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A mild and convenient one-pot two-step synthesis of hydroxyiminodihydrobenzofurans mediated by silica gel under microwave activation conditions

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ABSTRACT

A convenient one-pot two-step procedure for the synthesis of hydroxyiminodihydrobenzofurans assisted by microwave irradiation in presence of silica gel is described herein. Cyclic 1,3-dicarbonyl compounds reacted smoothly with various nitroolefins to furnish hydroxyiminodihydrobenzofuran derivatives as the mixture of *E* and *Z* isomers. Clean reaction conditions, no work-up procedure, easy isolation and good yields of the products are the salient features of the methodology.

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1. Introduction

Benzofurans are highly valuable molecular motifs found in various natural products.[1] Most of the compounds containing benzofuran framework exhibit interesting medicinal properties and biological activities.[2] In particular, tetrahydrobenzofurans are an important class of heterocyclic compounds that can be found as components in many life saving drugs. Moreover, these are also extensively utilized as useful building blocks in the preparation of a variety of natural products, such as evodone, pongamol, lanceolatin B, isoeupatin, tubipofurans, and paniculide A.[3]

In the view of their significance, several procedures toward the synthesis of tetrahydrobenzofurans have been investigated for years. The majority of approaches for the synthesis of tetrahydrobenzofurans have been accomplished via ionic or radical pathways through oxidative addition of 1,3-dicarbonyl compounds with the appropriate olefins. Some of these routes employ substituted phenol derivatives as the starting material.[4] The initial report of the base-catalyzed condensation of 1,3-cyclohexadione with β-nitrostyrene and the proposed structure for the product obtained remained unclear.[5] Subsequently, some other groups investigated the same reaction and suggested some probable structures for the above Michael adduct.[6] Later on, Jones and his co-workers successfully obtained the cyclized product of the Michael adduct under mild basic conditions and assigned the correct structure by crystallographic technique.[7] The next development included the synthesis of 3-(4-Bromophenyl)-6,7-dihydro-2-hydroxyiminobenzofuran-4(5*H*)-one from the Michael adduct obtained from nitroolefin and cyclohexane-1,3-dione catalyzed by the mild base.[8] Yoshikoshi and his co-workers studied the reaction of dimedone with aliphatic nitroolefin, which has no α-alkyl substituent (1-nitro-propene). The product obtained was the stereoisomeric mixture of (hydroxyimino)dihydrobenzofurans.[9] Recently, Ishikawa accomplished the synthesis of (hydroxyimino)dihydrobenzofuran derivatives by the conjugative addition of cyclic 1,3-diones with various nitroalkenes.[10] However, most of the procedures employed for the synthesis of (hydroxyimino)dihydrobenzofurans involve the use of complex mixture of basic reagents and also require tedious work-up procedures leading to the generation of a large amount of toxic waste.

Hence, an efficient and more convenient route for the synthesis of (hydroxyimino)dihydrobenzofurans has still remained a task far from perfection. The earlier reported methods suggest the synthesis of (hydroxyimino)dihydrobenzofurans in the presence of basic reagents or catalysts. In continuation of our research work on functionalization of nitroolefins[11] we were interested to investigate the synthesis of (hydroxyimino)dihydrobenzofurans under mild acidic catalyst. In the present days, many reports emerged in the literature the use of silica gel as the vital promoter for various reactions.[12] Moreover, the surface of silica gel is mild acidic[13] in nature, which not only acts as the acidic catalyst but also as an activator for diverse organic transformations.[14] The use of silica gel has been highlighted due to its technical advantages such as high surface area, insolubility in organic and aqueous solvents, thermal, and mechanical stabilities.[15]

Similarly, the application of microwave irradiation is a widely accepted tool in organic synthesis due to its rate enhancements, higher yields and often improved selectivity with respect to conventional reaction conditions.[16] Many reactions with great success have been reported with microwave irradiation.[17] In view of these advantages, we would like to report the one-pot two-step synthesis of hydroxyiminodihydrobenzofurans involving the Michael

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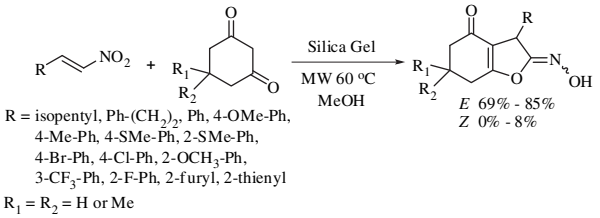
addition of nitroalkenes with 1,3-dicarbonyl compounds followed by intramolecular cyclization in presence of silica gel under microwave irradiation (Scheme 1).



Scheme 1. Synthesis of 2-hydroxyimino-3-substituted-tetrahydrobenzofurans.

2. Results and discussion

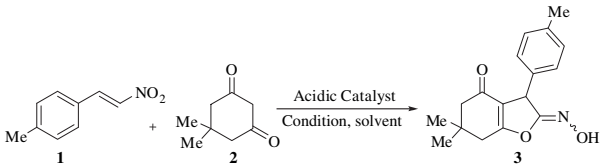
At the outset of our study, we examined the Michael reaction of 1-methyl-4-(2-nitrovinyl)benzene with dimedone (5,5-dimethylcyclohexane-1,3-dione) in aqueous medium under sonication at room temperature conditions. The reaction proceeded well to afford the Michael adduct in quantitative yield. Upon purification of the crude reaction mixture by column chromatography, surprisingly the cyclized product hydroxyiminodihydrobenzofuran of the Michael adduct was obtained. This interesting result further prompted us to investigate the appropriate conditions and the reason for the formation of hydroxyiminodihydrobenzofuran.

We speculated that the mild acidic nature of the silica gel may be the cause to affect the cyclization of the Michael adduct. Hence, we conducted the reaction of 1-methyl-4-(2-nitrovinyl)benzene with dimedone under the same reaction conditions in the presence of silica gel. We were able to obtain quantitative yield of hydroxyiminodihydrobenzofuran as a mixture of isomers (Table 1, entry 1). The ^{1}H NMR spectra of the crude reaction mixture revealed a mixture of *E* and *Z* isomers. The C-3 methine proton of the *E* isomer exhibited a signal at 5.01 ppm and *Z* isomer displayed a signal at 4.93 ppm both in a ratio of (9:1), respectively. The structure assignment (*E* and *Z*) was in accordance with the reported literature.[7]

Encouraged by the above interesting results, we proceeded further to optimize the reaction conditions to study the effect of solvent and mild acidic heterogeneous medium by using the model reaction of nitroolefin **1** and dimedone **2**. When the reaction was performed in presence of silica gel and methanol at room temperature stirring only 30% of the product was obtained in 12 h (Table 1, entry 2). Under sonication conditions, the yield of the product was improved to 80% in 6 h (entry 3). The product yield was drastically increased to 91% upon microwave irradiation with an excellent selectivity of *E*/*Z* (9:1) (Table 1, entry 7). The earlier reported procedures also suggested the formation of *E* isomer of hydroxyiminodihydrobenzofuran as the major product in presence of base.[8] In our study, we were able to obtain the similar products ratios in the presence of mild acidic reagent. Under similar reaction conditions various other mild acidic reagents, such as montmorillonite K-10, Amberlyst-15, and aluminum oxide were tested and found to be ineffective in terms of yields and conversion. Hence, according to Table 1, the best yield of the cyclized Michael adduct was accomplished with the acidic silica gel in methanol under microwave irradiation conditions.

To explore the scope and limitations of this methodology, we conducted the reaction of dimedone with various nitroolefins under the optimized reaction conditions. It is evident from Table 2, that the reaction proceeded smoothly with aliphatic and aromatic

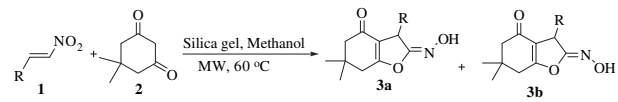
Table 1
Optimization of reaction conditions

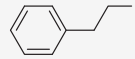
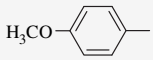
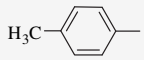
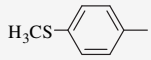
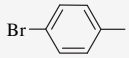
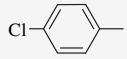
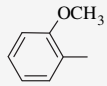
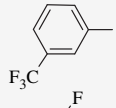
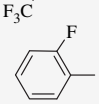


Entry	Acidic catalyst	Solvent	Time (h)	Yield[a] % (*E*:*Z*)
1[c]	Silica gel	Water	10	77 (5:1)
2[b]	Silica gel	Methanol	12	30 (2:1)
3[c]	Silica gel	Methanol	6	80 (7:1)
4[d]	Mont. K-10	Methanol	12	30 (2:1)
5[d]	Amberlyst-15	Methanol	12	45 (3:1.5)
6[d]	Al_2O_3	Methanol	12	40 (3:1)
7[d]	Silica gel	Methanol	4	91 (9:1)
8[d]	—	Methanol	1	Michael adduct

[a] Isolated yields.
[b] Ambient conditions.
[c] Sonication conditions.
[d] Microwave conditions.

Table 2
Synthesis of 3-substituted 6,7-dihydro-2-hydroxy iminobenzofuran-4-(5*H*)-one



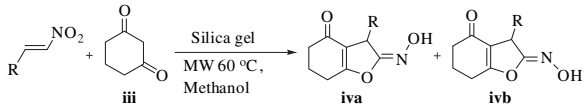
Entry	R	Time (h)	Yield[a] (%)	
			E	*Z*
1		5	68 (**1a**)	—
2		6	74 (**2a**)	—
3		2	82 (**3a**)	8 (**3b**)
4		6	78 (**4a**)	—
5		4	85 (**5a**)	6 (**5b**)
6		5	80 (**6a**)	5 (**6b**)
7		4	81 (**7a**)	—
8		4	68 (**8a**)	—
9		2	76 (**9a**)	6 (**9b**)
10		6	76 (**10a**)	7 (**10b**)
11		1	82 (**11a**)	6 (**11b**)
12		1	78 (**12a**)	—
13		2	69 (**13a**)	—

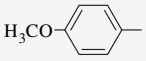
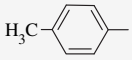
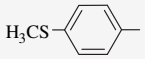
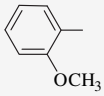
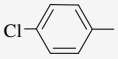
[a] Isolated yields.

nitroolefins. Aliphatic nitroolefin, such as 4-methyl-1-nitropent-1-ene reacted smoothly with dimedone under the present reaction conditions to furnish the corresponding product favoring exclusively the *E* isomer (Table 2, entry 1). The reaction time varied according to the nature of the substituent on the aromatic nitroolefin. For example, the reaction of aromatic nitroolefin containing the electron donating group, such as methyl and methoxy required longer reaction times for the completion of the reaction (entries 4, 5, 7, and 10). Whereas, the reaction of β-nitrostyrenes bearing electron-withdrawing groups, such as bromo, chloro, fluoro, and trifluoromethyl required short reaction times to afford their corresponding dihydroxyiminodihydrobenzofuran-4(5*H*)-ones in good yields (Table 2, entries 8, 9, 11, and 12). Acid sensitive moieties like thiophene also survived under the present reaction conditions.

Similarly, 1,3-cyclohexadione reacted efficiently with various nitroolefins to afford the corresponding products in good yields (Table 3, entries 1–8). The β-diketones to undergo this reaction are dimedone and cyclohexe-1,3-dione. The reaction failed with 1,3-cyclopentadione. It is noteworthy that hydroxyimino dihydobenzofuran derivatives upon long standing on the column silica gel bed undergo slow isomerization to *E* isomer from the *Z* form during the purification process. The single crystal X-ray structure of the *E* and *Z* adducts is shown in Figure 1 and 2, respectively.

Table 3
Synthesis of 3-substituted 3,5,6,7-dihydro-2-hydroxyiminobenzofuran-4(5*H*)-one



Entry	R	Time (h)	Yield[a] (%)	
			E	*Z*
1		5	72 (**14a**)	—
2		4	70 (**15a**)	8 (**15b**)
3		8	82 (**16a**)	5 (**16b**)
4		4	78 (**17a**)	5 (**17b**)
5		5	75 (**18a**)	6 (**18b**)
6		1	80 (**19a**)	6 (**19b**)
7		6	78 (**20a**)	8 (**20b**)
8		2	85 (**21a**)	5 (**21b**)

[a] Isolated yield.

There are also structural limitations in the reactant 1,3-dicarbonyl compounds. Under similar reaction conditions the reaction of β-nitrostyrene with the aliphatic 1,3-dicarbonyl compound, such as pentane-2,4-dione afforded only the Michael adduct in good yeild (Scheme 2). No cylcised adduct was observed with aliphatic 1,3-dicarbonyl substrates. Hence this methodology limits its

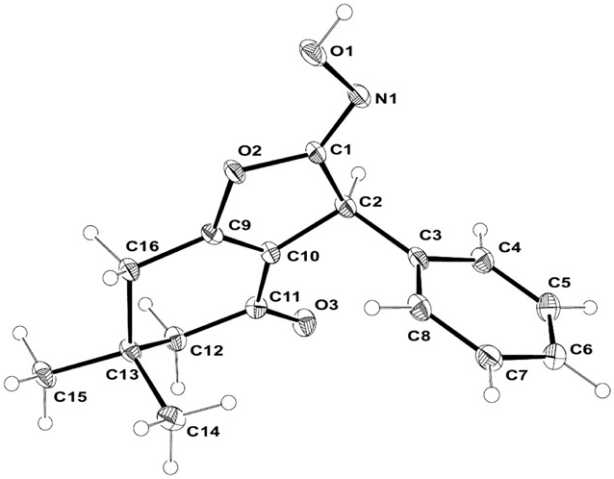


Figure 1. X-ray crystal structure of (*Z*)-2-(hydroxyimino)-6,6-dimethyl-3-phenyl-2,3,6,7-tetrahydrobenzofuran-4(5*H*)-one (ORTEP view).[18]

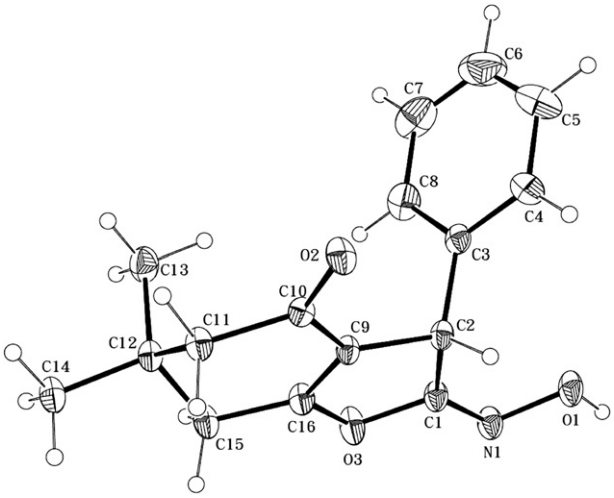
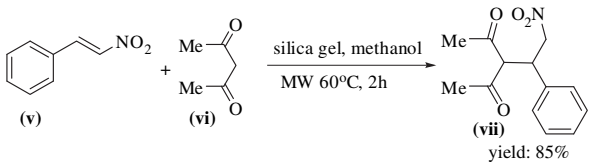


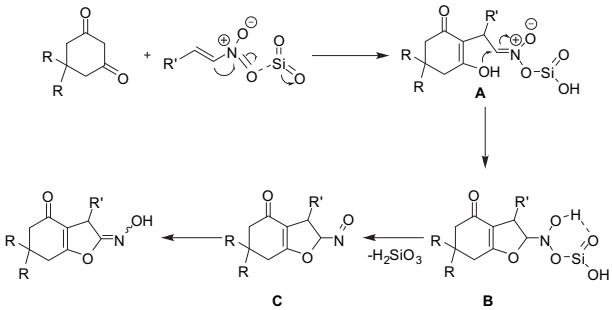
Figure 2. X-ray crystal structure of (*E*)-2-(hydroxyimino)-6,6-dimethyl-3-phenyl-2,3,6,7-tetrahydrobenzofuran-4(5*H*)-one (ORTEP view).[18]

applicability to cyclic β-diketones. The reason may be due to the instability of the cyclized Michael adduct or lesser reactivity of acyclic 1,3-dicarbonyl compounds with the β-nitrostyrene.



Scheme 2. Michael reaction of pentane-2,4-dione and β-nitrostyrene.

One of the major advantages of this protocol is the simple isolation and purification. After completion of the reaction, the silica gel was filtered and the solvent was evaporated to obtain the crude product, which was purified by column chromatography. Hence no work-up procedure was necessary, the silica gel obtained as the residue was washed with methanol for several times and activated in the oven for the next cycle. After each recycle the loss of activity was observed with diminishing product yields.



Scheme 3. Plausible mechanism of the reaction.

We speculate that silica gel may activate the nitro group of nitroalkene thereby generating an electron deficient carbon at 2-position of the β-nitroalkene. This species was attacked by the diketone to form intermediate (A), which undergoes intramolecular cyclization to generate intermediate (B). Intermediate B upon losing H_2SiO_3 molecule to generate nitroso compound (C). This nitroso compound tautomerises to give the 2-hydroxyimino-3-substituted-tetrahydrobenzofuran (Scheme 3).

3. Conclusion

In summary, we have developed a simple and efficient procedure for the synthesis of 2-hydroxyimino-3-substituted-tetrahydrobenzofuran derivatives in the presence of acidic silica gel. Operational simplicity, inexpensive reagents, and good yields of the products are the key advantages over the existing methods.

4. Experimental

4.1. General

All the reactions were performed in oven (130 °C) dried glassware under an inert atmosphere of argon unless otherwise specified. Solvents for extraction and chromatography were distilled before use. All the chemicals used in this study were of commercial grade and used after distillation. Analytical thin layer chromatography was performed with E. Merck silica gel 60 F_{254} aluminum plates. All purifications were carried out by flash chromatography using 230–400 mesh silica gel. ^{1}H and ^{13}C NMR were recorded with Bruker Avance EX 400 FT NMR. Chemical shifts were reported in parts per million (δ) using TMS as internal standard and coupling constants were expressed in hertz. Mass spectra were obtained on a JOEL SX-102A spectrometer at an ionization potential of 70 eV and data are reported as mass/charge (*m*/*z*) with the percent relative abundance. High-resolution mass spectra (HRMS) were acquired with a FINNIGAN MAT-95XL spectrometer. Microwave reactions were carried out in a commercially available monomode system (CEM Discover). The reactor has a variable power output from 0 to 300 W.

4.2. General procedure for the synthesis of 2-hydroxyimino-3-substituted-tetrahydrobenzofurans

A mixture of β-nitrostyrene **1** (1.2 mmol) and 1,3-dicarbonyl compound **2** (1 mmol) was added into a thick walled glass vial containing 500 mg of silica gel and 4 mL of methanol. The reaction mixture in the microwave reactor was heated to 60 °C. The progress of the reaction was monitored by TLC. After completion, methanol was evaporated under reduced pressure. The crude reaction mixture was adsorbed in silica gel and was purified by column chromatography to obtain the pure product. Both the *E* and *Z* isomers were separated by column chromatography.

*4.2.1. (E)-2-(Hydroxyimino)-3-isobutyl-6,6-dimethyl-2,3,6,7-tetrahydrobenzofuran-4(5H)-one (**1a**).* White solid; mp: 145–147 °C. IR (NaCl) ν/cm^{-1}: 3270, 2864, 1628, 1394, 949. ^{1}H NMR (DMSO-d_6) δ 10.35 (s, 1H), 3.70–3.66 (m, 1H), 2.54 (d, *J*=17.6 Hz, 1H), 2.50 (dd, *J*=17.6, 2.2 Hz, 1H), 2.20 (d, *J*=16.0 Hz, 1H), 2.19 (d, *J*=16.0 Hz, 1H), 1.87–1.83 (m, 1H), 1.63–1.56 (m, 1H), 1.52–1.46 (m, 1H), 1.04 (s, 6H), 0.64 (s, 3H), 0.65 (s, 3H). ^{13}C NMR (DMSO-d_6) δ 193.1, 171.0, 156.6, 115.8, 50.7, 40.7, 37.6, 35.8, 33.8, 28.0, 27.7, 24.2, 23.2, 21.5. MS (EI) (*m*/*z*) (relative intensity) 251 (M$^+$, 10), 234 (20), 195 (100), 178 (15). HRMS calcd for $C_{14}H_{21}NO_3$ (M$^+$) 251.1512, found 251.1512.

*4.2.2. (E)-2-(Hydroxyimino)-6,6-dimethyl-3-phenethyl-2,3,6,7-tetrahydrobenzofuran-4(5H)-one (**2a**).* White solid; mp: 130–132 °C. IR (NaCl) ν/cm^{-1}: 3294, 2922, 1639, 951. ^{1}H NMR (DMSO-d_6) δ 10.49 (s, 1H), 7.28–7.23 (m, 2H), 7.18–7.08 (m, 3H), 3.78–3.37 (m, 1H), 2.61–2.57 (m, 2H), 2.56 (d, *J*=17.2 Hz, 1H), 2.52 (dd, *J*=17.2, 2.5 Hz, 1H), 2.19 (d, *J*=16.0 Hz, 1H), 2.21 (d, *J*=16.0 Hz, 1H), 2.02–1.97 (m, 2H), 1.07 (s, 3H), 1.05 (s, 3H). ^{13}C NMR (DMSO-d_6) 193.2, 171.4, 156.2, 141.2, 128.8, 128.1, 128.0, 127.3, 114.9, 50.6, 35.8, 33.7, 32.7, 31.0, 27.9, 27.8. MS (EI) (*m*/*z*) (relative intensity) 299 (M$^+$, 65), 255 (23), 207 (44), 194 (100), 178 (48). HRMS calcd for $C_{18}H_{21}NO_3$ (M$^+$) 299.1516, found 299.1528.

*4.2.3. (E)-2-(Hydroxyimino)-6,6-dimethyl-3-phenyl-2,3,6,7-tetrahydrobenzofuran-4(5H)-one (**3a**).* White solid; mp: 132–134 °C. IR (NaCl) ν/cm^{-1}: 3293, 2869, 1647, 1391, 954. ^{1}H NMR (DMSO-d_6) δ 10.18 (s, 1H), 7.28–7.26 (m, 2H), 7.22–7.20 (m, 3H), 5.01 (s, 1H), 2.74 (d, *J*=17.2 Hz, 1H), 2.62 (dd, *J*=17.2, 2.4 Hz, 1H), 2.21 (d, *J*=16.1 Hz, 1H), 2.15 (d, *J*=16.1 Hz, 1H), 1.08 (s, 3H), 1.06 (s, 3H). ^{13}C NMR (DMSO-d_6) δ 192.4, 172.1, 156.3, 139.0, 128.4, 127.5, 127.1, 115.6, 50.7, 44.8, 35.8, 33.8, 28.0, 27.0. MS (EI) (*m*/*z*) (relative intensity) 272 ((M+1)$^+$, 30), 271 (M$^+$, 100), 254.1 (83), 240 (38). HRMS calcd for $C_{16}H_{17}NO_3$ (M$^+$) 271.1203, found 271.1203.

*4.2.4. (Z)-2-(Hydroxyimino)-6,6-dimethyl-3-phenyl-2,3,6,7-tetrahydrobenzofuran-4(5H)-one (**3b**).* White solid; mp: 154–156 °C. IR (NaCl) ν/cm^{-1}: 3267, 1636, 1391, 1030. ^{1}H NMR (DMSO-d_6) δ 10.46 (s, 1H), 7.32 (t, *J*=7.3 Hz, 2H), 7.24 (t, *J*=7.3 Hz, 1H), 7.19 (d, *J*=6.9 Hz, 2H), 4.93 (s, 1H), 2.74 (d, *J*=17.4 Hz, 1H), 2.64 (dd, *J*=17.4, 2.4 Hz, 2H), 2.27 (d, *J*=16.2 Hz, 1H), 2.21 (d, *J*=16.2 Hz, 1H), 1.08 (s, 3H), 1.06 (s, 3H). ^{13}C NMR (DMSO-d_6) δ 191.7, 172.2, 165.2, 136.5, 128.2, 127.8, 126.8, 116.5, 50.6, 38.8, 35.8, 33.8, 28.1, 27.8.

*4.2.5. (E)-2-(Hydroxyimino)-3-(4-methoxyphenyl)-6,6-dimethyl-2,3,6,7-tetrahydrobenzofuran-4(5H)-one (**4a**).* White solid; mp: 142–144 °C. IR (NaCl) ν/cm^{-1}: 3350, 2803, 1639, 1391, 1030. ^{1}H NMR (DMSO-d_6) δ 10.40 (s, 1H), 7.09 (d, *J*=8.6 Hz, 2H), 6.87 (d, *J*=8.6 Hz, 2H), 4.86 (s, 1H), 3.74 (s, 3H), 2.68 (d, *J*=18.0 Hz, 1H), 2.56 (dd, *J*=17.9, 2.4 Hz, 1H), 2.24 (d, *J*=15.9 Hz, 1H), 2.18 (d, *J*=15.9 Hz, 1H), 1.10 (s, 3H), 1.09 (s, 3H). ^{13}C NMR (DMSO-d_6) δ 192.4, 171.8, 158.3, 156.5, 130.9, 128.5, 115.7, 113.8, 55.0, 50.7, 44.0, 35.8, 33.8, 28.0, 27.9. MS (EI) (*m*/*z*) (relative intensity) 301 (M$^+$, 100), 284 (85), 271 (30), 217 (10). HRMS calcd for $C_{17}H_{19}NO_4$ (M$^+$) 301.1304, found 301.1301.

*4.2.6. (E)-2-(Hydroxyimino)-6,6-dimethyl-3-p-tolyl-2,3,6,7-tetrahydrobenzofuran-4(5H)-one (**5a**).* White solid; mp: 178–180 °C. IR (NaCl) ν/cm^{-1}: 3271, 2925, 1636, 1392, 1030. ^{1}H NMR (DMSO-d_6) δ 10.17 (s, 1H), 7.07–7.12 (m, 4H), 4.98 (s, 1H), 2.68 (d, *J*=17.9 Hz, 1H), 2.57 (dd, *J*=17.8, 2.0 Hz, 1H), 2.27 (s, 3H), 2.18 (d, *J*=16.2 Hz, 1H), 2.13 (d, *J*=16.2 Hz, 1H) 1.08 (s, 3H), 1.07 (s, 3H). ^{13}C NMR (DMSO-d_6) δ 191.7, 172.0, 165.3, 135.9, 133.5, 128.7, 127.6, 116.6, 50.6, 44.0, 35.8, 33.8, 28.1, 27.7, 20.5. MS (EI) (*m*/*z*) (relative intensity) 285 (M$^+$, 100), 268 (98), 254 (39), 201 (30). HRMS calcd for $C_{17}H_{19}NO_3$ (M$^+$) 285.1365, found 285.1362.

*4.2.7. (Z)-2-(Hydroxyimino)-6,6-dimethyl-3-p-tolyl-2,3,6,7-tetrahydrobenzofuran-4(5H)-one (**5b**).* White solid; mp: 172–174 °C. IR

(NaCl) ν/cm^{-1}: 3270, 1635, 1391, 1172, 1003. ^{1}H NMR (DMSO-d_6) δ 10.39 (s, 1H), 7.11–7.03 (m, 4H), 4.85 (s, 1H), 2.25 (s, 3H), 2.69 (d, J=17.9 Hz, 1H), 2.52 (dd, J=17.8, 2.0 Hz, 1H), 2.22 (d, J=16.1 Hz, 1H), 2.20 (d, J=16.1 Hz, 1H), 1.11 (s, 3H), 1.09 (s, 3H). ^{13}C NMR (DMSO-d_6) 192.3, 171.9, 156.4, 136.1, 136.0, 128.9, 127.3, 115.7, 50.6, 44.4, 35.8, 33.8, 27.9, 20.5, 14.0.

*4.2.8. (E)-2-(Hydroxyimino)-6,6-dimethyl-3-(4-(methylthio) phenyl)-2,3,6,7-tetrahydrobenzofuran-4(5H)-one (**6a**).* White solid; mp: 162–164 °C. IR (NaCl) ν/cm^{-1}: 3272, 2924, 1635, 1391, 1031. ^{1}H NMR (DMSO-d_6) δ 10.21 (s, 1H), 7.18–7.13 (m, 4H), 4.98 (s, 1H), 2.65 (d, J=17.9 Hz, 1H), 2.56 (dd, J=17.8, 2.0 Hz, 1H), 2.43 (s, 3H), 2.15 (d, J=16.1 Hz, 1H), 2.13 (d, J=16.1 Hz, 1H), 1.07 (s, 3H), 1.05 (s, 3H). ^{13}C NMR (DMSO-d_6) δ 191.8, 172.3, 165.1, 136.4, 133.2, 128.4, 125.8, 116.4, 50.6, 43.9, 35.8, 28.1, 27.8, 14.7. MS (EI) (m/z) (relative intensity) 317 (M$^+$, 100), 300 (22), 253 (30). HRMS calcd for $C_{17}H_{19}NO_3S$ (M$^+$) 317.1080, found 317.1091.

*4.2.9. (Z)-2-(Hydroxyimino)-6,6-dimethyl-3-(4-(methylthio) phenyl)-2,3,6,7-tetrahydrobenzofuran-4(5H)-one (**6b**).* White solid; mp: 147–149 °C. IR (NaCl) ν/cm^{-1}: 3372, 2925, 1638, 1388, 956 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ 10.40 (s, 1H), 7.11 (d, J=8.0 Hz, 2H), 7.04 (d, J=8.0 Hz, 2H), 4.86 (s, 1H), 2.60 (s, 3H), 2.69 (d, J=18.0 Hz, 1H), 2.56 (dd, J=18.0, 2.1 Hz, 2H), 2.24 (d, J=16.0 Hz, 1H), 2.19 (d, J=16.0 Hz, 1H), 1.11 (s, 3H), 1.09 (s, 3H). ^{13}C NMR (DMSO-d_6) 192.3, 172.0, 156.2, 136.8, 135.6, 128.0, 126.1, 115.5, 50.6, 44.3, 35.8, 33.8, 27.9, 14.7.

*4.2.10. (E)-2-(Hydroxyimino)-6,6-dimethyl-3-o-tolyl-2,3,6,7-tetrahydrobenzofuran-4(5H)-one (**7a**).* White solid; mp: 171–173 °C. IR (NaCl) ν/cm^{-1}: 3373, 2945, 1638, 1358, 956 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ 10.40 (s, 1H), 7.19–6.94 (m, 3H), 6.93 (d, J=7.8 Hz, 1H), 2.76 (d, J=18.2 Hz, 1H), 2.56 (dd, J=18.2, 2.3 Hz, 1H), 5.12 (s, 1H), 2.42 (s, 3H), 2.46 (d, J=15.9 Hz, 1H), 2.22 (d, J=15.9 Hz, 1H), 1.14 (s, 3H), 1.10 (s, 3H). ^{13}C NMR (DMSO-d_6) δ 192.3, 172.0, 156.5, 137.3, 135.8, 130.4, 126.9, 126.0, 115.8, 50.6, 41.8, 35.8, 33.9, 28.2, 27.9, 19.3. MS (EI) (m/z) (relative intensity) 285 (M$^+$, 100), 268 (90) 183 (45). HRMS calcd for $C_{17}H_{19}NO_3$ (M$^+$) 285.1359, found 285.1359.

*4.2.11. (E)-3-(4-Bromophenyl)-2-(hydroxyimino)-6,6-dimethyl-2,3,6,7-tetrahydrobenzofuran-4(5H)-one (**8a**).* Brown solid; mp: 142–144 °C. IR (NaCl) ν/cm^{-1}: 3352, 2922, 1637, 1399, 1031 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ 10.25 (s, 1H), 7.47 (d, J=8.4 Hz, 2H), 7.17 (dd, J=8.4 Hz, 2H), 5.04 (s, 1H), 2.66 (d, J=17.8 Hz, 1H), 2.57 (dd, J=17.8, 2.3 Hz, 1H), 2.18 (d, J=16.1 Hz, 1H), 2.14 (d, J=16.1 Hz, 1H), 1.07 (s, 3H), 1.05 (s, 3H). ^{13}C NMR (DMSO-d_6) 191.7, 172.4, 164.7, 136.0, 131.0, 130.0, 119.8, 116.1, 50.6, 43.9, 35.8, 33.8, 28.0, 27.8. MS (EI) (m/z) (relative intensity) 299 (M$^+$, 65), 255 (23), 207 (44), 194 (100), 178 (48). HRMS calcd for $C_{16}H_{16}BrNO_3$ (M$^+$) 349.0308, found 349.0308.

*4.2.12. (E)-3-(4-Chlorophenyl)-2-(hydroxyimino)-6,6-dimethyl-2,3,6,7-tetrahydrobenzofuran-4(5H)-one (**9a**).* White solid; mp: 158–160 °C. IR (NaCl) ν/cm^{-1}: 3166, 2924, 1640, 1391, 1016 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.26 (s, 1H), 7.34 (d, J=8.0 Hz, 2H), 7.23 (dd, J=8.1 Hz, 2H), 5.06 (s, 1H), 2.66 (d, J=17.4 Hz, 1H), 2.57 (dd, J=17.4, 2.2 Hz, 1H), 2.18 (d, J=16.4 Hz, 1H), 2.14 (d, J=16.4 Hz, 1H), 1.07 (s, 3H), 1.06 (s, 3H). ^{13}C NMR (DMSO-d_6) δ 192.4, 172.3, 155.9, 137.9, 131.7, 129.4, 128.4, 115.3, 50.6, 44.1, 35.8, 33.8, 28.0, 27.9. MS (EI) (m/z) (relative intensity) 305 (M$^+$, 100), 288.0 (58), 252.1 (32), 221.0 (38). HRMS calcd for $C_{16}H_{16}ClNO_3$ (M$^+$) 305.0815, found 305.0815.

*4.2.13. (Z)-3-(4-Chlorophenyl)-2-(hydroxyimino)-6,6-dimethyl-2,3,6,7-tetrahydrobenzofuran-4(5H)-one (**9b**).* White solid; mp: 151–153 °C. IR (NaCl) ν/cm^{-1}: 3277, 2924, 1638, 1391, 1031. ^{1}H NMR (DMSO-d_6) δ 10.49 (s, 1H), 7.37 (d, J=8.0 Hz, 2H), 7.20 (d, J=8.0 Hz, 2H), 4.98 (s, 1H), 2.68 (d, J=16.4 Hz, 1H), 2.57 (dd, J=16.4, 2.4 Hz, 1H), 2.28 (d, J=16.2 Hz, 1H), 2.23 (d, J=16.2 Hz, 1H), 1.14 (s, 3H), 1.09 (s, 3H). ^{13}C NMR (DMSO-d_6) 191.7, 172.4, 164.8, 135.5, 131.4, 129.6, 128.4, 116.2, 50.5, 43.8, 35.8, 33.8, 28.0, 27.8.

*4.2.14. (E)-2-(Hydroxyimino)-3-(2-methoxyphenyl)-6,6-di methyl-2,3,6,7-tetrahydrobenzofuran-4(5H)-one (**10a**).* White solid; mp: 149–151 °C. IR (NaCl) ν/cm^{-1}: 3271, 2924, 1638, 1392, 1031. ^{1}H NMR (DMSO-d_6) δ 9.88 (s, 1H), 7.19–7.07 (m, 2H), 6.97–6.83 (m, 2H), 5.75 (s, 1H), 3.72 (s, 3H), 2.59 (d, J=17.4 Hz, 1H), 2.56 (dd, J=17.4, 2.4 Hz, 1H), 2.17 (d, J=15.9 Hz, 1H), 2.11 (d, J=15.9 Hz, 1H), 1.04 (s, 3H), 0.97 (s, 3H). ^{13}C NMR (DMSO-d_6) δ 191.5, 172.1, 165.3, 156.7, 156.5, 130.2, 128.0, 124.9, 120.2, 111.2, 55.5, 50.6, 40.8, 35.9, 33.8, 28.5, 27.0. MS (EI) (m/z) (relative intensity) 302 (M+1, 18), 301 (M$^+$, 65), 284 (100), 228 (15).

*4.2.15. (Z)-2-(Hydroxyimino)-3-(2-methoxyphenyl)-6,6-dimethyl-2,3,6,7-tetrahydrobenzofuran-4(5H)-one (**10b**).* White solid; mp: 181–183 °C. IR (NaCl) ν/cm^{-1}: 3308, 2923, 1643, 1391, 952. ^{1}H NMR (DMSO-d_6) δ 10.18 (s, 1H), 7.24–7.20 (m, 1H), 7.10 (d, J=7.4 Hz, 1H), 6.97 (d, J=8.0 Hz, 1H), 6.89–6.85 (m, 1H), 4.98 (s, 1H), 3.72 (s, 3H), 2.64 (d, J=17.2 Hz, 1H), 2.50 (dd, J=17.2, 2.3 Hz, 1H), 2.17 (d, J=16.0 Hz, 1H), 2.03 (d, J=16.0 Hz, 1H), 1.09 (s, 3H), 1.07 (s, 3H). ^{13}C NMR (DMSO-d_6) δ 192.2, 171.8, 156.7, 156.5, 129.4, 128.4, 126.8, 120.2, 115.0, 111.5, 55.5, 50.7, 40.9, 35.9, 33.8, 28.3, 27.4.

*4.2.16. (E)-2-(Hydroxyimino)-6,6-dimethyl-3-(3-(trifluoro methyl)-phenyl)-2,3,6,7-tetrahydrobenzofuran-4(5H)-one (**11a**).* White solid; mp: 139–141 °C. IR (NaCl) ν/cm^{-1}: 3309, 2933, 1641, 1394, 942. ^{1}H NMR (DMSO-d_6) δ 10.30 (s, 1H), 7.58–7.52 (m, 4H), 5.23 (s, 1H), 2.69 (d, J=16.2 Hz, 1H), 2.59 (dd, J=16.2, 2.2 Hz, 1H), 2.45 (d, J=15.8 Hz, 1H), 2.17 (d, J=15.8 Hz, 1H), 1.08 (s, 3H), 1.06 (s, 3H). ^{13}C NMR (DMSO-d_6) δ 191.8, 172.6, 165.0, 156.0, 136.5, 132.9, 128.7, 127.6 (q, J=2.0 Hz), 126.4 (q, J=6.0 Hz), 125.9 (q, J=272.0 Hz), 115.8, 50.6, 41.2, 35.8, 33.7, 27.9, 27.6. MS (EI) (m/z) (relative intensity) 339 (M$^+$, 100), 322 (62), 255 (38). HRMS calcd for $C_{17}H_{16}FNO_3$ (M$^+$) 339.1077, found 339.1085.

*4.2.17. (E)-3-(2-Fluorophenyl)-2-(hydroxyimino)-6,6-dimethyl-2,3,6,7-tetrahydrobenzofuran-4(5H)-one (**12a**).* White solid; mp: 138–140 °C. IR (NaCl) ν/cm^{-1}: 3307, 2927, 1647, 1374, 956, 759. ^{1}H NMR (DMSO-d_6) δ 10.17 (s, 1H), 7.28–7.23 (m, 2H), 7.13–7.08 (m, 2H), 5.16 (s, 1H), 2.63 (d, J=16.4 Hz, 1H), 2.62 (dd, J=16.4, 2.3 Hz. 1H), 2.19 (d, J=16.0 Hz, 1H), 2.10 (d, J=16.0 Hz, 1H), 1.05 (s, 3H), 1.02 (s, 3H). ^{13}C NMR (DMSO-d_6) δ 191.6, 172.6, 164.6, 159.8 (d, J=244.0 Hz), 130.0 (d, J=13.0 Hz), 128.9 (d, J=8.2 Hz), 124.3, 115.4, 115.0 (d, J=22.0 Hz), 50.5, 38.7, 33.9, 29.3, 28.2, 27.4. MS (EI) (m/z) (relative intensity) 289.0 (M$^+$, 100), 272 (78), 236 (42), 204 (62). HRMS calcd for $C_{16}H_{16}FNO_3$ (M$^+$) 289.1142, found 289.1155.

*4.2.18. (Z)-3-(2-Fluorophenyl)-2-(hydroxyimino)-6,6-dimethyl-2,3,6,7-tetrahydrobenzofuran-4(5H)-one (**12b**).* White solid; mp: 144–146 °C. IR (NaCl) ν/cm^{-1}: 3280, 2923, 1641, 1392, 956. ^{1}H NMR (DMSO-d_6) δ 10.44 (s, 1H), 7.31–7.28 (m, 1H), 7.25–7.21 (m, 1H), 7.21–7.18 (m, 2H), 5.09 (s, 1H), 2.68 (d, J=17.8 Hz, 1H), 2.58 (dd, J=17.8, 2.4 Hz, 1H), 2.19 (d, J=16.4 Hz, 1H), 2.10 (d, J=16.4 Hz, 1H), 1.09 (s, 3H), 1.07 (s, 3H). ^{13}C NMR (DMSO-d_6) δ 191.8, 173.7, 161.2, 157.4 (d, J=243.0 Hz), 129.8, 129.2 (d, J=9.0 Hz), 125.8 (d, J=13.0 Hz), 115.7, 115.5 (d, J=22.0 Hz), 50.5, 38.7, 33.9, 29.3, 28.2, 27.4.

*4.2.19. (E)-2-(Hydroxyimino)-6,6-dimethyl-3-(thiophen-2-yl)-2,3,6,7-tetrahydrobenzofuran-4(5H)-one (**13a**).* Brown solid; mp: 160–162 °C. IR (NaCl) ν/cm^{-1}: 3246, 2854, 1635, 1392, 1030. ^{1}H NMR (DMSO-d_6) δ 10.45 (s, 1H), 7.35 (d, J=4.0 Hz, 1H), 6.95–6.92 (m, 2H),

5.35 (s, 1H), 2.67 (d, J=17.3 Hz, 1H), 2.62 (dd, J=17.3, 2.4 Hz, 1H), 2.24 (d, J=16.0 Hz, 1H), 2.18 (d, J=16.0 Hz, 1H), 1.10 (s, 3H), 1.09 (s, 3H). ^{13}C NMR (DMSO-d_6) δ 192.1, 173.1, 164.1, 138.9, 127.0, 126.9, 125.1, 116.4, 51.0, 36.3, 34.3, 28.8, 27.9. MS (EI) (m/z) (relative intensity) 277 (M^+, 58), 260 (100), 247 (30). HRMS calcd for $C_{14}H_{15}NO_3S$ (M^+) 277.0765, found 277.0766.

*4.2.20. (E)-2-(Hydroxyimino)-3-isobutyl-2,3,6,7-tetrahydro benzofuran-4(5H)-one (**14a**).* White solid; mp: 138–140 °C. IR (NaCl) ν/cm^{-1}: 3265, 2945, 1627, 1395, 949. ^{1}H NMR (DMSO-d_6) δ 10.35 (s, 1H), 3.67–3.64 (m, 2H), 2.30–2.26 (m, 2H), 2.01–1.98 (m, 2H), 1.90–1.86 (m, 1H), 1.64–1.57 (m, 1H), 1.50–1.45 (m, 2H), 0.85 (s, 3H), 0.84 (s, 3H). ^{13}C NMR (DMSO-d_6) δ 193.6, 172.3, 156.3, 117.1, 40.8, 37.7, 36.4, 24.1, 23.1, 22.8, 20.9. MS (EI) (m/z) (relative intensity) 224 (M+1, 38), 206 (22), 166 (100), 149 (43), 136 (18). HRMS calcd for $C_{12}H_{17}NO_3$ 223.1208, found 223.1210.

*4.2.21. (E)-2-(Hydroxyimino)-3-phenyl-2,3,6,7-tetrahydro benzofuran-4(5H)-one (**15a**).* White solid; mp: 149–151 °C. IR (NaCl) ν/cm^{-1}: 3272, 2922, 1634, 1361, 1003 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.17 (s, 1H), 7.29–7.17 (m, 5H), 4.98 (s, 1H), 2.79–2.69 (m, 2H), 2.32–2.26 (m, 2H), 2.06–1.98 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 192.3, 172.6, 164.9, 136.4, 128.1, 127.9, 126.8, 117.7, 44.4, 36.4, 22.4, 20.9. MS (EI) (m/z) (relative intensity) 243 (M^+, 100), 226 (85), 212 (42), 187 (38). HRMS calcd for $C_{14}H_{13}NO_3$ (M^+) 243.0890, found 243.0895.

*4.2.22. (Z)-2-(Hydroxyimino)-3-phenyl-2,3,6,7-tetrahydro benzofuran-4(5H)-one (**15b**).* White solid; mp: 155–157 °C. IR (NaCl) ν/cm^{-1}: 3367, 2921, 1643, 1391, 955. ^{1}H NMR (DMSO-d_6) δ 10.40 (s, 1H), 7.65–7.17 (m, 5H), 4.87 (s, 1H), 3.29–2.69 (m, 2H), 2.52–2.33 (m, 2H), 2.12–1.98 (m, 1H). ^{13}C NMR (DMSO-d_6) δ 192.3, 172.6, 164.9, 136.4, 128.1, 127.9, 126.8, 117.7, 44.4, 36.4, 22.4, 20.9.

*4.2.23. (E)-2-(Hydroxyimino)-3-(4-methoxyphenyl)-2,3,6,7-tetrahydrobenzofuran-4(5H)-one (**16a**).* White solid; mp: 170–172 °C. IR (NaCl) ν/cm^{-1}: 3283, 2928, 1639, 1511, 1391, 955. ^{1}H NMR (DMSO-d_6) δ 10.14 (s, 1H), 7.13 (d, J=8.5 Hz, 2H), 6.82 (d, J=8.4 Hz, 2H), 4.92 (s, 1H), 2.78–2.67 (m, 2H), 2.32–2.26 (m, 2H), 2.04–2.01 (m, 2H). ^{13}C NMR (DMSO-d_6) δ 192.9, 173.4, 158.1, 156.3, 131.5, 128.5, 128.3, 116.9, 113.7, 113.5, 113.1, 55.0, 44.1, 36.5, 22.5, 20.9. MS (EI) (m/z) (relative intensity) 273 (M^+, 100), 256 (70), 243 (24). HRMS calcd for $C_{15}H_{15}NO_5$ (M^+) 273.0996, found 273.0997.

*4.2.24. (Z)-2-(Hydroxyimino)-3-(4-methoxyphenyl)-2,3,6,7-tetrahydrobenzofuran-4(5H)-one (**16b**).* White solid; mp: 145–147 °C. IR (NaCl) ν/cm^{-1}: 3404, 2911, 1636, 1510, 1393, 1172 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ 10.36 (s, 1H), 7.14–7.08 (m, 2H), 6.86–6.81 (m, 2H), 4.81 (s, 1H), 3.71 (s, 3H), 2.74–2.68 (m, 2H), 2.30–2.23 (m, 2H), 2.06–1.98 (m, 2H). ^{13}C NMR (DMSO-d_6) 193.0, 173.5, 165.1, 158.1, 130.9, 128.9, 117.7, 113.5, 55.0, 43.6, 36.4, 22.4, 20.9.

*4.2.25. (E)-2-(Hydroxyimino)-3-p-tolyl-2,3,6,7-tetrahydro benzofuran-4(5H)-one (**17a**).* White solid; mp: 180–182 °C. IR (NaCl) ν/cm^{-1}: 3252, 2918, 1635, 1391, 956. ^{1}H NMR (DMSO-d_6) δ 10.15 (s, 1H), 7.13 (d, J=8.0 Hz, 1H), 7.06 (d, J=8.0 Hz, 1H), 4.95 (s, 1H), 2.79–2.63 (m, 2H), 2.26–2.25 (m, 2H), 2.23 (s, 3H), 2.05–1.99 (m, 2H). ^{13}C NMR (DMSO-d_6) δ 192.3, 173.5, 165.0, 135.9, 133.4, 128.7, 127.7, 117.7, 44.0, 36.4, 22.4, 20.9, 20.6. MS (EI) (m/z) (relative intensity) 257 (M^+, 100), 240 (96), 226 (50), 201 (30). HRMS calcd for $C_{15}H_{15}NO_3$ (M^+) 257.1046, found 257.1045.

*4.2.26. (Z)-2-(Hydroxyimino)-3-p-tolyl-2,3,6,7-tetrahydro benzofuran-4(5H)-one (**17b**).* White solid; mp: 162–163 °C. IR (NaCl) ν/cm^{-1}: 3261, 2918, 1637, 1388, 954. ^{1}H NMR (DMSO-d_6) δ 10.36 (s, 1H), 7.10–7.04 (m, 4H), 4.81 (s, 1H), 2.81–2.69 (m, 2H), 2.34–2.25 (m, 5H), 2.08–2.07 (m, 2H). ^{13}C NMR (DMSO-d_6) δ 192.9, 173.3, 156.2, 136.2, 135.9, 128.7, 127.3, 116.8, 44.5, 36.4, 22.5, 20.9, 20.6.

*4.2.27. (E)-2-(Hydroxyimino)-3-(4-(methylthio)phenyl)-2,3,6,7-tetrahydrobenzofuran-4(5H)-one (**18a**).* White solid; mp: 172–174 °C. IR (NaCl) ν/cm^{-1}: 3283, 2922, 1645, 1391, 953. ^{1}H NMR (DMSO-d_6) δ 10.22 (s, 1H), 7.25–7.12 (m, 4H), 4.98 (s, 1H), 2.78–2.63 (m, 2H), 2.44 (s, 3H), 2.26–2.23 (m, 2H), 2.04–2.02 (m, 2H). ^{13}C NMR (DMSO-d_6) 199.0, 168.4, 148.6, 140.2, 131.7, 130.2, 125.8, 124.5, 87.2, 42.5, 36.6, 19.6, 14.2. MS (EI) (m/z) (relative intensity) 289 (M+1, 100), 272 (85), 236 (30), 205 (80). HRMS calcd for $C_{15}H_{15}NO_3S$ (M^+) 289.0767, found 289.0780.

*4.2.28. (Z)-2-(Hydroxyimino)-3-(4-(methylthio)phenyl)-2,3,6,7-tetrahydrobenzofuran-4(5H)-one (**18b**).* White solid; mp: 163–165 °C. IR (NaCl) ν/cm^{-1}: 3284, 2676, 2945, 1678, 1341, 1093. ^{1}H NMR (DMSO-d_6) δ 10.19 (s, 1H), 7.18–7.16 (m, 4H), 4.95 (s, 1H), 2.74–2.69 (m, 2H), 2.44 (s, 3H), 2.26–2.04 (m, 2H), 2.03–1.98 (m, 2H). ^{13}C NMR (DMSO-d_6) δ 192.3, 173.7, 164.8, 136.4, 133.1, 128.5, 126.1, 125.8, 117.6, 43.9, 36.4, 22.4, 20.9, 14.7.

*4.2.29. (E)-3-(2-Fluorophenyl)-2-(hydroxyimino)-2,3,6,7-tetrahydrobenzofuran-4(5H)-one (**19a**).* White solid; mp: 150–152 °C. IR (NaCl) ν/cm^{-1}: 3386, 2920, 1636, 1392, 1003. ^{1}H NMR (DMSO-d_6) δ 10.16 (s, 1H), 7.28–7.22 (m, 2H), 7.12–7.08 (m, 2H), 5.14 (s, 1H), 2.78–2.70 (m, 2H), 2.25–2.21 (m, 2H), 2.08–2.01(m, 2H). ^{13}C NMR (DMSO-d_6) δ 192.2, 173.9, 164.4, 161.2 (d, J=245.0 Hz), 129.8, 128.8 (d, J=8.0 Hz), 124.3, 123.9 (d, J=13.0 Hz), 116.6, 115.2 (d, J=21.0 Hz), 38.4, 36.3, 22.5, 20.9. MS (EI) (m/z) (relative intensity) 262 (M+1, 20), 261 (M^+, 100), 244 (30), 205 (62). HRMS calcd for $C_{14}H_{12}FNO_3$ (M^+) 261.0796, found 261.0807.

*4.2.30. (Z)-3-(2-Fluorophenyl)-2-(hydroxyimino)-2,3,6,7-tetra hydrobenzofuran-4(5H)-one (**19b**).* White solid; mp: 141–143 °C. IR (NaCl) ν/cm^{-1}: 3274, 2918, 1639, 1390, 957. ^{1}H NMR (DMSO-d_6) δ 10.43 (s, 1H), 7.33–7.27 (m, 1H), 7.24–7.15 (m, 1H), 7.15–7.08 (m, 2H), 5.06 (s, 1H), 2.75–2.69 (m, 2H), 2.30–2.27 (m, 2H), 2.09–1.98 (m, 2H). ^{13}C NMR (DMSO-d_6) δ 193.3, 174.2, 161.7, 159.2 (d, J=244.0 Hz), 130.3, 129.7 (d, J=9.0 Hz), 126.3 (d, J=13.0 Hz), 116.2, 116.1 (d, J=22.0 Hz), 38.6, 36.8, 23.0, 21.4.

*4.2.31. (E)-2-(Hydroxyimino)-3-(2-methoxyphenyl)-2,3,6,7-tetrahydrobenzofuran-4(5H)-one (**20a**).* White solid; mp: 162–163 °C. IR (NaCl) ν/cm^{-1}: 3283, 2917, 1637, 1390, 954. ^{1}H NMR (DMSO-d_6) δ 9.87 (s, 1H), 7.23–7.14 (m, 1H), 7.05 (d, J=8.2 Hz, 1H), 6.96 (d, J=8.2 Hz, 1H), 6.86 (d, J=8.3 Hz, 1H), 5.07 (s, 1H), 3.74 (s, 3H), 2.70–2.63 (m, 2H), 2.27–2.22 (m, 2.H), 2.08–2.01 (m, 2H). ^{13}C NMR (DMSO-d_6) δ 192.2, 173.3, 165.2, 156.8, 129.0, 128.4, 128.0, 120.3, 116.2, 55.8, 38.8, 36.5, 22.5, 21.0. MS (EI) (m/z) (relative intensity) 273 (M^+, 45), 256 (100), 228 (25), 214 (14). HRMS calcd for $C_{15}H_{15}NO_4$ (M^+) 273.0996, found 273.1006.

*4.2.32. (Z)-2-(Hydroxyimino)-3-(2-methoxyphenyl)-2,3,6,7-tetrahydrobenzofuran-4(5H)-one (**20b**).* White solid; mp: 170–171 °C. IR (NaCl) ν/cm^{-1}: 3400, 2921, 1638, 1390, 954. ^{1}H NMR (DMSO-d_6) δ 10.20 (s, 1H), 7.21 (d, J=7.7 Hz, 1H), 7.06 (d, J=7.2 Hz, 1H), 6.97 (d, J=8.2 Hz, 1H), 6.86 (d, J=7.3 Hz, 1H), 4.99 (s, 1H), 3.74 (s, 3H), 2.72–2.63 (m, 2H), 2.27–2.24 (m, 2H), 2.08–2.03 (m, 2H). ^{13}C NMR (DMSO-d_6) δ 192.7, 173.4, 165.1, 156.3, 129.9, 128.0, 127.0, 120.3, 116.2, 111.7, 55.7, 38.8, 36.5, 30.6, 21.0.

*4.2.33. (E)-3-(4-Chlorophenyl)-2-(hydroxyimino)-2,3,6,7-tetrahydrobenzofuran-4(5H)-one (**21a**).* White solid; mp: 145–146 °C. IR (NaCl) ν/cm^{-1}: 3271, 2922, 1637, 1390, 1004. ^{1}H NMR (DMSO-d_6) δ 10.25 (s, 1H), 7.33 (d, J=8.0 Hz, 2H), 7.25 (d, J=8.0 Hz, 2H), 5.02 (s, 1H), 2.74–2.69 (m, 2H), 2.08–2.06 (m, 2H), 2.08–2.03 (m, 2H). ^{13}C

NMR (DMSO-d_6) δ 192.8, 174.4, 165.0, 135.9, 131.9, 130.3, 128.5, 117.8, 44.3, 22.9, 21.4, 21.2. MS (EI) (m/z) (relative intensity) 277 (M^+, 100), 220 (50), 190 (25). HRMS calcd for $C_{14}H_{12}ClNO_3$ (M^+) 277.0500, found 277.0511.

*4.2.34. (Z)-3-(4-Chlorophenyl)-2-(hydroxyimino)-2,3,6,7-tetra hydrobenzofuran-4(5H)-one (**21b**).* White solid; mp: 168–170 °C. IR (NaCl) ν/cm^{-1}: 3272, 2925, 2698, 1638, 1388, 956. ^{1}H NMR (DMSO-d_6) δ 10.15 (s, 1H), 7.13 (d, J=8.4 Hz, 2H), 6.82 (d, J=8.6 Hz, 2H), 4.90 (s, 1H), 2.78–2.67(m, 2H), 2.26–2.23 (m, 2H), 2.04–1.99 (m, 2H). ^{13}C NMR (DMSO-d_6) δ 193.0, 173.9, 164.5, 137.9, 135.4, 131.6, 129.8, 116.4, 44.2, 36.4, 22.5, 20.9.

*4.2.35. 3-(1-Nitro-2-phenylethyl)pentane-2,4-dione (**vii**).* White solid; mp: 100–102 °C. IR (NaCl) ν/cm^{-1}: 2924, 1644, 1375, 1167, 1003. ^{1}H NMR (DMSO-d_6) δ 7.45–7.24 (m, 5H), 4.82–4.73 (m, 2H), 4.09–4.03 (m 1H), 4.65 (d, J=8.0 Hz, 1H), 2.23 (s, 3H), 1.89 (s, 3H). ^{13}C NMR (DMSO-d_6) 201.8, 201.7, 136.9, 128.6, 128.3, 127.7, 78.2, 68.9, 42.9, 30.7, 30.6. HRMS calcd for $C_{13}H_{15}NO_4$ (M^+) 249.1001, found 249.1006.

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18. CCDC number of the *anti* and *syn* adducts are 725383 and 725385 respectively. These data can be obtained free of charge from Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/datarequest/cif.