaction Conditions for Bis(thio)hydantoins

Product	X	Y	Time (h)	Yield (%)
115	O	O	4	82
116	O	S	2.5	84
117	CH ₂	O	3	80
118	CH ₂	S	2.5	82

9 Hydantoin-Based Hybrid Molecules

Hybrid molecules are defined as chemical entities with two or more structural domains that have different biological functions and a dual activity. The design and the synthesis of new types of pharmacologically interesting hybrid compounds for drug discovery have received much attention in recent years.^{109–115} By combining two pharmacophoric groups, new compounds with mixed mechanisms of action could arise. Synthetic chemists have magnificently designed several novel hybrids of natural or synthetic products by combining structurally two different pharmacophoric groups in a single molecule, leading to new classes of drug molecules.^{116,117} The chemical synthesis of hybrid natural products is a promising approach to obtaining struc-

turally diverse chemical substances for pharmacological testing. This approach, coupled with combinatorial chemistry, should be a powerful and practically feasible method for making thousands of compounds within a relatively short period. Taking our inspiration from Nature and from the literature, we initiated a research program to synergize the bioactivity of hydantoin with other vital heterocycles. In this approach, the hydantoin ring system was coupled with 1,2,3-triazole, isoxazoline, or phosphate groups to generate triazolohydantoin, isoxazolohydantoin, and phosphorylated hydantoin, respectively, which we hoped would display features of both moieties to reveal potent bioactivities. To the best of our knowledge, these kinds of the hybrid molecule had not been previously reported in the literature. The synthesis and biological activities of these hybrids are under investigation.

9.1 Hydantoin–Triazole Hybrid Molecules

1,2,3-Triazole moieties have attractive functionality, as they are stable to metabolic degradation and are capable of hydrogen bonding, which can favor binding to biomolecular targets and improve solubility.^{118,119} This moiety does not occur in nature, although synthetic molecules containing 1,2,3-triazole units show various biological activities, such as anti-HIV,¹²⁰ antimicrobial,¹²¹ selective β 3 adrenergic receptor agonist,¹²² and antiallergic actions.¹²³ Given the importance of these two classes of compounds, we intended to design a new class of hybrid structures that would combine hydantoin and 1,2,3-triazole motifs, as shown in Figure 10.

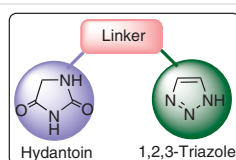
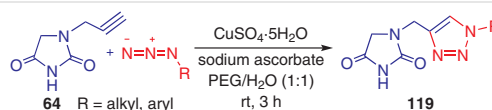


Figure 10 Molecular design of novel hydantoin–1,2,3-triazole hybrids

Our design for a synthesis of these hybrid molecules was based on the overall transformation of an amino group and alkyne functional groups into hydantoin and 1,2,3-triazole motifs, respectively. Hydantoin functionality was generated by following our previously developed strategy to give 1-propargylhydantoin (**64**). This derivative undergoes Huisgen 1,3-dipolar cycloaddition^{124,125} to give hydantoin–1,2,3 triazole hybrids **119** (Scheme 11). We believe that this is the first approach to the synthesis of a new class of hydantoin–1,2,3-triazole hybrids.

The reaction of **64** with various organic azides afforded regioselectively 1,4-disubstituted 1,2,3-triazoles containing hydantoin with great efficiency. The reaction of **64** with azides takes place in presence of hydrated copper sulfate and sodium ascorbate at room temperature in a 1:1 mixture



Scheme 11 Synthetic scheme for hydantoin–1,2,3-triazole hybrid **119**

of poly(ethylene glycol) (PEG) and water (1:1) as the solvent, giving novel triazolohydantoin derivatives **119** in good yields.¹²⁶ The chemical structures of the synthesized compounds were established by IR, ¹H NMR, and ¹³C NMR spectroscopy and by mass spectrometry.¹²⁷ Further studies to explore the biological applications of these hybrids and modified hybrids are in progress.

9.2 Hydantoin–Isoxazoline Hybrids

Isoxazolines are pharmacophores present in several pharmaceutically important compounds.¹²⁸ These compounds have been extensively used to modulate various other bioactive properties.^{129–131} In our series of synthetic developments, we next designed and investigated the coupling of isoxazolines with hydantoin (Figure 11) to yield (isoxazolylmethyl)hydantoin (**120**).¹³²

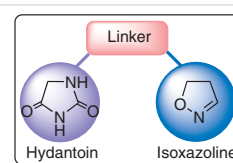
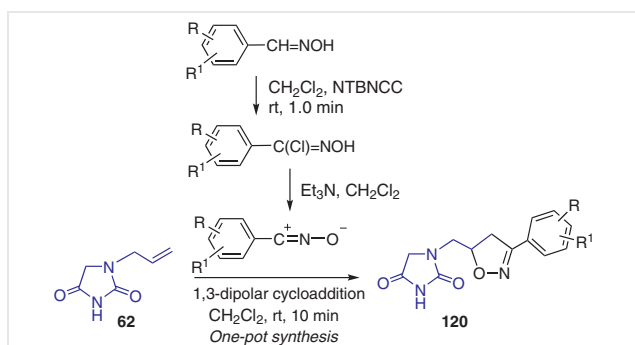


Figure 11 Molecular design of hydantoin–isoxazoline hybrids

These novel compounds were synthesized by 1,3-dipolar cycloaddition (Scheme 12). The final reaction takes place between 1-allylhydantoin (**62**) and various nitrile oxides in CH₂Cl₂ for 10–20 minutes at room temperature, and it provides very good yields of the desired products **120**.¹³³ The nitrile oxides, which are useful precursors in organic synthesis, were prepared by our strategy using *N*-tert-butyl-*N*-chlorocyanamide (NTBNCC).¹³⁴ Products **120** were characterized by spectroscopic techniques.¹³⁵ A series of derivatives of (isoxazolylmethyl)hydantoin were prepared by this strategy and are being evaluated for in vitro antimicrobial activities. Our initial findings indicate that some of the derivatives as such, or with some structural modification, might display bioactivities. This work is in progress and will be reported in due course.

9.3 Hydantoin–Phosphate Hybrids: Phosphorylated Hydantoin

While exploring our new class of hydantoin-based hybrid molecules, we became interested in synthesizing phosphorylated hydantoin derivatives and investigating their bi-



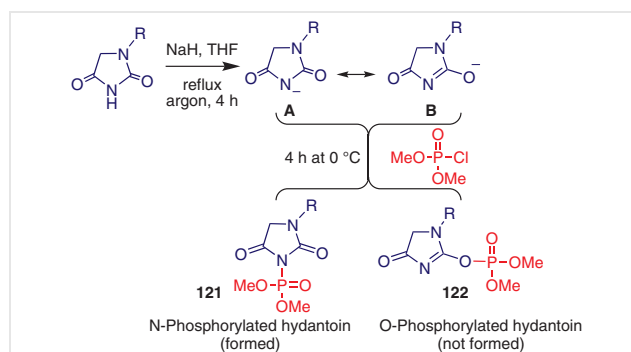
Scheme 12 Synthetic scheme for (isoxazolymethyl)imidazolidinones

ological properties, essentially because phosphorylated hydantoin derivatives have been shown to display a wide range of biological activities. Fosphenytoin (**36**; Figure 5) has been used as anticonvulsant²⁹ and ulosantoin (**47**; Figure 6) is an AChE inhibitor that exhibits marked insecticidal activity against tobacco hornworm larvae and cockroaches by inhibiting the AChE enzyme.¹³⁶ AChE inhibition is also well recognized as a major pharmacological approach to the treatment of Alzheimer's disease.^{137,138}

In our research, a series of novel phosphorylated hydantoin derivatives were synthesized and characterized. Our synthetic pathways leading to these new hydantoin derivatives are shown in Scheme 13. The target compounds **121** were prepared by the reaction of 1-alkyl- or 1-arylhydantoin with dimethyl chlorophosphate in the presence of sodium hydride. In the first step, the 1-substituted hydantoin reacts with sodium hydride to give its sodium salt, which can exist in two tautomeric forms **A** and **B** (Scheme 13). Dimethyl chlorophosphate attacks at the unsubstituted nitrogen to give the N-phosphorylated hydantoins **121** (Scheme 13).¹³⁹ The products were characterized by means of FTIR and NMR (¹H, ¹³C, and ³¹P) spectroscopy, and mass spectrometry.¹⁴⁰ XRD studies unequivocally confirmed the formation of the N-phosphorylated form and eliminated the possibility of O-phosphorylation. Preliminary studies suggested that some of the derivatives of these compounds exhibit AChE-inhibitory properties in vitro with IC₅₀ values in the low micromolar range. Studies on the syntheses of various derivatives of phosphorylated hydantoins and their bioactivities are underway, and will be reported in detail in due course.

10 Summary and Outlook

In this Account, I have briefly summarized the significant role of hydantoin, thiohydantoin, selenohydantoin, and iminohydantoin in organic chemistry and in medicinal chemistry owing to their wide range of pharmacological properties. Over the past few decades, development in this



Scheme 13 Synthetic scheme for phosphorylated hydantoins

area has shifted from academic research to successful drug development. There is no doubt that these heterocycles have proven to be excellent core units that are widely utilized in diverse fields of chemical science, such as medicinal chemistry, synthetic organic chemistry, supramolecular chemistry, and biomimetic chemistry. Because of its importance, numerous approaches have been put forward for the synthesis and structural modification of this scaffold. In the synthesis of hydantoin, the major limitation of the most widely used protocols is the nonavailability of the precursors, and the selective functionalization of the hydantoin unit at various positions, such as N-1, N-3, or C-5, is the most crucial aspect. Functionalization at the desired position is required to modulate and evaluate the chemical and biological activities of the various products. In particular, substitution of the hydantoin ring at the N-1 position is generally achieved in poor yields through a protection-deprotection strategy. Moreover, the existing methods cannot be applied to products with aryl or secondary or tertiary alkyl substituents.

The synthetic strategies described in this account provide us with diversely substituted hydantoins, thiohydantoins, or iminohydantoin substituted at various positions with a full range of substituents (primary, secondary, or tertiary alkyl, cycloalkyl, or aryl). This simple, clean, green, practical, and high-yielding protocol proceeds from easily accessible substrates, i.e., primary amines. By using this approach, a beautiful and fruitful itinerary was followed, passing through the creation of the hydantoin ring to the formation of thiohydantoins and iminohydantoins from a common precursor. Moreover, our approach has been effectively extended to the synthesis of structurally diverse products, such as fused or bicyclo(thio)hydantoins and multivalent (thio)hydantoins. The accessibility of various products by the novel routes has opened up an avenue for the design and synthesis of several classes of hydantoin-based hybrid molecules. In an attempt to synergize the bioactivity of hydantoin with other vital heterocycles, the scaffold has been coupled with triazole, isoxazoline, or phosphate groups to generate triazolohydantoins, isoxazolinohydantoins, and phosphorylated hydantoins, which have

features of both moieties, in an attempt to discover potent bioactivities. We sincerely hope that the developed strategies and the huge library of products will inspire many of us to take up research in a new dimension in the area of organic and medicinal chemistry that will also permit easy access to further diversified hydantoin-based bioactive products.

Conflict of Interest

The authors declare no conflict of interest.

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- (126) 1-[(1-Benzyl-1*H*-1,2,3-triazol-4-yl)methyl]imidazolidine-2,4-dione (**119**, R = Bn): **Typical Procedure**
1-Propargylhydantoin (**64**; 0.3 g) was dissolved in 1:1 PEG-H₂O. To this solution were added BnN₃ (0.29 g), CuSO₄·5H₂O (0.02 g), and sodium ascorbate (0.04 g) in one portion, and the mixture was stirred for 3 h at rt until the reaction was complete (TLC). The mixture was then diluted with H₂O and extracted with EtOAc (3 × 10 mL). The organic layer was washed with H₂O (2 × 10 mL). Evaporation of the solvent in a rotary evaporator gave a white crystalline solid; yield: 490 mg (84%); mp 214–216 °C.
- (127) **119** (R = Bn): IR (KBr): 3134, 3039, 2749, 172662, 1726, 1469, 1322, 1230 cm⁻¹. ¹H NMR (400 MHz, DMSO-*d*₆): δ = 3.9 (s, 2 H, CH₂), 3.449 (s, 2 H, CH₂), 5.56 (s, 2 H, CH₂), 7.29–7.39 (m, 5 H, ArH), 8.14 (s, 1 H, CH), 10.83 (s, 1 H, NH). ¹³C NMR (100 MHz, DMSO-*d*₆): δ = 37.2, 50.7, 53.0, 123.5, 128.0, 128.2, 128.8, 136.1, 142.9, 156.9, 171.7. TOF-MS (ESI): *m/z* = 272.1 [M + H]⁺.
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- (133) **1**-[(3-Phenyl-4,5-dihydroisoxazol-5-yl)methyl]hydantoin (**120**, R = Ph)
N-*tert*-Butyl-*N*-chlorocyanamide (0.55 g, 4.1 mmol) was added dropwise to a solution of benzaldoxime (0.5 g, 4.1 mmol) in CH₂Cl₂ (10 mL) at rt. Initially, a blue color appeared that immediately turned to yellow, indicating the formation of benzalhydroxymoyl chloride, as confirmed by TLC. To this mixture was added a solution of 1-allylhydantoin (0.57 g) (4.1 mmol) in CH₂Cl₂ (5 mL), followed by Et₃N (0.62 g, 6.1 mmol) in CH₂Cl₂ (5 mL). The exothermic reaction that occurred was sufficient to induce cycloaddition of the nitrile oxide formed during the reaction to the 1-allylhydantoin. The reaction was complete in 10 min (TLC). The mixture was diluted with CH₂Cl₂ (20 mL) and then washed with H₂O (3 × 50 mL). The filtrate was dried (Na₂SO₄) and the solvent was evaporated in a rotary evaporator. The resulting viscous liquid was triturated with Et₂O to give a white crystalline solid; yield: 600 mg (60%); mp 166–170 °C.
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- (135) **120** (R = Ph): IR (KBr): 3203, 2929, 1756, 1713, 1469, 1359, 1233 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ = 3.15–3.23 (dd, *J* = 7.6, 7.6 Hz, 2 H, CH₂), 3.44–3.72 (m, 2 H, CH₂), 4.10–4.22 (q, *J* = 18 Hz, 2 H, CH₂), 4.92–4.98 (m, 1 H, OCH), 7.38–7.66 (m, 5 H, ArH), 8.46 (s, 1 H, NH). ¹³C NMR (100 MHz, acetone-*d*₆): δ = 38.3, 46.4, 53.2, 80.7, 127.5, 129.6, 130.6, 130.9, 157.8, 158.3, 172.2. TOF-MS (ESI): *m/z* = 260.4 [M + H]⁺.
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- (139) **Dimethyl (3-Methyl-2,5-dioximidazolidin-1-yl)phosphonate (121; R = Me)**
1-Methylhydantoin (1 g, 8.77 mmol) was dissolved in anhyd THF (25 mL). To this solution, was added a 60% oil suspension of NaH (0.3 g) in three portions at 0 °C. The mixture was stirred for 0 °C for 1 h, refluxed for 2 h, and then cooled to 0 °C. A solution of dimethyl chlorophosphate (1.6 g) in anhyd THF (10 mL) was added and the mixture was stirred for 4 h at 0 °C until the reaction was complete (TLC). The mixture was filtered and the solvent was evaporated to one-fourth of its original volume. Et₂O (30 mL) was added, and a viscous yellow oily liquid settled out as impurities after 20 min. The solution was decanted and kept for 2 h in a refrigerator to give white crystals; yield: 1700 mg (88%); mp 214–216 °C.
- (140) The ¹H NMR spectrum for **121** (R = Me) showed a singlet at δ = 2.92 for N-CH₃ and a singlet at δ = 3.94 for -CH₂. The two methyl groups attached to the phosphorus atom appeared as a doublet (*J*_{PH} = 11 Hz) at δ = 3.92. The ¹³C NMR peaks for the N-CH₃, OCH₃, -NCH₂-, C=O (C-2), and C=O (C-4) groups appeared at δ = 29.5, 52.3–52.4, 55.60, 153.9–154.0, and 168.5 respectively. The ³¹P-decoupled NMR showed a singlet at δ = -6.44.