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Chemistry of Dimedone for Synthesis of Oxygen-, Nitrogen-, and Sulfur-Containing Heterocycles from 2-(3-Hydroxy-5,5-dimethylcyclohex-2-enylidene)malononitrile

Poulomi Majumdar [a], Prajna Parimita Mohanta [a], Rajani K. Behera [a] & Ajaya Kumar Behera [a]

[a] Organic Synthesis Laboratory, School of Chemistry, Sambalpur University, Odisha, India

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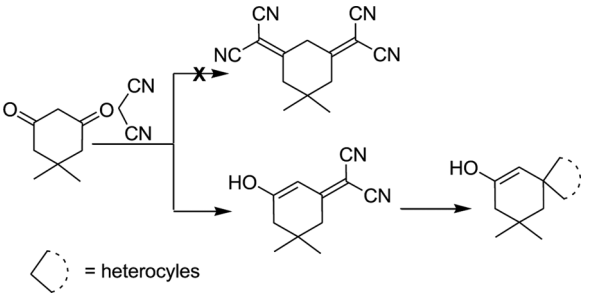
CHEMISTRY OF DIMEDONE FOR SYNTHESIS OF OXYGEN-, NITROGEN-, AND SULFUR-CONTAINING HETEROCYCLES FROM 2-(3-HYDROXY-5,5-DIMETHYLCYCLOHEX-2-ENYLIDENE)MALONONITRILE

Poulomi Majumdar, Prajna Parimita Mohanta, Rajani K. Behera, and Ajaya Kumar Behera
Organic Synthesis Laboratory, School of Chemistry, Sambalpur University, Odisha, India

GRAPHICAL ABSTRACT



Abstract *A series of new oxygen-, nitrogen- and sulfur- containing spiro heterocycles was synthesized by reactions of 2-(3-hydroxy-5,5-dimethylcyclohex-2-enylidene)malononitrile with some active methylene and bidentate compounds.*

Keywords Active methylene; bidentates; dimedone; malononitrile; spiro heterocycles

INTRODUCTION

Malononitrile is a commonly known and widely used reagent in the synthesis of heterocyclic compounds, pharmaceuticals, pesticides, fungicides, solvatochromic dyes, and charge-transfer salts. The unique reactivity of this compound has led to its widespread applications in organic chemistry, similar to or even more than other such acids such as malonate and cyanoacetic esters.[1] Alkylidenemalononitriles (α,β-unsaturated nitriles) containing an activated double bond together with reactive CN groups are

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Address correspondence to Ajaya Kumar Behera, Organic Synthesis Laboratory, School of Chemistry, Sambalpur University, Jyoti Vihar, Burla 768019, Odisha, India. E-mail: ajaykumar.behera@yahoo.com

also common reagents utilized in heterocylic synthesis.[2–7] It has also been well known that dimedone is a versatile precursor for synthesis of a number of heterocycles.[8] Furthermore, the synthesis of spiro compounds has drawn considerable attention of chemists, because of their interesting conformational features[9,10] and their structural implications on biological systems.[11–21]

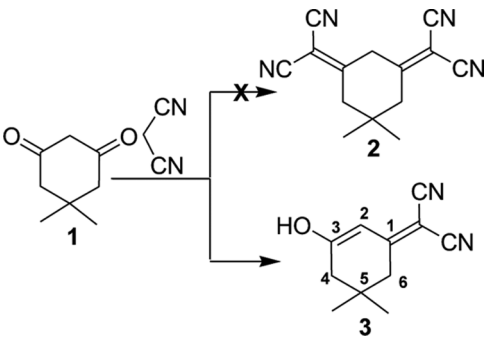
The syntheses, reactions, and biological activities of compounds containing pyrazole, [22–27] pyrimidine, [28–32] pyranopyrimidine, [33–35] thiazole, [36] thiazolidinone, [37–42] pyrrole[43–46] or thiazine stand as an ever- expanding area of research in heterocyclic chemistry, and these structural moieties appear in a large number of chemotherapeutic agents and natural products.

The biological importance of spiro-compounds and nitrogen, oxygen, and sulfur heterocycles, along with our continued interest in the synthesis of heterocycles,[47] led us to synthesize spiro heterocycles using 2-(3-hydroxy-5,5-dimethylcyclohex-2-enylidene)malononitrile derivative **3** as the synthetic precursor obtained from dimedone and malononitrile.

RESULTS AND DISCUSSION

The base- catalyzed condensation of dimedone **1** with malononitrile resulted in the formation of the 2-(3-hydroxy-5,5-dimethylcyclohex-2-enylidene)malononitrile derivative **3** rather than compound **2** (Scheme 1).

Initially, dimedone **1** was treated with 2 equivalents molar ratio of a malononitrile in the presence of a catalytic amount of piperidine in refluxing ethanol targeting dienylidene malononitrile **2** as the product. The analytical and spectral data of the product did not match the expected structure **2**. These data suggest structure **3** for the product. The results of elemental analyses is compatible with **3**. Further, the product **3** was supported by the infrared (IR) spectrum with characteristic signals of the nitrile and hydroxy groups at 2216 cm^{-1} and 3174–3236 cm^{-1}, respectively, and $[M-1]^+$ ion peak at m/z 187 in the mass spectrum. The PMR spectrum of **3** exhibited four distinct separate singlets at δ 1.09, 2.23, 2.54, and 6.18 corresponding to six protons of the gem dimethyl group present at C-5 and two methylene protons each at C-6, C-4, and enylidene proton at C-2, respectively. The distinct peaks at δ 27.8, 32.8, 42.4, 42.5, 100.1 and 113.6, 114 corresponding to two gem dimethyl



Scheme 1. Synthesis of 2-(3-hydroxy-5,5-dimethylcyclohex-2-enylidene)malononitrile.

carbons, C-5, C-6, C-4, C-2, and two nitrile carbons, respectively, along with pronounced signals at δ 177, 174.7, and 68.4 assignable to C-1, C-3, and $C(CN)_2$, respectively, in the ^{13}C NMR spectrum serve as a conclusive evidence in favor of **3**. We also examined this reaction using 1 equivalent of malononitrile and in different solvents (i.e. dioxane and dimethylformamide [DMF]). In all the reaction conditions the same 2-(3-hydroxy-5,5-dimethylcyclohex-2-enylidene)malononitrile **3** was formed, suggesting Knoevenagel condensation of malononitrile with one of the carbonyl groups of **1**.

The failure in the formation of dienylidene malononitrile **2** is almost certainly due to enolization in **1**. In $CDCl_3$ solution it is clearly a mixture of the two tautomers. ^1H-NMR and ^{13}C-NMR of the mixture with the peaks of the dione is depicted by stars (*) in Fig. 1 and Fig. 2, respectively. The majority of the sample is indeed 5,5-dimethylcyclohexane-1,3-dione (dimedone) **1A**. The other component has a similar spectrum and is a similar compound, **1B**: It has the six-proton singlet for the CMe_2 group and the two CH_2 groups at the side of the ring; it also has five signals in its ^{13}C NMR spectrum (Fig. 2). However, it has a sharp signal at δ 5.5 in the double-bond region. It also has two different sp^2 carbon atoms. All this fits the *enol* structure (Fig. 3). These forms are in equilibrium and cannot be separated at room temperature. Dimedone is just one example of the class of dicarbonyl compounds, which contain substantial amounts of enol and may even be completely enolized in polar solvents. This enol is very stable. The main reason is that this unique (1,3) arrangement of the two carbonyl groups leads to enols that is conjugated like a carboxylic acid (Fig. 4).

It is interesting to note that the two CH_2 groups in the ring seemed to be the same, though they are different (a and b), and the delocalization also does not make them the same. This must mean that the enol is in rapid equilibrium with another identical enol. Thus, this is not delocalization because a proton is moving: It is tautomerism (Fig. 5). Thus the two enols equilibrate fast with each other in $CDCl_3$ solution but equilibrate slowly enough with the keto form for the two spectra to be recorded at the same time. In CD_3OD solution, the ^1H NMR and ^{13}C NMR spectra show that only the enol form exists, presumably stabilized by hydrogen bonding (Fig. 6).[48,49]

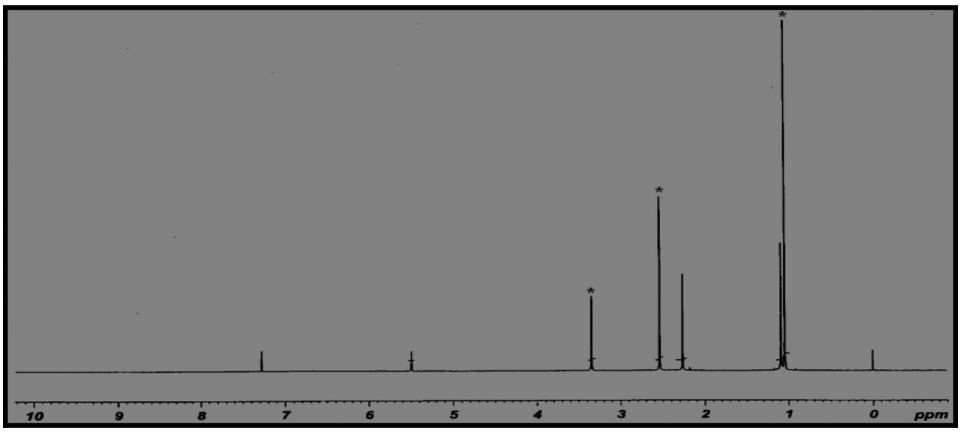


Figure 1. PMR spectra of dimedone.

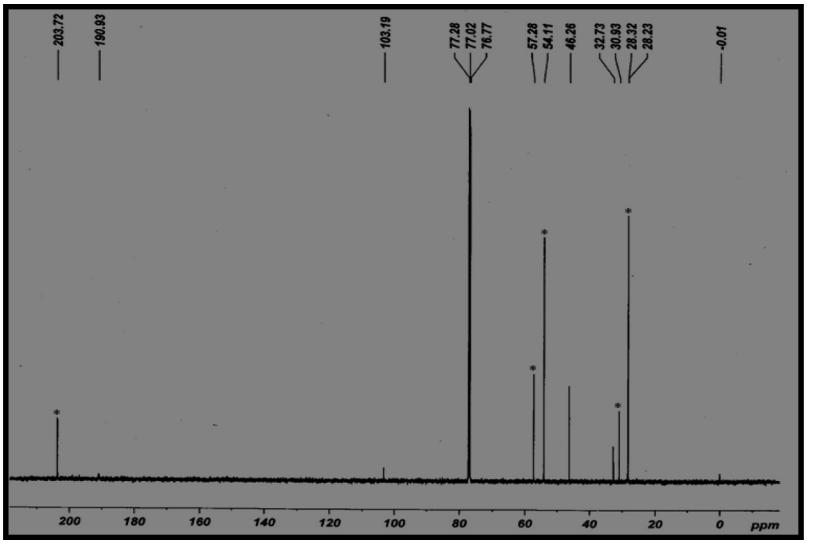


Figure 2. ^{13}C NMR spectra of dimedone.

2-(3-Hydroxy-5,5-dimethylcyclohex-2-enylidene)malononitrile derivative **3** was reacted with bidentate nucleophiles, namely thiourea, thioacetamide, thiosemicarbazide, urea, semicarbazide, and guanidine hydrochloride, with a view to achieving the corresponding aza spiro derivatives **4** (Scheme 2).

The first endeavor started on a refluxing equimolar mixture of malononitrile derivative **3** and thiourea in the presence of a catalytic amount of different bases such as piperidine, triethyl amine, triethanol amine, pyridine, and sodium acetate in ethanol with a view to obtaining spiro derivative **4a** (R=NH_2, X=S). Suprisingly, in all the cases the isolated product was found to be the same malononitrile derivative **3** on the basis of their physical, analytical, and infrared (IR) spectral data. However, the reaction of malononitrile derivative **3** and thiourea in acetic acid in a oil bath at 150 °C led to an unusual 4-oxo-3-aza-spiro[5.5]undeca-2,7-diene-5-carbonitrile **5a** (R=NH_2, X=S) in moderate yield. The elemental analyses of the products ruled out the formation of the expected spiro compound **4a**, but it is agreeable to structure **5a**. In the ^1H NMR spectra of the product, two separate doublets appearing at δ 2.51 ($J = 21$ Hz) and δ 2.26 ($J = 21$ Hz) are attributable to each methylene protons at C-11 and C-9 of the cyclohexane ring, respectively. The C-5 and C-7 protons appeared as

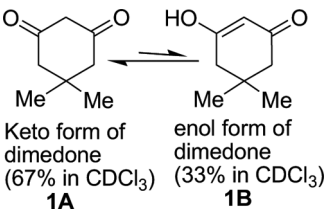


Figure 3. Keto-enol tautomerism of dimedone.

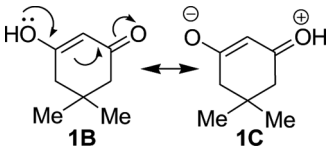


Figure 4. Delocalization in the enol form of dimedone.

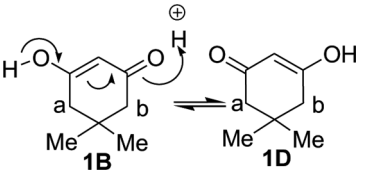


Figure 5. Equilibration of the enol form of dimedone.

singlets at δ 5.97 and δ 6.17, respectively. The unambiguous formation of spiran **5a** was favored by the appearance of distinct singals at δ 169.1, 117.9, and 54.3 assignable to carbonyl, C=N, and spiro carbon, respectively in the ^{13}C NMR spectrum. The peaks at δ 48.6, 94.9, 117.3, and 168.2 were observed due to carbons at C-5, C-7, CN, and C-8, respectively. The structural assignments made on the basis of the ^{1}H and ^{13}C NMR spectra of compound **5a** was supported by its IR spectrum which showed appearance of characteristic absorption bands at 3346, 3209, 2196, and 1658 cm^{-1} due to the OH, NH_2, nitrile, and carbonyl groups, respectively. The possible mechanism involves initially the in situ hydrolysis of one of the nitrile group of **3** in acetic acid medium and subsequent Michael addition of the mercapto groups at the ethylenic double bond followed by cyclization through nucleophilic attack of the imino group at the amidic carbonyl via intramolecular elimination of amonia to give the cyclized spiro derivatives **5**.

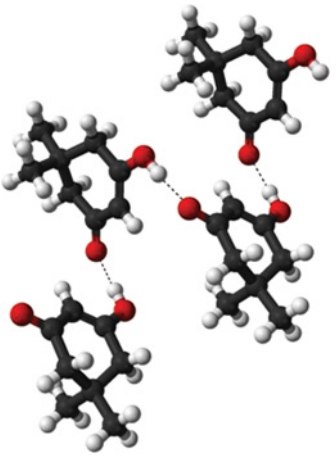
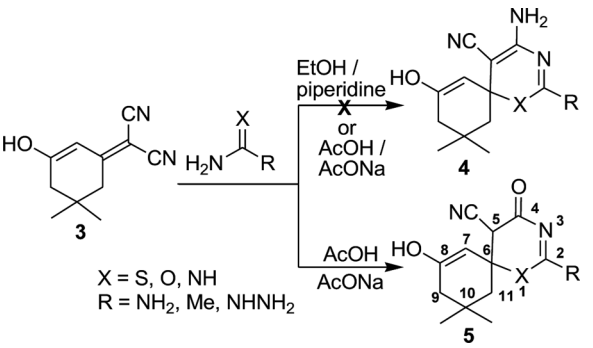
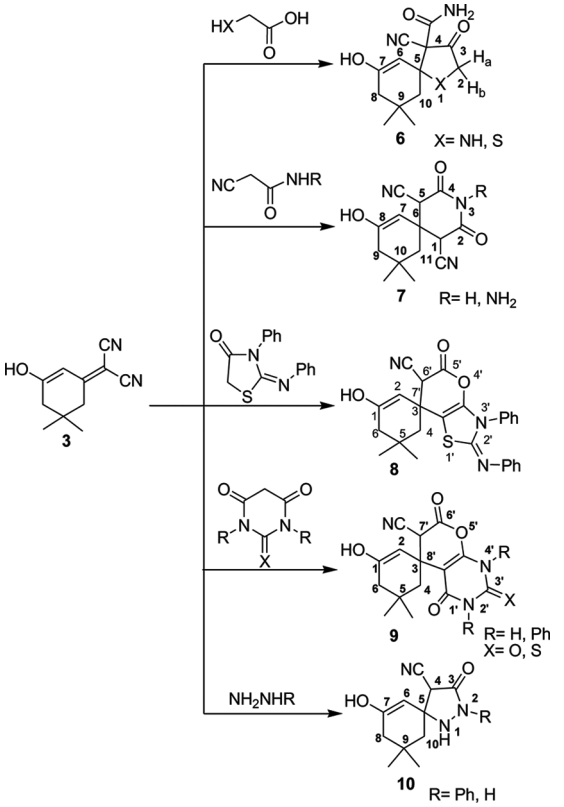


Figure 6. Crystalline dimedone contains chains of molecules, in the enol form, linked by hydrogen bonds.



Scheme 2. Synthesis of aza spiro derivatives **5**.

Under the similar reaction conditions described previously, another series of aza spiro derivatives **6** was obtained on treatment of 2-(3-hydroxy-5,5-dimethylcyclohex-2-enylidene)malononitrile derivative **3** separately with mercaptoacetic acid or glycine (Scheme 3). A similar mechanism for this series of azaspiro heterocycles has been attributed as discussed previously. During the reaction, the nucleophilic addition of



Scheme 3. Synthesis of aza spiro derivatives **6–10**.

the mercapto or amino group to the exocyclic double bond of **3** and subsequent dehydrative cyclization afforded the spiro derivatives **6**. In the PMR spectrum of compound **6a** (X=NH), two separate doublets centered at δ 4.04 ($J = 6$ Hz) and δ 4.13($J = 6$ Hz) for one proton each at C-2, respectively, and a triplet resonating at δ 8.67 ($J_{NH,\ Ha/Hb} = 6$ Hz) assignable to N1-H suggest the formation of spiro[4.5]dec-6-ene-4-carboxylic acid amide **6a**. The OH and NH_2 protons appeared as singlets at δ 13.07 and 9.07, respectively. In the ^{13}C NMR spectrum of **6a**, the signals for spiro and carbonyl carbons appeared at δ 49, 173.6 (amidic carbonyl) and, 200(C_3=O), respectively.

The active methylene compounds cyanoacetamide or 2-cyanomalonohydrazide, 3-phenyl-2-(phenylimino)thiazolidin-4-one, and barbiturates on refluxing with 2-(3-hydroxy-5,5-dimethylcyclohex-2-enylidene)malononitrile derivative **3** under the same reaction conditions described earlier formed the azaspiro derivatives **7, 8**, and **9**, respectively (Scheme 3). The reaction pathway initially follows a similar in situ hydrolysis of one of the nitrile groups of **3** in acetic acid medium and simultaneous formation of the carbanion of the active methylene compound followed by nucleophilic addition at the ethylenic bond and cyclization to give the spiro derivatives **7, 8**, and **9**.

In the IR spectrum of **7a** (R=H), the emergence of two broad peaks at about 3342 and 3221 and a sharp peak at 2204 cm^{-1} corresponding to -OH, -NH, and -C≡N stretching frequency, respectively, along with the carbonyl peak at 1662 cm^{-1}, suggests the formation of **7a**. The structure of **7a** has been confirmed on the basis of its PMR spectrum, which exhibits two distinct singlets at δ 5.79 and 5.96 for two protons at C-5 and C-1 and one proton at C-7, respectively. Two characteristic broad singlets centered at δ 8.18 and 8.47 assignable to N3-H, and OH, respectively, are agreeable to the proposed structure **7a**. The ^{13}C NMR spectrum of **7a** showed peaks at δ 47.5 and 169.1 for spiro and carbonyl carbons, respectively.

The appearance of a sharp peak at 1724 cm^{-1} corresponding to carbonyl stretching frequency in the IR spectrum along with two bands at 2214 and 3439 cm^{-1} assignable to nitrile and hydroxyl groups, respectively, tentatively suggests the structure of the product as tetrahydro-2*H*-spiro[cyclohex-1-ene]-3,7′-pyran[2,3-d]thiazole] **8**. The PMR spectral data display five separate singlets at δ 0.99, 2.47, 2.51, 4.17, and 5.98, corresponding to six methyl protons of the gem dimethyl group present at C-5, two methylene protons each at δ C-4, C-6, one proton each of C-6′ and C-2, respectively, along with a complex multiplet for 10 aromatic protos at δ 6.86–7.55, and in the ^{13}C NMR spectrum signals due to the spiro and carbonyl carbon appeared at δ 48 and 168.2, respectively, confirming the formation of spiro **8**.

In the IR spectrum, the appearance of bands at 1737, 1691, and 1656 cm^{-1} assignable to carbonyl groups along with additional peaks at 3468, 3385, 3126–3180, and 2214 cm^{-1} for OH, NH, and CN stretching frequency suggest the structure of spiro[cyclohex-1-ene-3,9′-pyrano[2,3-d]pyrimidine] derivative **9a** (R=H, X=O). The PMR spectrum of **9a** (R=H, X=O) gave five distinct singlets centered at δ 12.79, 10.19, 9.91, 6.66, and 4.39 assignable to OH, N-2′, N-4′, C-2, and C-7′, respectively. The appearance of two singlets at δ 2.48 and 2.25 corresponding to methylene protons at C-4 and C-6, respectively, along with peaks at δ 52.3 (spiro C-8′), 150.6 ($C_{3'}$=O), 164.2 ($C_{1'}$=O), and 169 ($C_{6'}$=O) in the ^{13}C NMR spectrum, confirms the formation of the spiro[cyclohex-1-ene-3,9′-pyrano[2,3-d]pyrimidine] derivative **9a** (R=H, X=O).

On the other hand, the cyclocondensation of 2-(3-hydroxy-5,5-dimethylcyclohex-2-enylidene)malononitrile derivative **3** with bidentate nucleophiles (namely phenyl hydrazine and hydrazine hydrate) under the reaction condition discussed previously formed the 1,2-diaza-spiro[4.5]dec-6-ene-4-carbonitrile **10** (Scheme 3). The IR spectra of **10a** (R=Ph) gave two sharp peaks at 1676 and 2206 cm^{-1} corresponding to carbonyl and nitrile group along with a broad peak at 3275 cm^{-1} for NH and OH group, indicating the formation of 1,2-diaza-spiro[4.5]-dec-6-ene-4-carbonitrile **10a.** The PMR spectrum of compound **10a** shows two singlets at δ 6.22 and δ 5.75 for protons at C-6 and C-4, respectively, along with two separate multiplets resonating at δ 7.09–7.12, and 7.28–7.36 for five phenyl protons equivocally suggest the formation of 1,2-diaza-spiro[4.5]dec-6-ene-4-carbonitrile **10a**. A broad singlet was observed for NH proton at δ 9.23. In the ^{13}C NMR spectrum of **10a** the signals for spiro and carbonyl carbons appeared at δ 56.5 and 168.9, respectively.

In summary, an efficient route to obtain a wide range of spiro heterocyclic scaffolds, which have the potential for useful biological properties, has been developed. Moreover, the exploitation of one of the carbonyl functions of dimedone for condensation with malonitrile and subsequent spirolization of enylidene malononitrile intermediate takes place with various bidentate nucleophiles and active ketomethylene compounds to build up spiroheterocycles.

EXPERIMENTAL

Melting points were taken in open capillaries using sulfuric acid bath and are uncorrected. Purity of the products were checked by thin-layer chromatography (TLC) on silica gel G (BDH) using toluene–ethylacetate (4:1) as irrigant. IR spectra were recorded with a Shimadzu FTIR Prestige-21 spectrophotometer in KBr using the diffuse reflectance spectra (DRS) technique. NMR spectra were recorded on Varian 400-MHz (^1H, 400 MHz; ^{13}C, 100 MHz) and Bruker Avance III 500-MHz (500 Hz for ^1H, 125 MHz for ^{13}C) NMR spectrometers in $CDCl_3$ or dimethylsulfoxide (DMSO), unless otherwise stated. Chemical shifts are expressed in parts per million downfield from tetramethylsilane (TMS) as an internal standard. Data are given in the following order: δ value, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad), number of protons, and coupling constants *J* (given in hertz). The mass spectra were taken on an API 2000 LC-MS mass spectrometer. Elemental analyses were performed by Flash 2000 elemental analyzer and were in agreement with the calculated values within ±0.4%. All the reagents and solvents were of the best grade available and were used without further purification.

Preparation of 2-(3-Hydroxy-5,5-dimethylcyclohex-2-enylidene) malononitrile (3)

A mixture of dimedone **1** (10 mmol, 1.4 g), malononitrile (10 mmol, 0.47 mL) and 3 drops of piperidine in dry ethanol (25 mL) was refluxed with stirring for 6 h. The reaction set was allowed to cool at room temperature and poured into crushed ice. The yellow solid thus separated out was filtered, dried, and recrystallized from aqueous ethanol to get the golden yellow crystals of compound **3**. Yield 75%; mp 118 °C. IR (KBr, DRS): ν_{max}/cm^{-1} 2216 (-CN), 3174–3236 (-OH); ^1H NMR

(500 MHz, $CDCl_3$): δ_H (ppm) 1.09 (s, 6H, 2 × Me), 2.23 (s, 2H, C6-H), 2.54 (s, 2H, C4-H), 6.18 (s, 1H, C2-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ_c (ppm) 27.8 (2 × Me), 32.8 (C-5), 42.4 (C-6), 42.5 (C-4), 68.4 [$C(CN)_2$], 100.1 (C-2), 113.6 (CN), 114 (CN), 177 (C-1), 174.7 (C-3). ES-MS, m/z: 187 $[M-1]^+$ (100%). Anal. calcd. for $C_{11}H_{12}N_2O$: C, 70.21; H, 6.38; N, 14.89. Found: C, 70.05; H, 6.25; N, 14.74.

Preparation of Aza Spiro Derivative (5)

General procedure. A mixture of enylidene malononitrile **3** (2 mmol), sodium acetate (2 mmol), and appropriate bidentates thiourea, thioacetamide, thiosemicarbazide, urea, semicarbazide, guanidine hydrochloride (2 mmol) was refluxed in acetic acid (15 ml) on an oil bath at 150 °C for 6 h. The reaction set was allowed to cool at room temperature and the solution was poured into crushed ice and neutralized with $NaHCO_3$ solution. The solid thus separated out was filtered, dried, and recrystallized from ethanol.

2-Amino-8-hydroxy-10,10-dimethyl-4-oxo-1-thia-3-aza-spiro[5.5]undeca-2,7-diene-5-carbonitrile (5a). Yield 82%; mp 158 °C. IR (KBr, DRS): ν_{max}/cm^{-1} 1658 (-C=O), 2196 (-CN), 3209 (-NH_2), 3346(-OH);^1H NMR (400 MHz, DMSO): δ_H(ppm) 1.08 (s, 6H, 2 × Me), 2.26 (d, 2H, $J = 21$ Hz, 1 × C9-H, 1 × C11-H), 2.51 (d, 2H, $J = 21$ Hz, 1 × C9-H, 1 × C11-H), 5.97 (s, 1H, C5-H), 6.17 (s, 1H, C7-H); ^{13}C NMR (100 MHz, DMSO): δ_c(ppm) 27.3 (Me), 27.4 (Me), 31.8 (C-9), 32.5 (C-10), 41.4 (C-11), 48.6 (C-5), 54.3 (C-6), 94.9 (C-7), 117.3 (CN), 117.9 (C-2), 168.2 (C-8), 169.1 (C-4). ES-MS, m/z: 265 $[M]^+$ (100%). Anal. calcd. for $C_{12}H_{13}N_3O_2$: C, 54.34; H, 5.66; N, 15.85. Found: C, 54.09; H, 5.39; N, 15.60.

8-Hydroxy-2,10,10-trimethyl-4-oxo-1-thia-3-aza-spiro[5.5]undeca-2,7-diene-5-carbonitrile (5b). Yield 76%; mp 264 °C. IR (KBr, DRS): ν_{max}/cm^{-1} 1647 (-C=O), 2212 (-CN), 3340 (-OH);^1H NMR (400 MHz, DMSO): δ_H(ppm) 1.00 (s, 6H, 2 × Me), 2.24–2.55 (m, 4H, 2 × C9-H, 2 × C11-H), 2.70 (s, 3H, Me), 5.77 (s, 1H, C5-H), 8.29 (s, 1H, C7-H), 12.20 (bs, 1H, OH); ^{13}C NMR (100 MHz, DMSO): δ_c(ppm) 27.2 (Me), 27.3 (Me), 27.4 (Me), 31.8 (C-9), 32.5 (C-10), 41.4 (C-11), 48.6 (C-5), 54.3 (C-6), 94.9 (C-7), 115.6 (CN), 116.1 (C-2), 168.1 (C-8), 169.1(C-4). ES-MS, m/z: 263 $[M-1]^+$ (100%). Anal. calcd. for $C_{13}H_{16}N_2O_2S$: C, 59.09; H, 6.06; N, 10.61. Found: C, 58.84; H, 5.80; N, 10.33.

2-Hydrazino-8-hydroxy-10,10-dimethyl-4-oxo-1-thia-3-aza-spiro[5.5]undeca-2,7-diene-5-carbonitrile (5c). Yield 79%; mp 195 °C. IR (KBr, DRS): ν_{max}/cm^{-1} 1687 (-C=O), 2208 (-CN), 3240, 3284 (-NH, -NH_2);^1H NMR (400 MHz, DMSO): δ_H(ppm) 0.99 (s, 6H, 2 × Me), 2.27–2.47 (m, 4H, 2 × C9-H, 2 × C11-H), 5.68 (bs, 2H, NH_2), 5.97 (s, 1H, C5-H), 6.3 (s, 1H, C7-H), 10.54 (bs, 1H, NH), 10.95 (bs, 1H, OH); ^{13}C NMR (100 MHz, DMSO): δ_c(ppm) 27.3 (Me), 27.4 (Me), 31.8 (C-9), 32.5 (C-10), 41.4 (C-11), 48.7 (C-5), 54.2 (C-6), 94.3 (C-7), 117.3 (CN), 118 (C-2), 168.2 (C-8), 170 (C-4). ES-MS, m/z: 279 $[M-1]^+$ (100%). Anal. calcd. for $C_{12}H_{16}N_4O_2S$: C, 51.43; H, 5.71; N, 20.00. Found: C, 51.16; H, 5.50; N, 19.75.

2-Amino-8-hydroxy-10,10-dimethyl-4-oxo-1-oxa-3-aza-spiro[5.5]undeca-2,7-diene-5-carbonitrile (5d). Yield 80%; mp 245 °C. IR(KBr, DRS): ν_{max}/cm^{-1}

1662 (-C=O), 2202 (-CN), 3215 (-NH_2), 3344 (-OH);^{1}H NMR (400 MHz, DMSO): δ_H (ppm) 1.03 (s, 6H, 2 × Me), 2.22 (d, 2H, $J = 21$ Hz, 1 × C9-H, 1 × C11-H), 2.48 (d, 2H, $J = 21$ Hz, 1 × C9-H, 1 × C11-H), 5.98 (s, 1H, C5-H), 6.22 (s, 1H, C7-H); ^{13}C NMR (100 MHz, DMSO): δ_c (ppm) 27.7 (Me), 27.7 (Me), 32 (C-9), 32.3 (C-10), 41 (C-11), 47.1 (C-5), 56.2 (C-6), 100 (C-7), 117 (CN), 118 (C-2), 168.2 (C-8), 170 (C-4). ES-MS, m/z: 249 $[M]^+$ (100%). Anal. calcd. for $C_{12}H_{15}N_3O_3$: C, 57.83; H, 6.02; N, 16.87. Found: C, 57.55; H, 5.78; N, 16.59.

2-Hydrazino-8-hydroxy-10,10-dimethyl-4-oxo-1-oxa-3-aza-spiro[5.5]undeca-2,7-diene-5-carbonitrile (5e). Yield 75%; mp 200 °C. IR (KBr, DRS): ν_{max}/cm^{-1} 1699 (-C=O), 2208 (-CN), 3269 (-NH, -NH_2), 3469 (-OH);^{1}H NMR (400 MHz, DMSO): δ_H (ppm) 1.00 (s, 6H, 2 × Me), 2.23–2.41(m, 4H, 2 × C9-H, 2 × C11-H), 5.65 (bs, 2H, NH_2), 5.80 (s, 1H, C5-H), 6.32 (s, 1H, C7-H), 10.57 (bs, 1H, NH), 11.01 (bs, 1H, OH); ^{13}C NMR (100 MHz, DMSO): δ_c(ppm) 27.6 (Me), 27.7 (Me), 32 (C-9), 32.3 (C-10), 41 (C-11), 47.1 (C-5), 56.2 (C-6), 100 (C-7), 117 (CN), 118 (C-2), 168.2 (C-8), 170 (C-4). ES-MS, m/z: 263$[M - 1]^+$ (100%). Anal. calcd. for $C_{12}H_{16}N_4O_3$: C, 54.54; H, 6.06; N, 21.21. Found: C, 54.30; H, 5.82; N, 20.96.

2-Amino-8-hydroxy-10,10-dimethyl-4-oxo-1,3-diaza-spiro[5.5]undeca-2,7-diene-5-carbonitrile (5f). Yield 71%; mp 250 °C. IR (KBr, DRS): ν_{max}/cm^{-1} 1656 (-C=O), 2202 (-C≡N), 3221, 3286 (-NH, -NH_2), 3338 (-OH);^{1}H NMR (400 MHz, DMSO): δ_H(ppm) 0.96 (s, 6H, 2 × Me), 2.19–2.42(m, 4H, 2 × C9-H, 2 × C11-H), 5.67 (bs, 2H, NH_2), 5.85 (s, 1H, C5-H), 6.41 (s, 1H, C7-H), 10.97 (bs, 1H, NH), 11.06 (bs, 1H, OH); ^{13}C NMR (100 MHz, DMSO): δ_c (ppm) 27.6 (Me), 27.7 (Me), 32.2 (C-9), 32.6 (C-10), 41.6 (C-11), 48.7 (C-5), 54.9 (C-6), 95.5 (C-7), 117.4 (CN), 118.1 (C-2), 168.5 (C-8), 169.7 (C-4). ES-MS, m/z: 247$[M - 1]^+$ (100%). Anal. calcd. for $C_{12}H_{16}N_4O_2$: C, 58.06; H, 6.45; N, 22.58. Found: C, 57.80; H, 6.23; N, 22.31.

Preparation of Spiro Derivative (6)

General procedure. A mixture of enylidene malononitrile **3** (2 mmol), sodium acetate (2 mmol), and glycine/or thioglycolic acid (2 mmol) was refluxed in acetic acid (15 ml) on an oil bath at 150 °C for 6 h. The reaction set was allowed to cool at room temperature, and the solution was poured into crushed ice and neutralized with $NaHCO_3$ solution. The solid thus separated out was filtered, dried, and recrystallized from ethanol.

4-Cyano-7-hydroxy-9,9-dimethyl-3-oxo-1-aza-spiro[4.5]dec-6-ene-4-carboxylic acid amide (6a). Yield 80%; mp 230 °C. IR (KBr, DRS): ν_{max}/cm^{-1} 1658 (-C=O), 1737 (-C=O pyrrolidine ring), 2216 (-C≡N), 3280 (-NH_2), 3361 (-OH);^{1}H NMR (400 MHz, DMSO): δ_H (ppm) 0.97 (s, 6H, 2 × Me), 2.30–2.5(m, 4H, 2 × C8-H, , 2 × C10-H), 4.04 (d, 1H, $J = 6$ Hz, 1 × C2-H), 4.13 (d, 1H, $J = 6$ Hz, 1 × C2-H), 5.96(s, 1H, C6-H), 8.67 (t, 1H, $J = 6$ Hz, N1-H), 9.07 (s, 2H, NH_2), 13.07 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO): δ_c (ppm) 27.7 (2 × Me), 32 (C-8), 32.5 (C-9), 41 (C-10), 49 (C-5), 54 (C-2), 67.3 (C-4), 95.3 (C-6), 114 (CN), 167.5 (C-7), 173.6 (C=ONH_2), 200 (C=O). ES-MS, m/z: 263 $[M]^+$ (100%). Anal. calcd. for $C_{13}H_{17}N_3O_3$: C, 59.32; H, 6.46; N, 15.97. Found: C, 59.18; H, 6.33; N, 15.84.

4-Cyano-7-hydroxy-9,9-dimethyl-3-oxo-1-thia-spiro[4.5]dec-6-ene-4-carboxylic acid amide (6b). Yield 63%; mp 215 °C. IR (KBr, DRS): ν_{max}/cm^{-1} 1653 (-C=O), 1724 (-C=O pyrrolidine ring), 2200 (-C≡N), 3199 (-NH_2), 3405 (-OH);^{1}H NMR (400 MHz, DMSO): δ_H (ppm) 0.99 (s, 6H, 2 × Me), 2.13–2.27(m, 4H, 2 × C8-H, 2 × C10-H), 3.72 (s, 2H, C2-H), 5.38 (s, 1H, C6-H), 8.62 (s, 2H, NH_2); ^{13}C NMR (100 MHz, DMSO): δ_c (ppm) 27.3 (2 × Me), 31 (C-8), 31.9 (C-9), 39.9 (C-2), 41 (C-10), 48.2 (C-5), 67.3 (C-4), 95.3 (C-6), 114 (CN), 167.5 (C-7), 173.3 (C=ONH_2), 199.3 (C=O). ES-MS, m/z: 279 $[M-1]^+$ (100%). Anal. calcd. for $C_{13}H_{16}N_2O_3S$: C, 55.71; H, 5.71; N, 10.00. Found: C, 55.43; H, 5.47; N, 9.71.

Preparation of Spiro Derivative (7)

General procedure. A mixture of enylidene malononitrile **3** (2 mmol), sodium acetate (2 mmol), and cyanoacetamide/or 2-cyanomalonohydrazide (2 mmol) was refluxed in acetic acid (15 ml) on an oil bath at 150 °C for 6 h. The reaction set was allowed to cool at room temperature, and the solution was poured into crushed ice and neutralized with $NaHCO_3$ solution. The solid thus separated out was filtered, dried, and recrystallized from ethanol.

8-Hydroxy-10,10-dimethyl-2,4-dioxo-3-azaa-spiro[5.5]undec-7-ene-1,5-dicarbonitrile (7a). Yield 70%; mp 196 °C. IR (KBr, DRS): ν_{max}/cm^{-1} 1662 (-C=O), 2204 (-CN), 3221 (-NH_2), 3342 (-OH);^{1}H NMR (400 MHz, DMSO): δ_H (ppm) 0.97 (s, 6H, 2 × Me), 2.32 (d, 2H, $J = 22$ Hz, 1 × C9-H, 1 × C11-H), 2.49 (d, 2H, $J = 22$ Hz, 1 × C9-H, 1 × C11-H), 5.79 (s, 1H, C1-H & C5-H), 5.96 (s, 1H, C7-H), 8.18 (s, 1H, N3-H), 8.47 (s, 1H, OH). ^{13}C NMR (100 MHz, DMSO): δ_c (ppm) 28 (2 × Me), 32 (C-10), 34.6 (C-11), 45.4 (C-9), 47.5 (C-6), 50.1 (C-1 & C-5), 100 (C-7), 115 (CN), 169.1 (2 × C=O), 172.3 (C-8). ES-MS, m/z: 272 $[M-1]^+$ (100%). Anal. calcd. for $C_{14}H_{15}N_3O_3$: C, 61.54; H, 5.49; N, 15.38. Found: C, 61.43; H, 5.34; N, 15.25.

3-Amino-8-hydroxy-10,10-dimethyl-2,4-dioxo-3-aza-spiro[5.5]undec-7-ene-1,5-dicarbonitrile (7b). Yield 74%; mp 190 °C. IR (KBr, DRS): ν_{max}/cm^{-1} 1674 (-C=O), 2212 (-CN), 3248 (-NH_2), 3450 (-OH);^{1}H NMR (400 MHz, DMSO): δ_H (ppm) 1.00 (s, 6H, 2 × Me), 2.36–2.49 (m, 4H, 2 × C9-H, 2 × C11-H), 5.52 (s, 1H, C1-H & C5-H), 5.81 (s, 1H, C7-H), 6.71 (s, 1H, N3-H), 10.50 (s, 1H, OH). ^{13}C NMR (100 MHz, DMSO): δ_c(ppm) 28 (2 × Me), 32 (C-10), 34.7 (C-11), 45.3 (C-9), 47.7 (C-6), 50 (C-1 & C-5), 100.1 (C-7), 115.1 (CN), 167.9 (2 × C=O), 172.3 (C-8). ES-MS, m/z: 287 $[M-1]^+$ (100%). Anal. calcd. for $C_{14}H_{16}N_4O_3$: C, 58.33; H, 5.56; N, 19.44. Found: C, 58.14; H, 5.32; N, 19.20.

Procedure for Preparation of 1-Hydroxy-5,5-dimethyl-6′-cyano-5′-oxo-3′-phenyl-2′-phenylimino-3′,5′,6′,7′-tetrahydro-2H-spiro[cyclohex-1-ene-3,7′-pyran[2,3-d]thiazole] (8)

A mixture of enylidene malononitrile **3** (1 mmol, 0.19 g), sodium acetate (1 mmol, 0.08 g), and 3-phenyl-2-(phenylimino)thiazolidin-4-one (1 mmol, 0.27 g) was refluxed in acetic acid (15 ml) on an oil bath at 150 °C for 6 h. The reaction set was allowed to cool at room temperature, and the solution was poured into crushed

ice and neutralized with $NaHCO_3$ solution. The straw-yellow-colored solid thus separated out was filtered, dried, and recrystallized from ethanol. Yield 89%; mp 160 °C. IR (KBr, DRS): ν_{max}/cm^{-1} 1724 (-C=O), 2214 (-CN), 3439 (-OH);^{1}H NMR (400 MHz, $CDCl_3$): δ_H (ppm) 0.99 (s, 6H, 2 × Me), 2.47 (s, 2H, C4-H), 2.51 (s, 2H, C6-H), 4.17 (s, 1H, C6′-H), 5.98 (s, 1H, C2-H), 6.86–7.55 (m, 10H, Ph-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_c (ppm) 28 (2 × Me), 34 (C-5), 38.2 (C-4), 42 (C-6), 48 (C-7′), 49.3 (C-6′), 68.2 (C-1′a), 99 (C-2), 115.1 (CN), 116.3, 119.1, 122.9, 127.6, 129.3, 133.2, 140, 149.1 (10 × Ar-C), 156.7 (C-3′a), 161.3 (C-2′), 168.2 (C-5′), 172.3 (C-1). ES-MS, m/z: 456$[M-1]^+$ (100%). Anal. calcd. for $C_{26}H_{23}N_3O_3S$: C, 68.27; H, 5.03; N, 9.19. Found: C, 68.14; H, 4.87; N, 9.04.

Preparation of Spiro Derivative (9)

General procedure. A mixture of enylidene malononitrile **3** (1 mmol), sodium acetate (1 mmol), and barbiturates (barbituric acid, 1,3-diphenyl thiobarbituric acid, or thiobarbituric acid) (1 mmol) was refluxed in acetic acid (15 ml) on an oil bath at 150 °C for 6 h. The reaction set was allowed to cool at room temperature and the solution was poured into crushed ice and neutralized with $NaHCO_3$ solution. The orange colored solid thus separated out was filtered, dried, and recrystallized from ethanol.

1-Hydroxy-5,5-dimethyl-2′,4′-diphenyl-7′-cyano-1′,3′,6′-trioxo-1′,3′,4′,6′,7′-pentahydro-2H-spiro[cyclohex-1-ene-3:8′-pyrano[2,3-d]pyrimidine] (9a). Yield 80%; mp > 300 °C. IR (KBr, DRS): ν_{max}/cm^{-1} 1737, 1691, 1656 (-C=O), 2214 (-CN), 3126–3180, 3385 (-NH), 3468 (-OH);^{1}H NMR (400 MHz, DMSO): δ_H (ppm) 1.25 (s, 6H, 2 × Me), 2.48 (s, 2H, C4-H), 2.25 (s, 2H, C6-H), 4.39 (s, 1H, C7′-H), 6.66 (s, 1H, C2-H), 9.91 (s, 1H, N4′-H), 10.19 (s, 1H, N2′-H), 12.79 (s, 1H, OH). ^{13}C NMR (100 MHz, DMSO): δ_c (ppm) 27.9 (2 × Me), 33.3 (C-5), 43 (C-4), 44.6 (C-6), 51.3 (C-7′), 52.3 (C-8′), 85.9 (C-1′a), 99.3 (C-2), 115 (CN), 150.6 ($C_{3'}=O$), 151 ($C_{4'a}$), 164.2 ($C_{1'}=O$), 169 ($C_{6'}=O$), 172.12 (C-1). ES-MS, m/z: 317 $[M]^+$ (100%). Anal. calcd. for $C_{15}H_{15}N_3O_5$: C, 56.78; H, 4.73; N, 13.25. Found: C, 56.59; H, 4.62; N, 13.09.

1-Hydroxy-5,5-dimethyl-8′-cyano-1′,6′-dioxo-3′-thioxo-1′,3′,4′,6′,7′-pentahydro-2H-spiro[cyclohex-1-ene-3:8′-pyrano[2,3-d]pyrimidine] (9b). Yield 79%; mp > 300 °C. IR (KBr, DRS): ν_{max}/cm^{-1} 1672 (-C=O), 2167 (-CN), 3161, 3356 (-NH), 3531 (-OH);^{1}H NMR (400 MHz, DMSO): δ_H(ppm) 1.26 (s, 6H, 2 × Me), 2.30 (s, 2H, C4-H), 2.08 (s, 2H, C6-H), 4.45 (s, 1H, C7′-H), 6.96 (s, 1H, C2-H), 10.54 (s, 1H, N4′-H), 11.45 (s, 1H, N2′-H), 14.00 (s, 1H, OH). ^{13}C NMR (100 MHz, DMSO): δ_c(ppm) 27.3 (2 × Me), 33.3 (C-5), 42.9 (C-4), 44 (C-6), 50 (C-8′), 51.3 (C-7′), 88.6 (C-1′a), 99.3 (C-2), 115 (CN), 159.9 ($C_{4'a}$), 162 ($C_{1'}=O$), 169.1 ($C_{6'}=O$), 174.9 (C-1), 177.9 ($C_{3'}=S$). ES-MS, m/z: 333 $[M]^+$ (100%). Anal. calcd. for $C_{15}H_{15}N_3O_4S$: C, 54.05; H, 4.50; N, 12.61. Found: C, 53.81; H, 4.25; N, 12.37.

1-Hydroxy-5,5-dimethyl-8′-cyano-1′,6′-dioxo-2′,4′-diphenyl-3′-thioxo-1′,2′,3′,4′,6′,7′-hexahydro-spiro[cyclohex-1-ene-3:8′-pyrano[2,3-d]pyrimidine] (9c). Yield 81%; mp 215 °C. IR (KBr, DRS): ν_{max}/cm^{-1} 1643, 1689 (-C=O), 3280–3300 (-OH);^{1}H NMR (400 MHz, $CDCl_3$): δ_H(ppm) 1.08 (s, 6H, 2 × Me), 2.19 (d, 2H, $J = 20.8$ Hz, 1 × C4-H, 1 × C6-H), 2.50 (d, 2H, $J = 20.8$ Hz, 1 × C4-H,

1 × C6-H), 6.04 (s, 1H, C7′-H), 6.17 (s, 1H, C2-H), 7.12–7.56(m, 10H, PhH), 12.23 (s, 1H, OH). ^{13}C NMR (100 MHz, DMSO): δ_c (ppm) 27.9 (2 × Me), 33.2 (C-5), 42 (C-4), 44 (C-6), 51 (C-8′), 51.2 (C-7′), 79 (C-1′a), 99.6 (C-2), 115.5 (CN), 128–130(closely spaced six peaks), 139, 144 (Ar-C), 156.3 ($C_{4'a}$), 162.2 ($C_{1'}$=O), 169 ($C_{6'}$=O), 173.9 (C-1), 176.3 ($C_{3'}$=S). ES-MS, *m/z*: 484 $[M-1]^+$ (100%). Anal. calcd. for $C_{27}H_{23}N_3O_4S$: C, 66.80; H, 4.74; N, 8.66. Found: C, 66.56; H, 4.53; N, 8.38.

Preparation of Spiro Derivative (10)

General procedure. A mixture of enylidene malononitrile **3** (2 mmol), sodium acetate (2 mmol), and phenyl hydrazine or hydrazinehydrate (2 mmol) was refluxed in acetic acid (15 ml) on an oil bath at 150 °C for 6 h. The reaction set was allowed to cool at room temperature, and the solution was poured into crushed ice and neutralized with $NaHCO_3$ solution. The solid thus separated out was filtered, dried, and recrystallized from ethanol.

7-Hydroxy-9,9-dimethyl-3-oxo-2-phenyl-1,2-diaza-spiro[4.5]dec-6-ene-4-carbonitrile (10a). Yield 71%; mp 190 °C. IR (KBr, DRS): ν_{max}/cm^{-1} 1676 (-C=O), 2206 (-CN), 3275 (-NH & -OH); ^{1}H NMR (400 MHz, DMSO): δ_H (ppm) 1.06 (s, 6H, 2 × Me), 2.08–2.51(m, 2H, 1 × C8-H, 1 × C10-H), 2.71–2.82(m, 2H, 1 × C8-H, 1 × C10-H), 5.75(s, 1H, C4-H), 6.22 (s, 1H, C6-H), 7.09–7.12 (m, 2H, Ph-H), 7.28–7.36(m, 3H, Ph-H), 9.23 (bs, 1H, NH). ^{13}C NMR (100 MHz, DMSO): δ_c (ppm) 28 (2 × Me), 31.6 (C-8), 32 (C-9), 42 (C-10), 46.2 (C-4), 56.5 (C-5), 95.1 (C-6), 117.3 (CN), 134.9, 121.6, 129, 124.4 (Ar-C), 168.9 (C=O), 175.3 (C-7). ES-MS, *m/z*: 296 $[M-1]^+$ (100%). Anal. calcd. for $C_{17}H_{19}N_3O_2$: C, 68.69; H, 6.40; N, 14.14. Found: C, 68.52; H, 6.28; N, 14.02.

7-Hydroxy-9,9-dimethyl-3-oxo-1,2-diaza-spiro[4.5]dec-6-ene-4-carbonitrile (10b). Yield 76%; mp 215 °C. IR (KBr, DRS): ν_{max}/cm^{-1} 1658 (-C=O), 2214 (-CN), 3182, 3338 (-NH), 3379 (-OH); ^{1}H NMR (400 MHz, DMSO): δ_H (ppm) 1.00 (s, 6H, 2 × Me), 2.03–2.45(m, 2H, 1 × C8-H, 1 × C10-H), 2.51–2.67(m, 2H, 1 × C8-H, 1 × C10-H), 5.78 (s, 1H, C4-H), 6.55 (s, 1H, C6-H), 8.61 (bs, 1H, NH), 9.35 (bs, 1H, NH). ^{13}C NMR (100 MHz, DMSO): δ_c (ppm) 28 (2 × Me), 31.6 (C-8), 32.1 (C-9), 41.9 (C-10), 48.4 (C-4), 57.5 (C-5), 96 (C-6), 117.4 (CN), 170 (C=O), 175.3 (C-7). ES-MS, *m/z*: 221 $[M]^+$ (100%). Anal. calcd. for $C_{11}H_{15}N_3O_2$: C, 59.73; H, 6.79; N, 19.00. Found: C, 59.49; H, 6.56; N, 18.73.

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