Synthesis of 5-(4'-Chlorobenzylidene) hydantoin and *N*-3 Substituted 5-(4'-Chlorobenzylidene)-3-Methylhydantoin

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Abstract

5-benzylidenehydantoins are well-known for their various biological activities. Two derivatives were synthesized. Overall, 5-(4'-chlorobenzylidene) hydantoin 2 was synthesized via condensation reaction between hydantoin 4 and 4-chlorobenzaldehyde 6 using ethanolamine 7 as a condensing agent in the mixture of ethanol-water (5:1), under 6 hours reflux. The same treatment was applied to prepare 5-(4'-chlorobenzylidene)-3-methylhydantoin 3, whereby 4 was replaced with 3-methylhydantoin 5 and the reaction took 10 hours longer.

The product of 2 and 3 was obtained by recrystallization from ethanol to yields of 12 % and 34 % respectively. Their physical properties (Mp_2= 292-294 °C and Mp_3= 270.5-273.4 °C) were estimated by melting point determination. Both structures 2 and 3 were identified using UV, IR, HR-TOF-MS ES$^+$, ^{1}H-NMR and ^{13}C-NMR. The results demonstrated a consistency towards 2 and 3 indicating that both compounds were successfully synthesized.

Keywords: Hydantoin, 5-benzylidenehydantoin, base catalyzed condensation reaction.

Introduction

5-benzalhydantoin or 5-benzylidene-imidazolidene-2,4-dione derivatives are well-known for their varied biological activities such as antimicrobal[1], antimycobacterial[2], antifungal[3], antiproliferative[4], anticonvulsant[5], anticancer[6] and antiviral[7] properties.

Several works in the literature that emphasize the synthesis of 5-benzylidenehydantoins have been published many years ago. Conventional methods such as using various acid catalysts: acetic anhydride[8], acetic acid[9], propionic acid[9] and base catalysts; piperidine[10], dietyhlamine[10] and ethanolamine[11] under reflux conditions have been reported obtaining many different yields. Moreover, modern advanced methods such as microwave assistance have also taken a role for developing these compounds [12,13].

The hydantoin moiety and aromatic aldehyde rings have enabled 5-benzylidenehydantoin's unique structure to be modified to produce many analogues, which potentially create a discovery to novel compounds. Considering how these derivatives play such an important role towards the development of medicinal chemistry, this research focuses on synthesizing efforts of two 5-benzalhydantoin derivatives, the structures of which have been modified in hydantoin's ring *N*-3 position using 4-chlorobenzaldehyde 6 as aromatic aldehyde.

Material and Methods

Materials: Hydantoin 4 and 4-chlorobenzaldehyde 6 were obtained commercially while 3-methylhydantoin 5 was obtained via methylation between dimethylsulphate and hydantoin 4 by Kania[14].

Method: Following the method of Eli Lilly Co., hydantoin 4 (5.1 mmol) and 3- methylhydantoin 5 (1 mmol) were dissolved in 5.1 mL and 1.14 mL of water respectively in a separated reflux system. Both mixtures were refluxed and stirred (70°C, oil bath), before sodium bicarbonate was added until the pH of the reaction mixtures was neutralized. Next, 0.45 mL and 0.091 mL of ethanolamine were dropped into the mixtures, as the temperature was warmed to 90°C. Both the reactions were reacted with 4-chlorobenzaldehyde 6 in 1:1 mol ratio which was dissolved in 2-5 mL of ethanol. The reactions were then monitored using thin layer chromatography until the aldehyde reacted. Upon cooling at room temperature, the mixtures gave precipitate which was collected and recrystallized from ethanol.

Data

(i) (*Z*)-5-(4'-chlorobenzylidene)hydantoin: (*Z*)-5-(4'-chlorobenzylidene)hydantoin as white needles (0.14 g, 12 %) m.p. 293-294°C (lit. 294-296°C). UVλ_{max} (MeOH) (ε_{max}): 0.431 (19.910). u_{max}(KBr): 3227, 3050, 1795.2, 1733, 1660.7, 1490,1382, 1190 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.28 (s, 1H), 10.59 (s, 1H), 7.63 (d, *J* = 7.7 Hz, 2H), 7.44 (d, *J* = 7.5 Hz, 2H), 6.40 (s, 1H).^{13}C NMR. (DMSO-d_6, 125 MHz): δ165.08 (C4), δ 155.33 (C2), 132.44 (C1'), 131.60 (C4′), 130.67 (C3′ and C5′), 128.14 (C5), 128.37 (C2′ and C6′) and 106.46 (C7′). Mass spectrum (ES-MS-E$^+$):*m*/*z* 223.0047 (M$^+$[^{35}Cl], 100%), 225.0085 (M$^+$[^{37}Cl], 40%) from $C_{10}H_7N_2O_2Cl$.

(ii) (*Z*)-5-(4'-chlorobenzylidene)-3-methylhydan-toin: (*Z*)-5-(4'-chlorobenzylidene)-3-methylhydantoin as white needles (0.084 g, 34 %) m.p. 270.5-273.4°C (lit. 271-272°C). UV λ_{max} (MeOH) (ε_{max}): 320.20 nm (45.933 x 10^3 M^{-1} cm^{-1}).u_{max}(KBr): 3296, 3050, 3150, 2950, 1715, 1790, 1650, 1456, 602, 475 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.82 (s, 1H), 7.65 (d, *J* = 1.0 Hz, 2H), 7.46 (d, *J* = 7.0 Hz,

2H), 6.52 (s, 1H), 2.96 (s, 3H).^{13}C NMR. (DMSO-d_6, 125 MHz): δ 164.60 (C4), 155.80 (C2), δ133.29 (C1′), δ132.25 (C4′), δ131.55 (C3′ and C5′), δ127.75 (C5), δ129.19 (C2′ and C6') and 108.20 (C7′); δ24.75 (C6). Mass spectrum (ES-MS-E$^+$): *m/z* 235.0269 (lit. = 235.0353) (M$^+$[^{35}Cl], 100%), 237.0250 (lit. = 237.0353) (M$^+$[^{37}Cl], 100%) from $C_{11}H_9N_2O_2Cl$.

Results and Discussion

Synthesis and physical determination: The synthesis of 5-(4'-chlorobenzylidene)-hydantoin 2 and 5-(4'-chlorobenzylidene)-3-methylhydantoin 3 is illustrated in Scheme I. The reactions between *p*-chlorobenzaldehyde 6 and hydantoins 4 and 5 were monitored using TLC silica GF_{254}. Both 2 and 3 differ in their reation time. Hydantoin 2 took six hours long to be produced, but 3, on the other hand took about 10 hours longer than the previous one, to be synthesized. Consequently, both reactions resulted in different yields (table 1). Based on the experiment, taking a longer reaction time would likely produce better yields. Crystal physical properties of 2 and 3 were determined using MP 50 melting point system Mettler Toledo (table 1).

Structure Determination

Ultraviolet spectra: According to table 2, the UV spectrum of compound 2 was observed. The K band was seen in λ_{max}= 319 nm, indicating the structure of 2 has a conjugating system. In addition, the benzenoid ring is representated in 275 nm. The UV spectrum of 3 shared similar observed bands with K and B systems showing 320 nm and 236 nm respectively.

Infrared spectra: Table 3 shows that compound 2 has a specific absorpstion towards its funcitonal groups. First, the strong absorption in 1733 and 1795 cm^{-1} represents its C=O stretching vibrations. Second, the N-H stretching vibration rises to give a strong absorption in 3300 cm^{-1}. Thirdly, compound 2 features α,β-unsaturated ketone moiety which according to Fields et al[15], is strongly absorbed in 1660 cm^{-1}. Lastly, C-H benzene stretching is represented by spectrum overlap in 3050 cm^{-1}. Apparently, the vibration of N-H, C=O and C=C unsaturated in Compound 3 did not appear to differ significantly.

According to the report by Tan et al[16], geometrical isomer of 5-benzylidenehydantoin could be identified using IR. Stretching frequency of C=C exocyclic in (*E*)-5-benzylidenehydantoin seems to be lower than in its (*Z*), recorded at 1635-1640 cm^{-1} for (*E*), while (*Z*) was recorded at 1660-1675 cm^{-1}. Hence, both 2 and 3 are classified to (*Z*) configuration.

Mass Spectra: Both synthesized (2 and 3) compound molecular weights are reported in table 4. Evidently, the presence of chlorine constituents in their structure was proven by separated peaks that have 3:1 signal ratio in their abundance.

^{1}H-NMR: The chemical shift data of 2 and 3 are shown in table 5. In compound 2, hydrogen of amines in *N*-3 and *N*-1 is represented in 11.28 and 10.59 ppm. Logically, due to the anisotropic effect from two carbonyl groups, hydrogen of *N*-3 position gave a lower field signal than that in *N*-1 position. Aryl hidrogen shift in the range span from 7.43-7.64 ppm resulted in the specific double doblet separation signal which indicates the benzene ring is *p*-substituted.

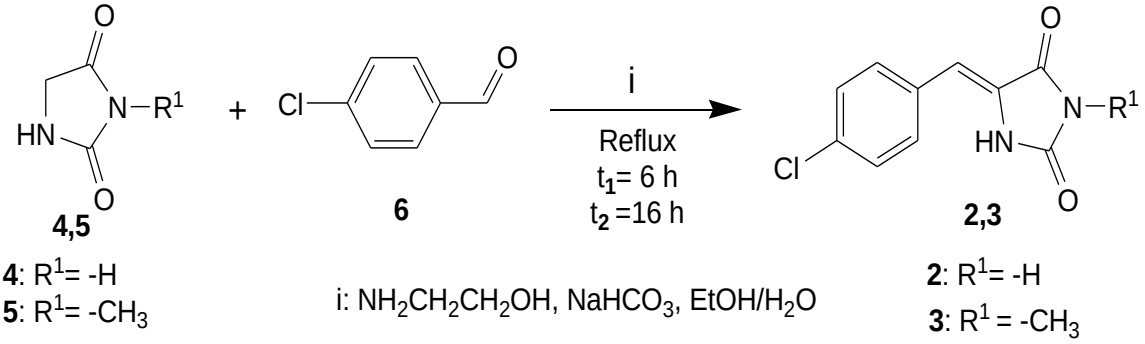
In addition, the chemical shift (δH,ppm) in 7.43 and in 7.45 ppm (*J*= 7.5 Hz) stands for hydrogen which binds to C-2' and C-6'. The chemical shift in 7.62 and in 7.64 ppm (*J*= 7.7 Hz) stands for C-3' and C-5'. The obtained *J* values show that the hydrogen position of C-2' and C-6' are ortho towards those in C-3' and C-5'. The last given signal accounts for 6.4 ppm, which represents the olefinic proton attached to C-7'. Based on this signal, we are able to conclude that the condensation reaction was proven to be sucessful. In compound 3, the addition of methyl group that binds in *N*-3 produces the shielded singlet signal in 2.9 ppm. As for the other groups, the signals shared many similarities with compound 2.

^{1}H-NMR is also able to detect the geometrical isomer (*E* and *Z*) of 5-benzylidenehydantoin caused by exocyclic double bond presence[16]. Anisotropic effect from C=O functional group in C-4 creates a (*Z*) isomer signal (6.40-7.00 ppm) which is a more deshielded signal than its (*E*) isomer (6.20-6.30 ppm)[16]. Hence, we propose that synthesized molecule targets 2 and 3 have a (*Z*) configuration.

^{13}C-NMR: To strenghten our data of the synthesized compound, ^{13}C-NMR analysis was performed. In compound 2, there are eight given signals, which are shown in table 6. Hydantoin moiety showed three separated signals. First, the carbonyl groups in C-4 shifted in 165.4 ppm. Secondly, the C-2 signal shifted in about 10 ppm lower in the magnetic field (155.6 ppm). Thirdly, C-5 of hydantoin is represented by the signal in 128.4 ppm. The carbon signal (δC, ppm) of benzene ring was extended from 128.1 to 132.4 ppm. Both quartener carbons (C_q) in C-1' and C-4' gave the signals in 132.4 and 131.6 ppm respectively. Next, in the same order, C-2' and C-3' shifts were detected in 128.4 ppm and 130.7 ppm. Lastly, hydantoin and benzene rings were connected by sp^2 carbon C-7'. The signal resided at 106.7 ppm. The methylation in *N*-3 of compound 3 added one carbon signal in ^{13}C-NMR spectrum, which was shown in the lowest field (24.3 ppm). Since 2 and 3 have a similar carbon structure, the signal from the other groups in 3 mimicked from signal 2.

Conclusion

The synthesis of 5-(4'-cholrobenzylidene)hydantoin 2 and 5-(4'-chlorobenzylidene)-3-methylhydantoin 3 was succesfully performed via base catalyst condensation reaction and elucidated using UV, IR, HR-TOF-MS ES$^+$, ^{1}H-NMR and ^{13}C-NMR.



Scheme 1: The Synthesis of 2 and 3 compounds (i: ethanolamine, sodium bicarbonate, etanol/water)

Table 1
Physical Properties of Compound 2 and 3.

Compound	Practical Melting Points (°C)	Literature Melting Points (°C)	Practical Mass (g)	Theoritical Mass (g)	Rf
2	292.0-294.0	294-296	0.1404	1.1125	0.625
3	270.5-273.4	271-272	0.1038	0.2360	0.630

Table 2
Ultraviolet Spectra of Compound 2 and 3.

Compound	λ (nm)	A	ε ($dm^3mol^{-1}cm^{-1}$)	Electronic Transistion	Band
2	319.5	0.431	19190.71	π→π*	K
	275	0.232	10330.03	π→π*	B
	268	0.233	10374.56	π→π*	B
3	320.2	0.973	45933	π→π*	K
	236.7	0.354	16758.36	π→π*	B
	201.2	0.377	17797	π→π*	E

Table 3
Infrared Spectra of Compound 2 and 3.

Compound	Functional Groups	ν(cm^{-1})	Intensity	Band Form
2	-NH	3227	Strong	Sharp
	aromatic -C-H	3050	Moderate	Overlap
	-C=O	1733 and 1795	Strong	Sharp
	-C=C sp^2	1660	Strong	Sharp
3	-NH	3296	Strong	Sharp
	Aliphatic -CH	3029.75	Moderate	Sharp
	Aromatic -CH	3114.29	Moderate	Sharp
	-C-H_3	2950	Moderate	Sharp
	-C=O	1715.71	Strong	Sharp
	-C=O	1771.43	Strong	Sharp
	-C=C sp^2	1672	Strong	Sharp
	aromatic -C=C sp^2	1456	Strong	Sharp
	-C-Cl	602	Moderate	Sharp

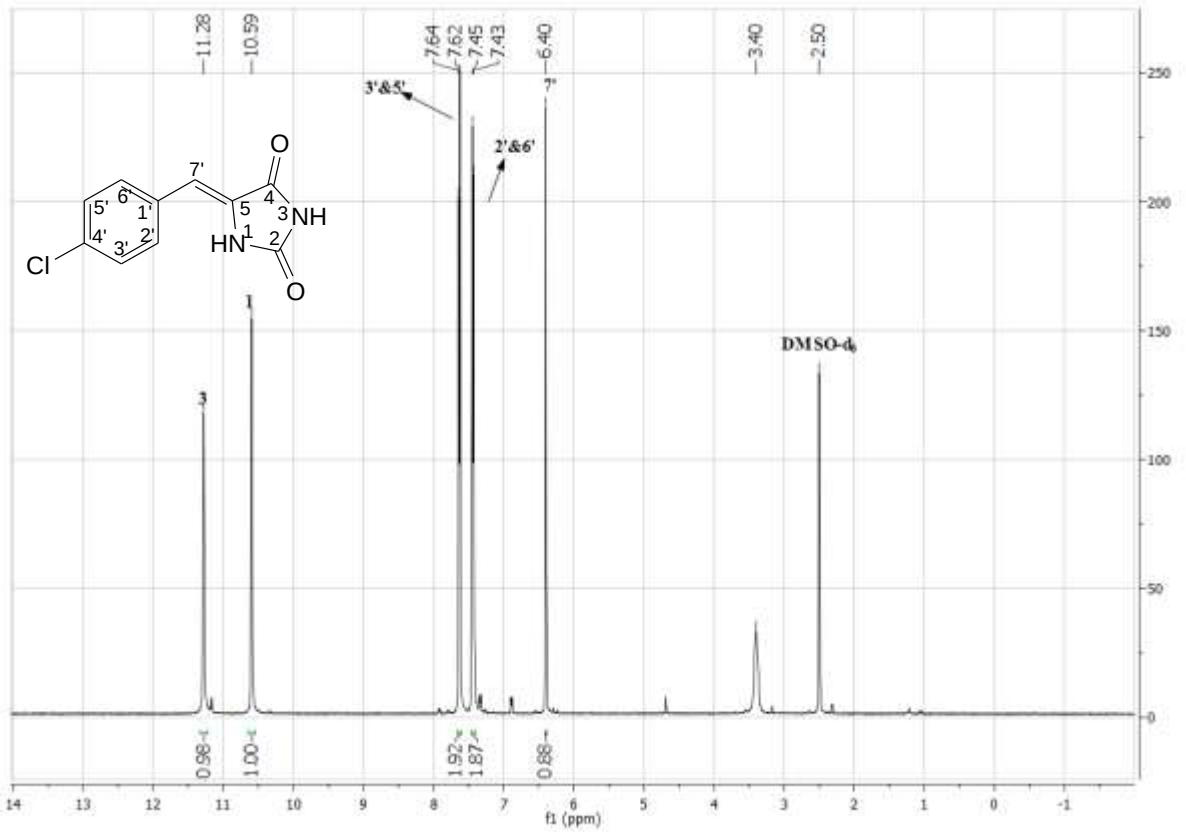


Figure 1: ^{1}H-NMR (500 MHz, DMSO-d$_6$) Spectrum of 5-(4′-chlorobenzylidene) hydantoin

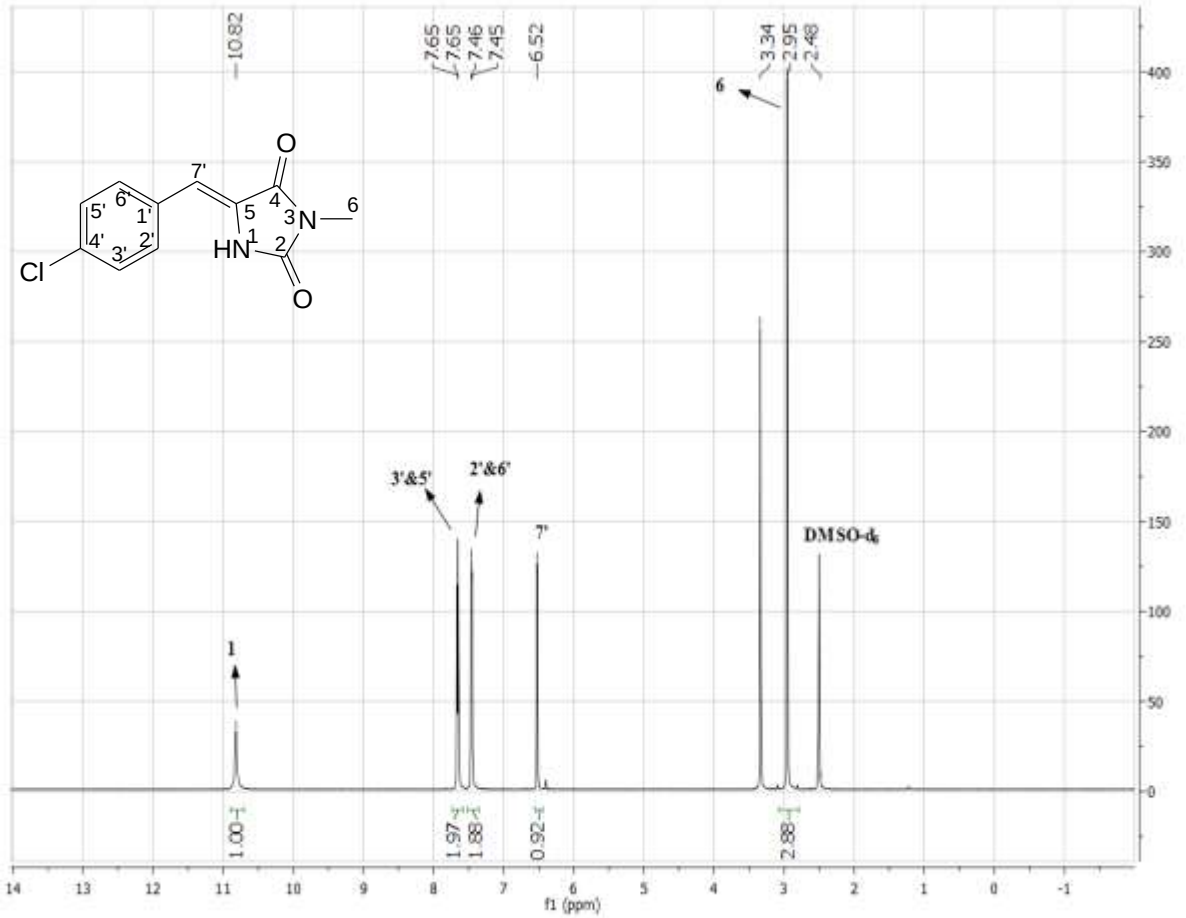


Figure 2: ^{1}H-NMR (500 MHz, DMSO-d$_6$) Spectrum of 5-(4′-chlorobenzylidene)-3-methylhydantoin

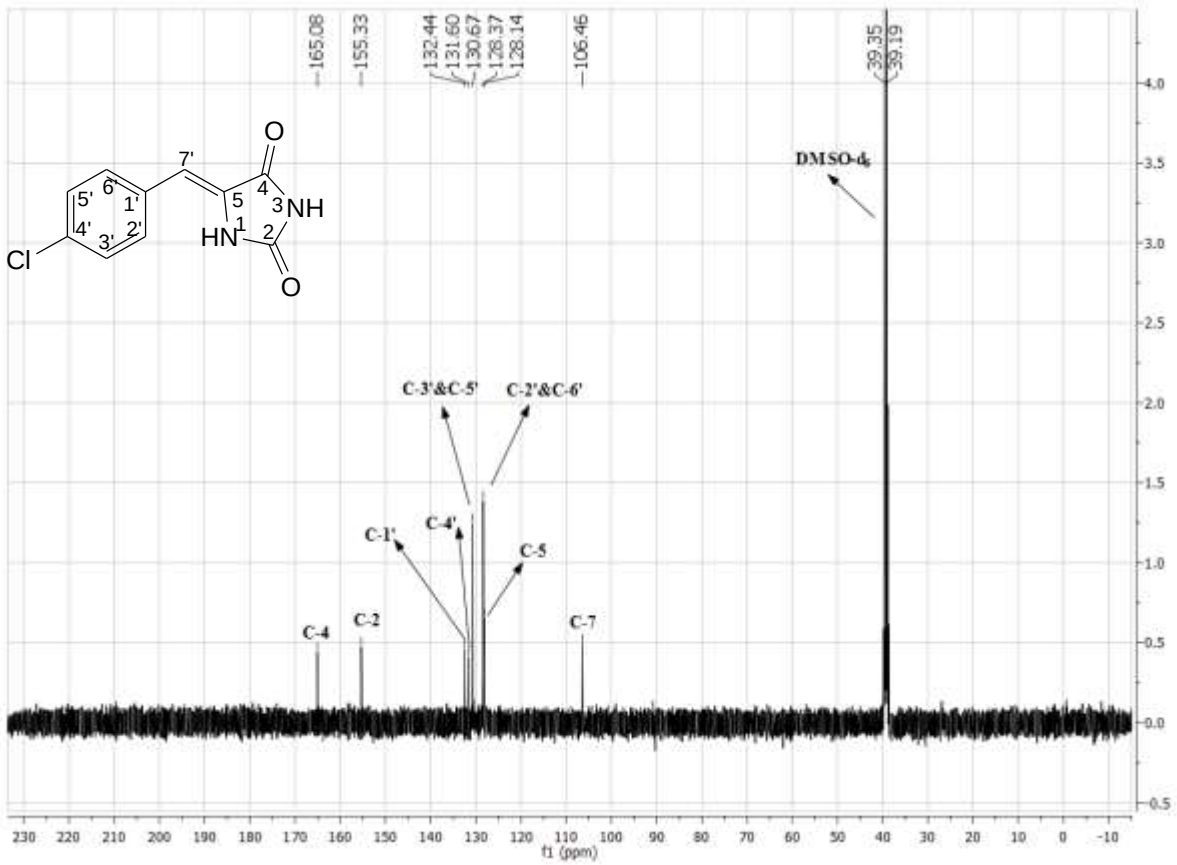


Figure 3: ^{13}C-NMR (125 MHz, DMSO-d_6) Spectrum of 5-(4'-cholrobenzylidene) hydantoin

Table 4
Mass Spectra of Compound 2 and 3.

Compound	(HR-TOF-MS ES$^+$) m/z	Molecular Formula
2	223.0047	$C_{10}H_7[^{35}Cl]N_2O_2$
	225.0085	$C_{10}H_7[^{37}Cl]N_2O_2$
3	235.0269	$C_{11}H_9[^{35}Cl]N_2O_2$
	237.025	$C_{11}H_9[^{37}Cl]N_2O_2$

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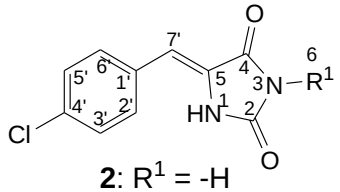
Table 5
^{1}H-NMR Shift of Compound 2 and 3 with DMSO-d_6.



2: R^1 = -H
3: R^1 = -CH_3

Compound	δH (ppm), m, ΣH	Literature[16]	Hydrogen Position[16]
2	6.40, s, 1H	6.40, s, 1H	H-C7’
	7.43-7.45, d, 2H (J=7.5 Hz)	7.42, d, 2H (J=9 Hz)	H$_m$-C2’ and H$_m$-C6’
	7.62-7.64, d, 2H (J=7.7 Hz)	7.65, d, 2H (J=9 Hz)	H$_o$-C3’ and H$_o$-C5’
	10.59, s, 1H	10.56, s, 1H	*N*1-H
	11.28, s, 1H	11.25, s, 1H	*N*3-H
3	2.95, s, 3H	2.96, s. 3H	H$_3$-C6
	6.52, s, 1H	6.49, s, 1H	H-C7’
	7.45-7.46, d, 2H (J=7.0 Hz)	7.41, d, 2H (J=9 Hz)	H$_m$-C2’ and H$_m$-C6’
	7.65, d, 2H (J=1.0 Hz)	7.62, d, 2H (J=9 Hz)	H$_o$-C3’ and H$_o$-C5’
	10.82, s,1H	10.71, s, 1H	*N*1-H

Table 6
^{13}C-NMR Shift of Compound 2 and 3 with DMSO-d_6.

Compound	Carbon Signal	δC (ppm)	δC (ppm)[16]	Functional Groups[16]
2	C-4	165.08	165.3	C=O
	C-2	155.33	155.6	C=O
	C-5	128.14	128.4	Cq sp^2
	C-2’ and C-6’	128.37	130.9	C aryl
	C-3’ dan C-5’	130.67	128.6	C aryl
	C-4’	131.60	131.9	Cq aryl, -C-Cl
	C-1’	132.44	132.8	Cq aryl, -CH sp
	C-7’	106.46	106.7	CH sp^2
3	C4	164.60	164.1	C=O
	C2	155.80	155.3	C=O
	C5	127.75	127.2	CH sp2
	C2’ and C6’	129.19	131.0	C aryl
	C-3’ and C-5’	131.55	128.7	C aryl
	C4’	132.25	131.7	Cq aryl, -C-Cl
	C1’	133.39	133.0	Cq aryl, -CH sp
	C7’	107.72	107.8	CH, sp^2
	C6	24.75	24.2	CH$_3$ sp^3

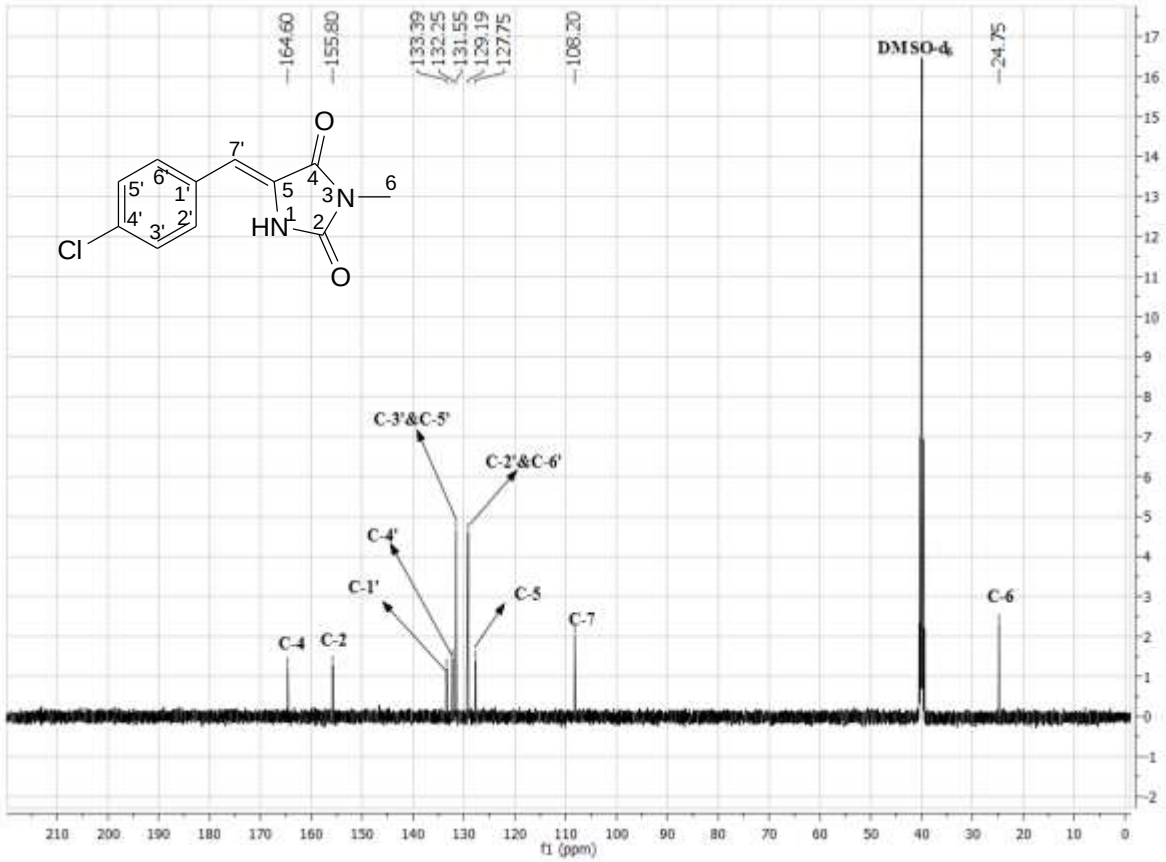


Figure 4: ^{13}C-NMR (125 MHz, DMSO-d_6) Spectrum of 5-(4'-chlorobenzylidene)-3-methylhydantoin

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