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THE PREPARATION AND CHARACTERIZATION OF NINETEEN NEW PHTHALIDYL SPIROHYDANTOINS

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This paper is dedicated to the memory of Professor Ivar Ugi, a great chemist, a noble man and a good friend.

Abstract - Nineteen new *N*,*N*'-disubstituted phthalidyl spirohydantoins **(6a-s)** were prepared for the purpose of pharmacological testing. Their structure was deduced from the IR, ^{1}H-NMR, ^{13}C-NMR, mass spectra and elemental analysis. The two possible structural isomers – only one of which is formed – can be distinguished unequivocally on the basis of selective diastereotopicity of the α-methylene hydrogens adjacent to *N*-3' of the hydantoin ring.

1. INTRODUCTION

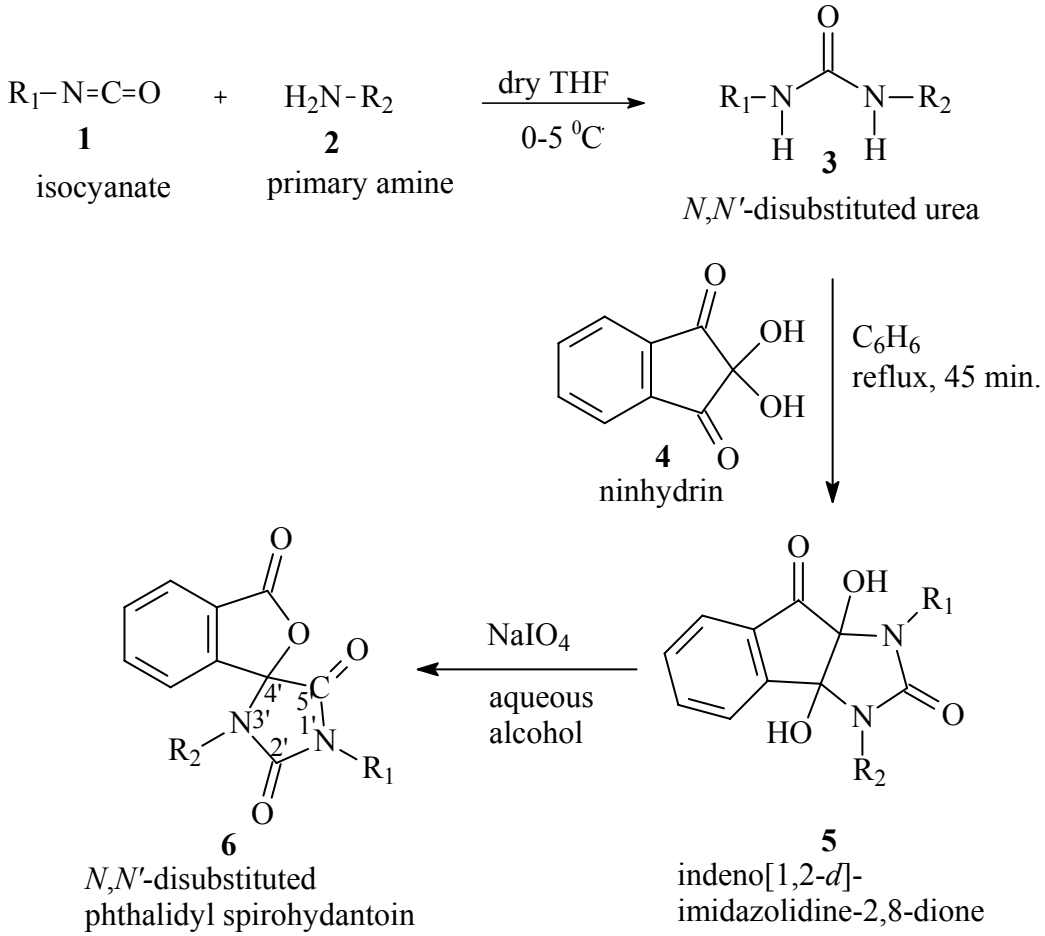
In a short communication some of us recently reported[1] the synthesis and pharmacological activity of thirteen phthalidyl spirohydantoins, albeit without experimental details and without physical and spectral properties of the products. Herein we give full characterization of nineteen new spirohydantoins (**6**, Scheme 1) and detailed experimental procedure of their synthesis.

2. RESULTS AND DISCUSSION

A. Synthesis

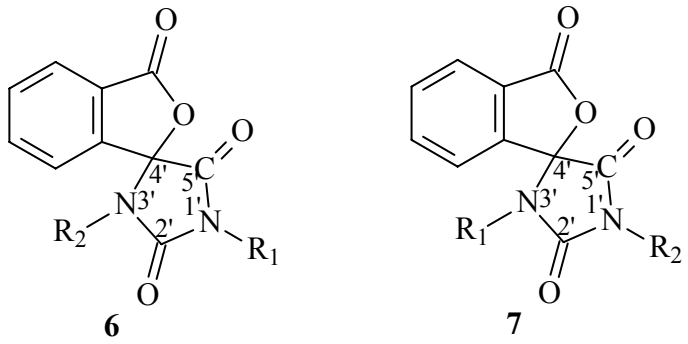
These compounds were synthesized in three previously reported steps, outlined in Scheme 1: the ureas not commercially available were prepared by the addition of a primary amine (**2**) to the appropriately substituted isocyanate (**1**)[2]. The disubstituted ureas (**3**) were then reacted with ninhydrin (**4**) to give indeno[1,2-*d*]imidazolidine-2,8-diones (**5**)[3], the oxidation of which with $NaIO_4$[4] yielding *exclusively one regioisomer* of the *N*,*N*'-disubstituted phthalidyl spirohydantoins (**6**).

Scheme 1. The synthesis of *N,N'*-disubstituted phthalidyl spirohydantoins, **6**.



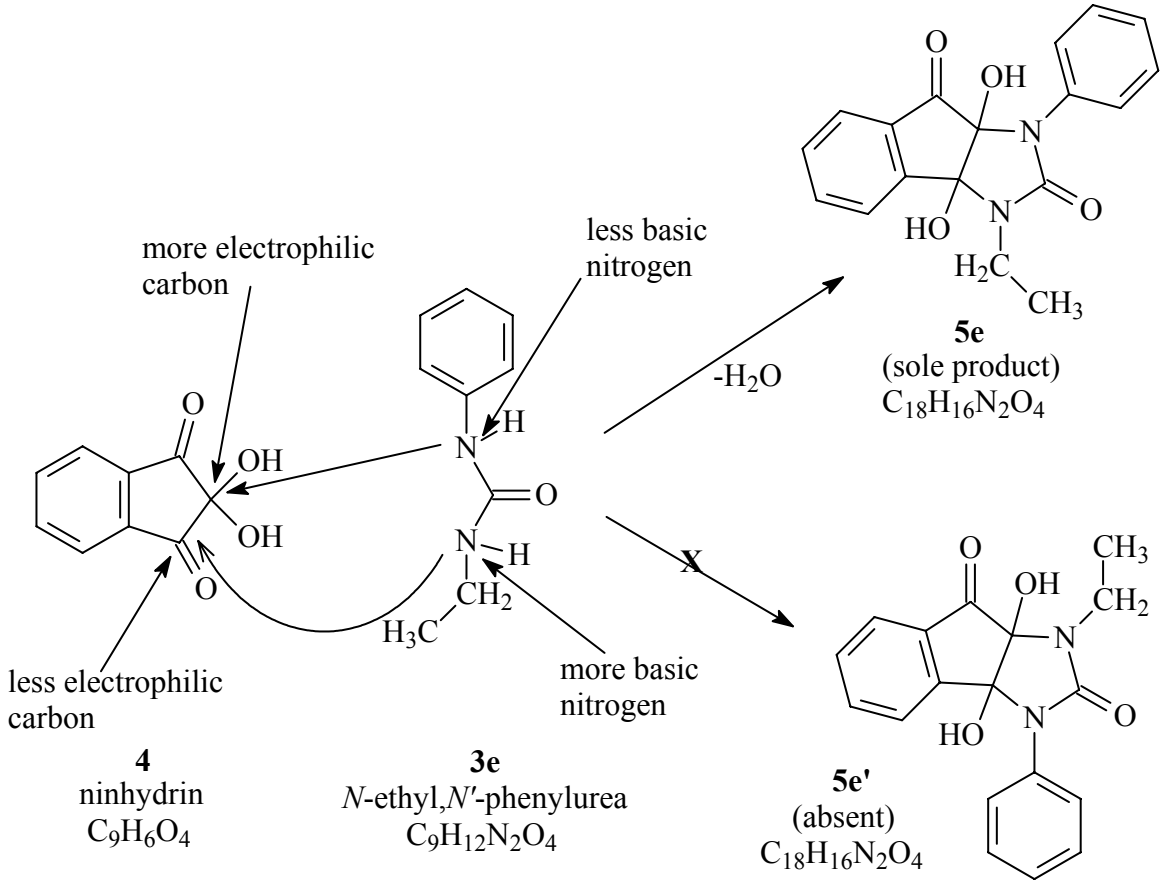
If unsymmetrically substituted ureas ($R_1 \neq R_2$) are used in the synthesis, two structural isomers are possible, **6** and **7** (Scheme 2), which differ from one another only in the site of attachment of the nitrogen substituents. Selective diastereotopicity of the α-methylene hydrogens adjacent to N-3' revealed that the actual structure of the product is **6** (*vide infra*).

Scheme 2. The two possible structures of *N,N'*-disubstituted phthalidyl spirohydantoins, **6** and **7**.



The apparent reason why only one of the two possible structural isomers is formed in the condensation reactions of the ureas with ninhydrin is that, as a rule, the more basic nitrogen of the unsymmetrically disubstituted ureas (**3**) attacks the less electrophilic carbon of ninhydrin (**4**), and the less basic nitrogen attacks the more electrophilic carbon. This principle can be illustrated by the reaction of *N*-ethyl-*N*'-phenylurea (**3e**) with ninhydrin, which gave only adduct **5e**, Scheme 3. No trace of the isomer **5e'** has been detected.

Scheme 3. In the urea-ninhydrin condensation reactions the more basic nitrogen of the urea attacks the less electrophilic carbon of the ninhydrin, giving a single product, eg. **5e**.



We prepared seventeen *N,N'*-disubstituted phthalidyl spirohydantoins by the synthesis outlined in Scheme 1, and recorded their ^{1}H-NMR spectra. All show diastereotopicity in the α-methylene protons attached to *N*-3', while none show diastereotopicity in the α-methylene group attached to *N*-1'. The chemical shift values, signal multiplicities, integration and coupling constants of the α-methylene protons in the 400 MHz ^{1}H-NMR spectra of the seventeen phthalidyl spirohydantoins prepared are listed in Table 1.

Table 1. The chemical shift values , δ (ppm), signal multiplicities, integration and coupling constants, J (Hz), of the α-methylene protons in the 400 MHz ^{1}H-NMR spectra of seventeen *N,N'*-disubstituted phthalidyl spirohydantoins **6**.

			***N-1'*-α-Methylene (R_1)**			***N-3'*-α-Methylene (R_2)**		
Compound No.	**R_1**	**R_2**	**δ ppm**	**multiplicity & integration**	**J (Hz)**	**δ ppm**	**multiplicity & integration**	**J (Hz)**
6a	C_2H_5	C_2H_5	3.65	quartet 2H	7.2	3.06	sextet 1H	7.3
						3.34	sextet 1H	7.3
6b	*n*-C_3H_7	*n*-C_3H_7	3.52	triplet 2H	7.0	2.89	quintet 1H	7.2
						3.29	quinlet 1H	7.4
6c	$CH_2C_6H_5$	$CH_2C_6H_5$	4.77	singlet 2H	N.A.*	4.28	doublet 1H	16.0
						4.49	doublet 1H	16.0
6d	CH_3	C_2H_5				3.00	sextet 1H	7.3
						3.28	sextet 1H	7.4
6e	C_6H_5	C_2H_5				3.14	sextet 1H	7.1
						3.39	sextet 1H	7.1
6f	*o*-F-C_6H_4	C_2H_5				3.15	sextet 1H	7.2
						3.42	sextet 1H	7.3
6g	*m*-F-C_6H_4	C_2H_5				3.13	sextet 1H	7.2
						3.38	sextet 1H	7.2
6h	*p*-F-C_6H_4	C_2H_5				3.14	sextet 1H	7.3
						3.37	sextet 1H	7.3
6i	*p*-O_2N-C_6H_4	C_2H_5				3.16	sextet 1H	7.2
						3.40	sextet 1H	7.3
6j	*p*-CH_3O-C_6H_4	C_2H_5				3.11	sextet 1H	7.1
						3.37	sextet 1H	7.3
6k	CH_3	*n*-C_3H_7				3.00	septet 1H	6.8
						3.36	septet 1H	8.0
6l	C_6H_5	*n*-C_3H_7				2.88	quintet 1H	7.3
						3.26	quintet 1H	8.0
6m	CH_3	$CH_2C_6H_5$				4.34	doublet 1H	15.8
						4.57	doublet 1H	15.8
6n	C_6H_5	$CH_2C_6H_5$				4.24	doublet 1H	16.0
						4.46	doublet 1H	16.0
6o	$CH_2CH_2C_6H_5$	$CH_2C_6H_5$	3.86	triplet 2H	6.9	4.22	doublet 1H	15.9
						4.36	doublet 1H	15.9
6p	C_2H_5	$CH(CH_3)_2$	3.56	quartet 2H	7.2	3.38	septet 1H	6.8
6q	$CH_2C(CH_3)_3$	$CH(CH_3)_2$	3.22	singlet 2H	N.A.*	3.37	septet 1H	6.8

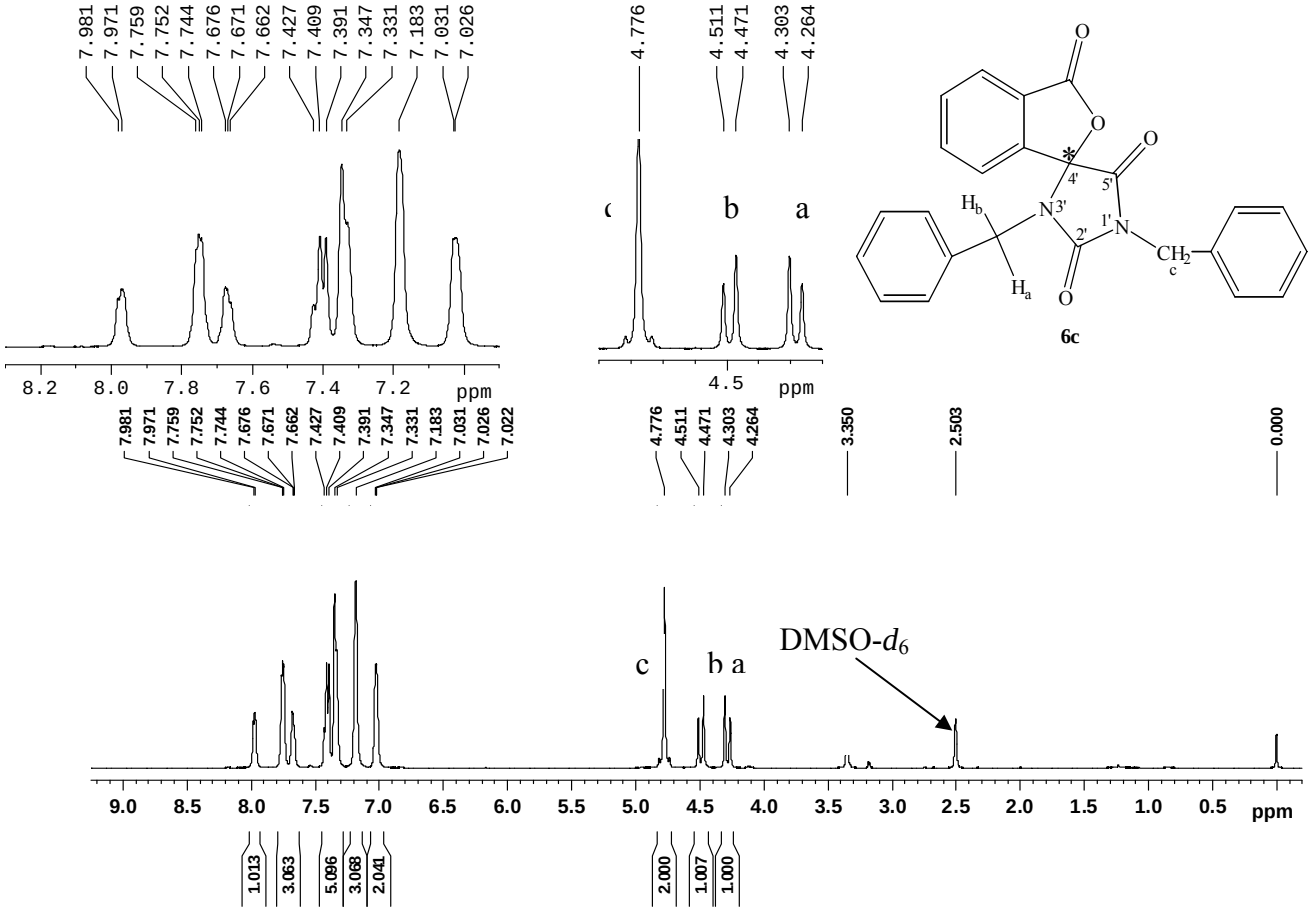
N.A.* = Not applicable

It should be noted that in our spectra none of the spin-spin multiplets of the diastereotopic hydrogens are sufficiently resolved to exhibit the theoretically calculated number of lines. However, this partial

degeneracy of the multiplets of the diastereotopic protons does not hamper interpretation. The phenomenon can perhaps be best illustrated with the dibenzyl derivative **6c**, which does not contain hydrogen-substituted β-alkyl carbons either on R_1 or R_2, its spectrum (Figure 1) therefore is not complicated by additional signal multiplicity.

Figure 1. The 400 MHz ^{1}H-NMR spectrum of *N*-1',*N*-3'-dibenzyl-2'*H*,3*H*,5'*H*-spiro[2-benzofuran-1,4'-imidazolidine]-2',3,5'-trione **6c**.

* chiral center

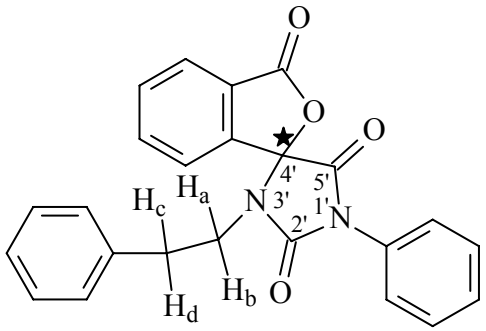


6c

The indeno[1,2-*d*]imidazolidine-2,8-dione intermediates (**5**), all of which contain two chiral centers, also exhibit diastereotopicity. Indeed, both the α- and β-methylene protons, where present, are diastereotopic, *in both the R_1 and R_2 substituents* (compare the ^{1}H-NMR spectra in the Experimental). For this reason, their diastereotopicity cannot be used for structure assignment. The ^{1}H-NMR spectra of those spirohydantoins which contain at least two adjacent methylene groups in R_2 (**6b, 6k, 6l**, **6r** and **6s**), also show diastereotopicity of the β-methylene protons e.g., **6r**, Scheme 4.

Scheme 4. Both the α- and β-methylene protons in *N*-1'-phenyl-*N*-3'-(2-phenylethyl)-2'*H*,3*H*,5'*H*-spiro-[benzofuran-1,4'-imidazolidine]-2',3,5'-trione, **6r**, are diastereotopic.

* chiral center

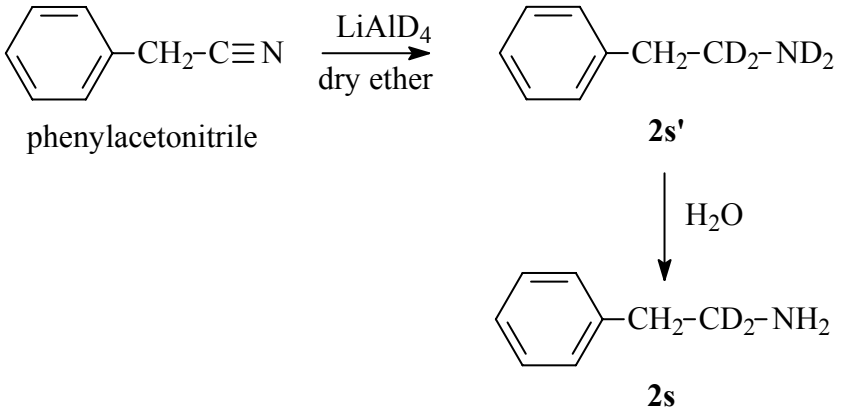


6r

R_2 α-CH_2:
a: 3.28 δ, septet, 1H
b: 3.60 δ, septet, 1H
R_2 β-CH_2:
c: 2.74 δ, sextet, 1H
d: 2.83 δ, sextet, 1H

At this point, the following question arose: would replacement of the two α-hydrogens in **6r** with deuterium affect the diastereotopicity of the β-methylene protons? To address this question, we synthesized *N*-1'-phenyl-*N*-3'-(α,α-dideuterio-2-phenylethyl)-2'*H*,3*H*,5'*H*-spiro[benzofuran-1,4'-imidazolidine]-2',3,5'-trione, **6s**. The required precursor for the synthesis of **6s** was α,α-dideuterio-2-phenylethylamine (**2s**) which was prepared from phenylacetonitrile with $LiAlD_4$ in ether, followed by hydrolysis of the resulting *N*,*N*-α,α-tetradeuterio-2-phenylethylamine (**2s'**) (Scheme 5)[5]. The ^{1}H-NMR spectrum of this compound, **6s**, (Figure 2) shows two symmetrical doublets, centered at 2.71 and 2.80 ppm, respectively, each for one hydrogen, with a coupling constant of 13.5-13.6 Hz, demonstrating that the β-methylene protons retained their diastereotopicity even in the absence of an α-CH_2 group. Simultaneously, the spectrum also proves that the α,α-dideuterio-2-phenylethyl substituent is attached to *N*-3' of the ring and that the structure of **6s** is the one depicted in Figure 2.

Scheme 5. The synthesis of α,α-dideuterio-2-phenylethylamine (**2s**) from phenylacetonitrile.



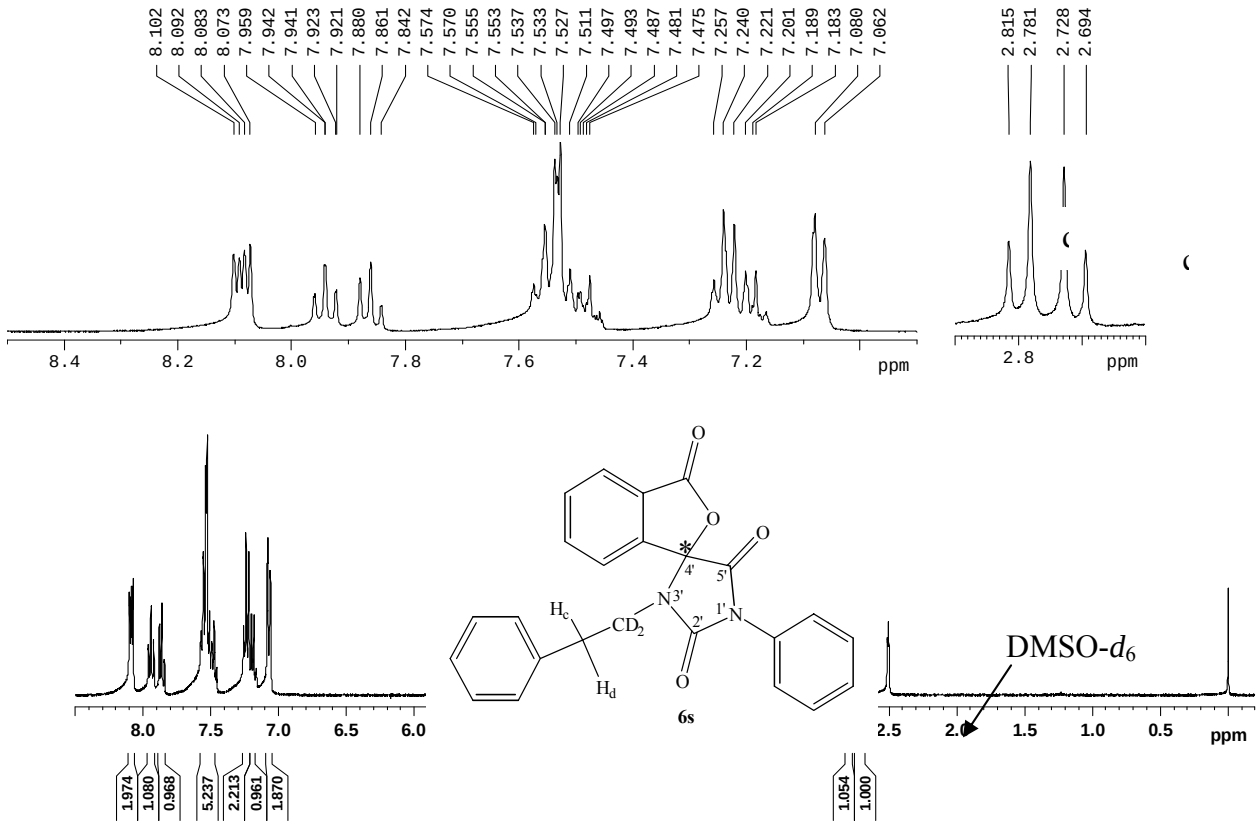
phenylacetonitrile

2s'

2s

Figure 2. The 400 MHz ^{1}H-NMR spectrum of *N*-1'-phenyl-*N*-3'-(α,α-dideuterio-2 phenylethyl)-2'*H*,3*H*,5'*H*-spiro [benzofuran-1,4'-imidazolidine]-2',3,5'-trione, **6s**.

- chiral center



The chemical shift values, signal multiplicities, integration and coupling constants of the five spirohydantoins which contain a β-methylene group in R_2 are listed in Table 2.

Table 2. The chemical shift values , δ (ppm), signal multiplicities, integration and coupling constants, J (Hz), of the β-methylene protons of R_2 in five spirohydantoins, (**6b, 6k, 6l, 6r, 6s**).

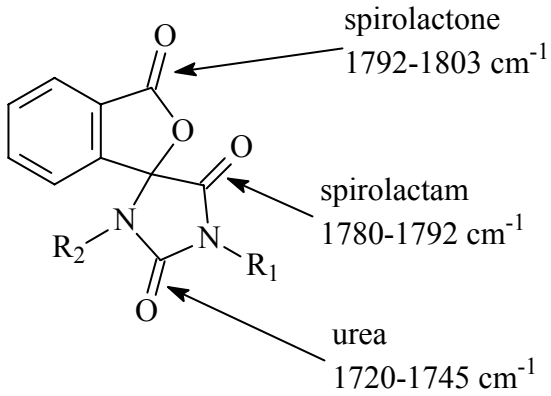
Compound No.	R_1	R_2	δ (ppm)	β-Methylene (R_2) multiplicity & integration	J (Hz)
6b	$CH_2CH_2CH_3$	$CH_2CH_2CH_3$	1.32	dodecet, 2H	7.2
6k	CH_3	$CH_2CH_2CH_3$	1.31	dodecet, 2H	6.9
6l	C_6H_5	$CH_2CH_2CH_3$	1.45	nonet, 2H	7.1
6r	C_6H_5	$CH_2CH_2C_6H_5$	2.74	sextet, 1H	6.9
			2.83	sextet, 1H	7.0
6s	C_6H_5	$CD_2CH_2C_6H_5$	2.71	doublet, 1H	13.6
			2.80	doublet, 1H	13.5

B. Structure Determination

The structure of the spirohydantoins was derived from infrared, NMR, mass spectra and elemental analysis data. All compounds gave satisfactory elemental analysis values, within ± 0.25% of the calculated ones.

A) Infrared Spectra

Scheme 6. The infrared absorption bands of the three carbonyl bonds in spirohydantoins **6**.



As listed in the Experimental section, the three carbonyl groups in the spirohydantoins show absorption bands in the following infrared ranges:

1. α, β-unsaturated γ-spirolactone: 1792-1803 cm^{-1}
2. spirolactam carbonyl: 1780-1792 cm^{-1}
3. urea: 1720-1745 cm^{-1}

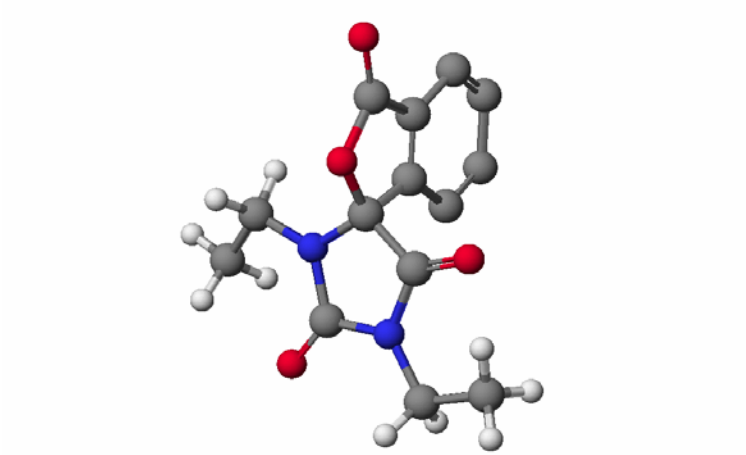
These values are well compatible with the proposed structure.

B) NMR Spectra

Diastereotopicity is well known and has been studied extensively; there are many examples reported in the literature.[6-11] *The decisive criterion is the absence of symmetry elements.* Diastereotopicity occurs when geminal protons have neither a rotation axis, nor a plane of symmetry, nor a center of symmetry, nor a rotation-reflection axis.[11]

Inspection of large molecular models of several spirohydantoins reveals the dissymmetric environment of the α-methylene protons adjacent to *N*-3'. The CACHE® molecular model confirms this (Figure 3). It is harder however, to discern the symmetry element causing the magnetic and stereochemical equivalence of the other α-methylene hydrogens, adjacent to *N*-1'.

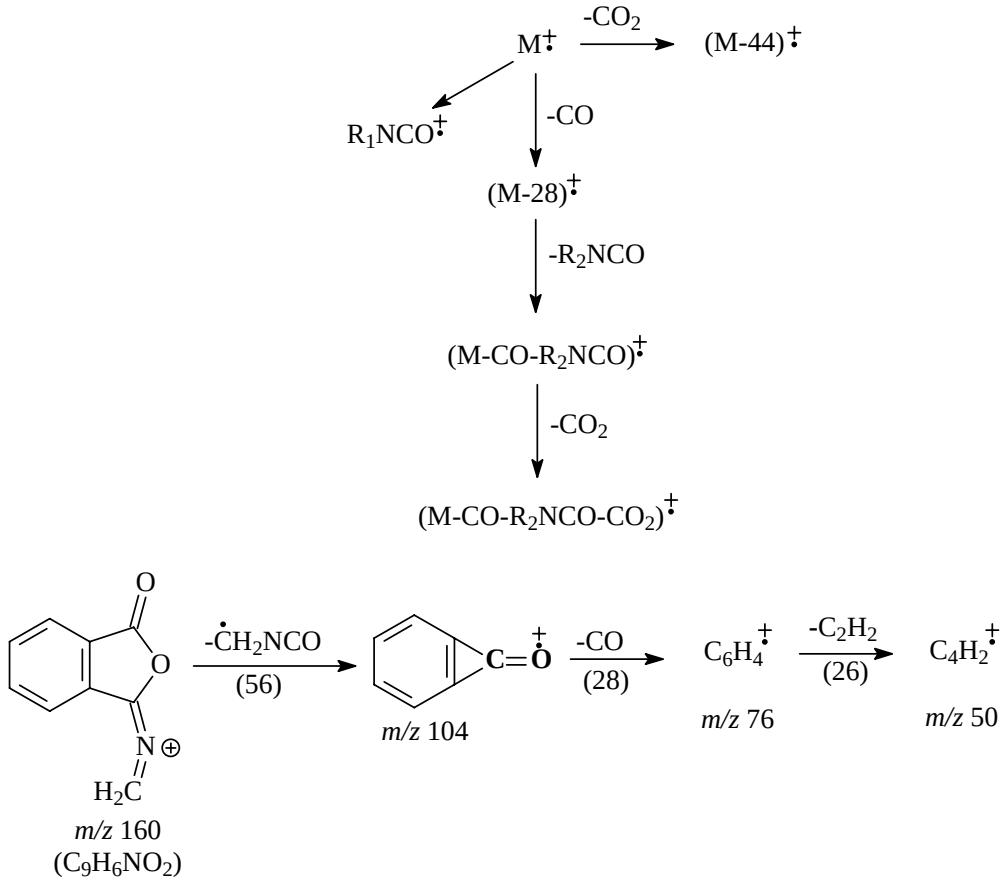
Figure 3. The CACHE® molecular model of *N*-1',*N*-3'-diethyl-2'*H*,3*H*,5'*H*-spiro[2-benzofuran-1,4'-imidazolidine]-2',3,5'-trione, **6a**.



C) Mass Spectra

The major primary fragmentation pathways of the molecular ions of the spirohydantoins prepared support and corroborate the proposed structure. Loss of carbon monoxide, carbon dioxide and an alkyl or aryl isocyanate constitute the predominant primary fragmentation paths, followed by ejection of a second molecule of CO_2 and RNCO (Scheme 7).

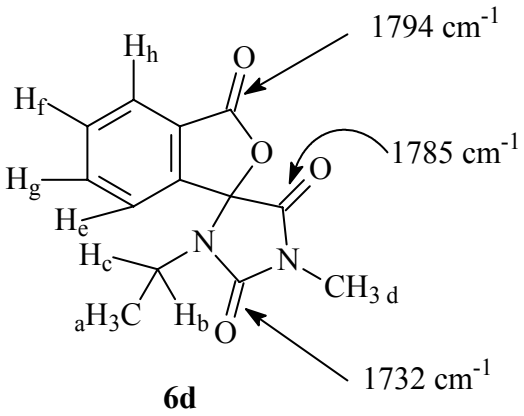
Scheme 7. Characteristic mass spectrometric fragmentation of phthalidyl spirohydantoins of type **6**.



Fragment ion *m/z* 160 ($C_9H_6NO_2$) is present in the mass spectra of all spirohydantoins prepared, and is the base peak in the spectra of eight of them. In the spectrum of the dideuterated derivative **6s** it is shifted to *m/z* 162, which confirms the structure and composition of this important ion (Scheme 7).

All new ureas (**3**), indeno[1,2-*d*]imidazolones (**5**), and phthalidyl spirohydantoins (**6**) synthesized during this study were characterized by a detailed and complete interpretation of the IR, ^{1}H-NMR, ^{13}C-NMR, APT (Attached Proton Test), and mass spectra. To illustrate how the structures of the spirohydantoins were determined, we provide a summary of the spectra interpretation for compound **6d** below:

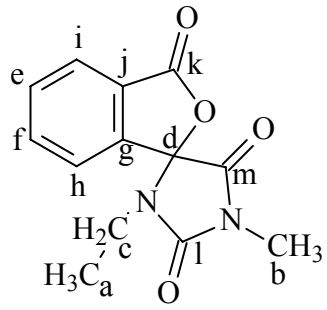
Scheme 8. IR and NMR Spectra of **6d**.



6d

IR (KBr): 1794, 1785, 1732 cm^{-1}

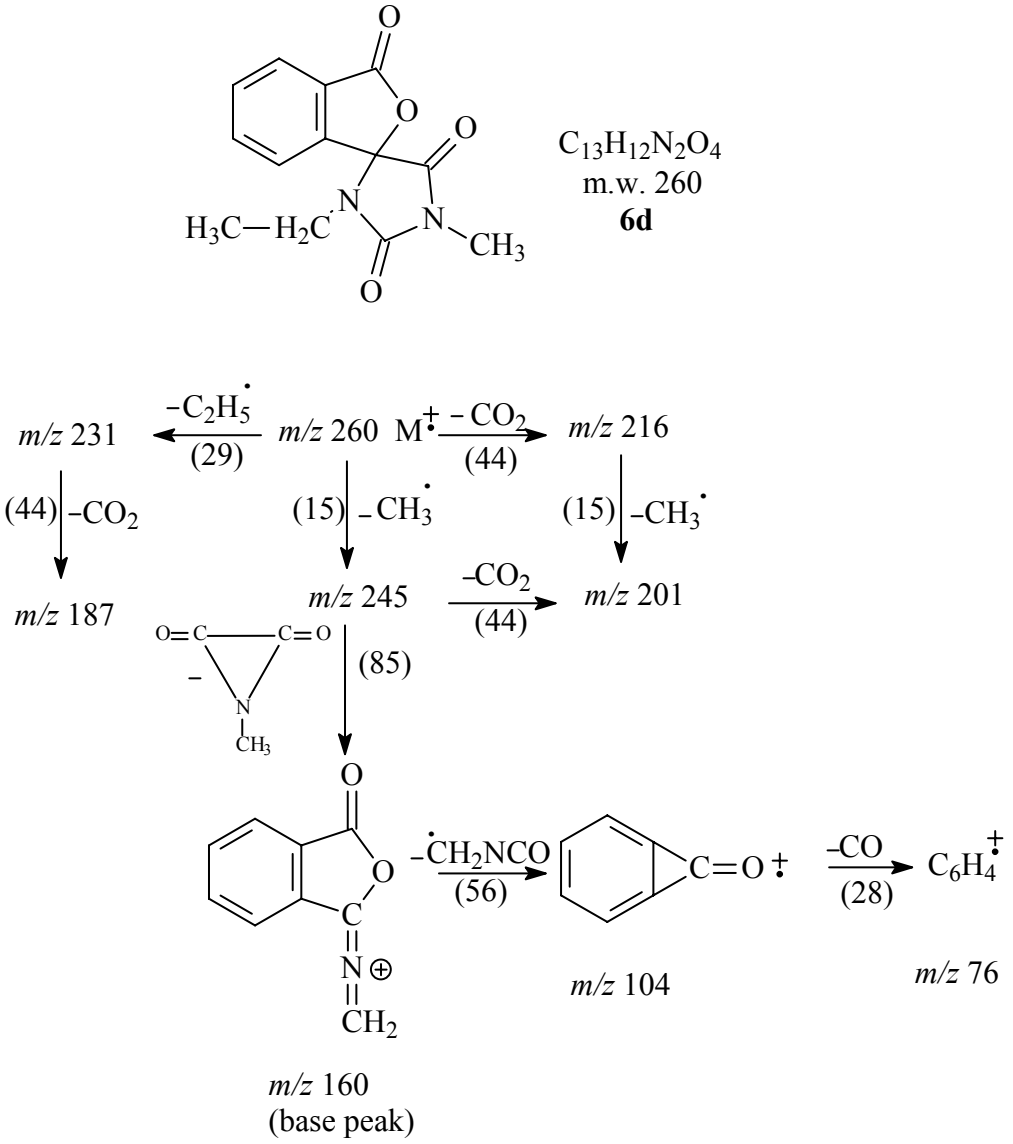
^{1}H-NMR (DMSO-d_6):
a: 0.93, t, 3H
b: 3.00, sextet, 1H
c: 3.28, sextet, 1H
d: 3.36, s, 3H
e: 7.79, d, 1H
f: 7.84, t, 1H
g: 7.94, t, 1H
h: 8.05, d, 1H



^{13}C-NMR (DMSO-d_6) of **6d**:
APT: CH_3, CH ↑
CH_2, C, C=O ↓

	δ	APT		δ	APT
a:	15.20	↑	h:	133.22	↑
b:	26.13	↑	i:	136.61	↑
c:	35.65	↓	j:	141.61	↓
d:	93.53	↓	k:	155.85	↓
e:	125.10	↑	l:	167.51	↓
f:	126.56	↑	m:	167.87	↓
g:	127.67	↓			

Scheme 9. The main mass spectrometric fragmentation pathways of spirohydantoin **6d**.



3. CONCLUSION

Nineteen new *N*-1'-*N*-3'-disubsituted phthalidyl spirohydantoins (**6a-s**) have been synthesized in three steps. Their structure was determined from the infrared, ^{1}H-NMR, ^{13}C-NMR, mass spectra and elemental analysis. An unequivocal distinction between two possible structural isomers - only one of which is formed - could be made on the basis of selective diastereotopicity of the α-methylene hydrogens adjacent to *N*-3' of the hydantoin ring.

The same method is applicable to β-methylene groups too, if the α-carbon in the R_2 substituent is dideuterated.

4. EXPERIMENTAL

Melting points were determined on a Thomas-Hoover Capillary Melting Point Apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 400 Ultrashield^{TM} spectrophotometer with tetramethylsilane as internal standard. Chemical shifts are reported in ppm (δ). IR spectra were recorded on Perkin-Elmer Spectrum 1000 FT-IR spectrophotometer. Mass spectra were recorded on a Hewlett-Packard GC-MS GCD system. For column chromatography, JT Baker silica gel (40 microns) was used. Thin layer chromatography (TLC) was performed with Analtech silica gel glass backed plates (250 micron). Elemental analyses were performed by Atlantic Microlab Inc., Norcross, Georgia.

I. α,α-Dideuterio-2-phenylethylamine 2s

To a cooled solution of lithium aluminium deuteride 2.5 g (0.06 moles) in anhydrous Et_2O(140 mL) was slowly added phenylacetonitrile 7.03 g (0.06 moles) in Et_2O(14 mL). After all of nitrile has been added, ice-bath was removed and the mixture was stirred at rt for another hour. With continued cooling and vigorous stirring, water(2.4 mL), 20% aqueous NaOH(1.8 mL) and water(8.4 mL) were slowly added in succession. The ether solution was decanted from the white, granular inorganic residue. This residue was washed twice with Et_2O and the combined ether fractions were washed thoroughly with water in a separatory funnel and dried. Pure product was obtained by distillation at 35 mm Hg with bp 112-113 ºC. Yield: 21.35%. ^{1}H-NMR (THF-d_8): δ = 2.65 (s, 3H), 7.16 (d, 2H), 7.22 (t, 2H), 7.32 (t, 1H). ^{13}C-NMR (THF-d_8): δ = 23.43, 41.26, 126.73, 129.13, 128.92, 129.83, 141.59.

II. *General procedure for the preparation of N-1,N-3-disubstituted ureas*

The appropriately substituted phenylisocyanate in THF(20 mL) was added dropwise to the appropriate alkylamine at 0ºC with stirring. The ice-bath was removed after the completion of addition of the isocyanate and the mixture was stirred at rt for 30 min then filtered with suction and the precipitate washed with water. The products were allowed to air-dry.

1-Ethyl-3-methylurea 3d ($R_1 = C_2H_5$, $R_2 = CH_3$)

Yield: 96.5%, mp 52-55 ºC (lit.,[12] 54-55 ºC). IR (KBr) *v*: 3359, 1641 cm^{-1}. MS: m/z 102 (M^+), 87, 74, 58, 44, 30 (base peak).

1-Ethyl-3-phenylurea 3e ($R_1 = C_2H_5$, $R_2 = C_6H_5$)

Yield: 77.3%, mp 92-95 ºC (lit.,[13] 94-95 ºC). IR (KBr) *v*: 3323, 1649 cm^{-1}. MS: m/z 164 (M^+), 135, 106, 93 (base peak), 77, 66, 44.

1-Ethyl-3-(2'-fluorophenyl)urea 3f ($R_1 = C_2H_5$, $R_2 = o$-F-C_6H_4)

Yield: 91.4%, mp 112-116 ºC (lit.,[14, 15] 115-116 ºC). IR (KBr) *v*: 3337, 1638 cm^{-1}. MS: m/z 182 (M^+), 153, 137, 111 (base peak), 95, 91, 83, 75, 64, 44.

1-Ethyl-3-(3'-fluorophenyl)urea 3g ($R_1 = C_2H_5$, $R_2 = m$-F-C_6H_4)

Yield: 91.8%, mp 111-113 ºC. IR (KBr) *v*: 3327, 1650 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ = 1.06 (t, 3H), 3.12 (quintet, 2H), 6.58 (s, 1H), 6.91 (d, 1H), 7.07 (t, 1H), 7.16 (t, 1H), 8.14 (t, 1H), 8.23 (s, 1H). ^{13}C-NMR (DMSO-d_6): δ = 15.30, 33.92, 114.61, 120.15, 121.39, 124.32, 128.36, 150.39, 154.77. MS: m/z 182 (M^+), 153, 137, 111 (base peak), 95, 83, 75, 63, 44. Anal. Calcd for $C_9H_{11}FN_2O_4$: C, 59.33; H, 6.09; N, 15.38. Found C, 59.38; H, 6.04; N, 15.19

1-Ethyl-3-(4'-fluorophenyl)urea 3h ($R_1 = C_2H_5$, $R_2 = p$-F-C_6H_4)

Yield: 75.3%, mp 173-175 ºC. IR (KBr) *v*: 3326, 1632cm^{-1}. MS: m/z 182 (M^+), 153, 137, 111 (base peak), 95, 83, 75, 44. Anal. Calcd for $C_9H_{11}FN_2O_4$: C, 59.33; H, 6.09; N, 15.38. Found C, 59.38; H, 6.04; N, 15.19.

1-Ethyl-3-(4'-nitrophenyl)urea 3i ($R_1 = C_2H_5$, $R_2 = p$-NO_2-C_6H_4)

Yield: 94.6%, mp 157-160 ºC. IR (KBr) *υ*: 3326, 1632, 1559, 1339 cm^{-1}. MS: m/z 209 (M^+), 180, 165, 164, 138 (base peak), 122, 108, 90, 75, 65.

1-Ethyl-3-(4'-methoxyphenyl)urea 3j ($R_1 = C_2H_5$, $R_2 = p$-OCH_3-C_6H_4)

Yield: 93.6%, mp 132-135 ºC. IR (KBr) υ: 3326, 1632, 1244, 1031 cm^{-1}. MS: m/z 194 (M^+), 149, 134, 123, 108 (base peak), 80, 65, 52.

1-Methyl-3-*n*-propylurea 3k ($R_1 = CH_3$, $R_2 = n$-C_3H_7)

Yield: 98.0%, mp 59-61 ºC, (lit.,[16] 61-62 ºC). IR (KBr) υ: 3347, 2961, 1631 cm^{-1}. MS: m/z 116 (M^+), 101, 87, 74, 58 (base peak), 56, 44, 43, 40.

1-Phenyl-3-*n*-propylurea 3l ($R_1 = C_6H_5$, $R_2 = n$-C_3H_7)

Yield: 55.6%, mp 114-116 ºC (lit.,[13, 15] 113-114 ºC). IR (KBr) υ: 3325, 2961, 1644 cm^{-1}. MS: m/z 178 (M^+), 149, 135, 119, 93 (base peak), 77, 66, 65, 51, 43.

1-Benzyl-3-methylurea 3m ($R_1 = CH_2C_6H_5$, $R_2 = CH_3$):

Yield: 71.8%, mp 94-96 ºC (lit.,[17] 97-98 ºC). IR (KBr) υ: 3331, 1628 cm^{-1}. MS: m/z 164 (M^+), 134, 133,

132, 106 (base peak), 91, 79, 77, 65, 58, 51, 39.

1-Benzyl-3-phenylurea 3n ($R_1 = CH_2C_6H_5$, $R_2 = C_6H_5$):
Yield: 84.2%, mp 169-170 ºC (lit.,[18] 169-171 ºC). IR (KBr) υ: 3330, 1635 cm^{-1}. MS: m/z 226 (M^+), 133, 119, 106, 104, 93 (base peak), 91, 77, 66, 65, 51.

1-Benzyl-3-(2'-phenylethyl)urea 3o ($R_1 = CH_2C_6H_5$, $R_2 = CH_2CH_2C_6H_5$)
Yield: 94.3%, mp 93-96 ºC (lit.,[19, 20] 95-96 ºC). IR (KBr) υ: 3345, 3030, 1626 cm^{-1}. MS: m/z 254 (M^+), 177, 163, 147, 133, 106, 104, 91 (base peak), 77, 65, 51.

1-Ethyl-3-*i*-propylurea 3p ($R_1 = C_2H_5$, $R_2 = i\text{-}C_3H_7$)
Yield: 60.2%, mp 153-155 ºC (lit.,[13] 155-157 ºC). IR (KBr) υ: 3341, 2970, 1625 cm^{-1}. MS: m/z 130 (M^+), 115, 73, 72, 58, 44 (base peak).

1-Neopentyl-3-*i*-propylurea 3q ($R_1 = CH_2(CH_3)_3$, $R_2 = i\text{-}C_3H_7$)
Yield: 98.0%, mp 153-155 ºC. IR (KBr) υ: 3348, 2965, 1630 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ = 0.81 (s, 9H), 1.01 (d, 6H), 2.75 (d, 2H), 3.66 (septet, 1H), 5.63 (d, 1H), 5.72 (t, 1H). ^{13}C-NMR (DMSO-d_6): δ = 22.96, 23.60, 23.98, 26.83, 27.31, 31.81, 41.35, 50.44, 157.71. MS: m/z 172 (M^+), 157, 117, 116, 115, 101 (base peak), 86, 72, 58, 57, 44. Anal. Calcd for $C_9H_{20}N_2O$: C, 62.75; H, 11.70; N, 16.26. Found C, 62.82; H, 11.71; N, 16.26.

1-(2'-Phenylethyl)-3-phenylurea 3r ($R_1 = CH_2CH_2\ C_6H_5$, $R_2 = C_6H_5$)
Yield: 97.7%, mp 152-154 ºC (lit.,[21, 22] 153.5-154.5 ºC). IR (KBr) *v*: 3346.53, 1647 cm^{-1}. MS: m/z 240 (M^+), 149, 147, 136, 119, 105, 93 (base peak), 91, 77, 65, 51.

1-(α,α-Dideuterio-2-phenylethyl)-3-phenylurea 3s ($R_1 = CH_2CD_2C_6H_5$, $R_2 = C_6H_5$)
Yield: 93.5%, mp 152-153 ºC. IR (KBr) *v*: 3304, 1645, 1595, 1564 cm^{-1}. ^{1}H-NMR δ = 2.73 (s, 2H), 6.09 (s, 1H), 6.88 (t, 1H), 7.19-7.25 (multiplet, 5H), 7.31 (t, 2H), 7.38 (d, 2H), 8.47 (s, 1H). ^{13}C-NMR (DMSO-d_6): δ = 36.06, 41.32, 120.38, 121.49, 123.30, 124.26, 126.63, 127.68, 137.81, 138.81, 157.52. MS: m/z 242 (M^+), 151, 149, 136, 135, 119, 107, 93 (base peak), 91, 77, 65, 51. Anal. Calcd for $C_{15}H_{14}D_2N_2O_4$: C, 74.35; H, 6.71; N, 11.65. Found C, 73.97; H, 6.51; N, 11.77.

III. ***General procedure for the synthesis of indeno[1,2-d]imidazolones, 5, (ninhydrin-1,3-disubstituted urea adducts)***

Ninhydrin (20-35 mmol) was added to benzene(100 mL) containing an equivalent amount of the appropriately substituted urea in a 500 mL round-bottom flask and refluxed for 45 min with stirring. The mixture was cooled, filtered with suction, and the precipitate washed with water. The crude product was allowed to air-dry overnight and recrystallized from aqueous MeOH (~ 90%) to a constant melting point.

1,3,3a,8a-Tetrahydro-3a,8a-dihydroxy-1,3-diethylindeno[1,2-*d*]imidazole-2,8-dione (5a)

Diethylurea,(7.9 g ,50.0 mmol) was reacted with ninhydrin (8.9 g , 50.0 mmol). The product was recrystallized two times from aqueous MeOH and resulted in **5a** as white crystals. Yield: 74.8 %, mp 235-237 ºC. TLC (70% toluene: 30% MeCN) R_f = 0.36. IR (KBr) *v*: 3420, 3310, 2974, 2935, 1721, 1683 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ = 1.09 (t,3H), 1.12 (t, 3H), 3.36 (q, 2H), 3.44 (q, 2H), 6.82 (s,1H), 6.96 (s,1H), 7.68 (t, 1H), 7.84 (d, 1H), 7.92 (t, 1H), 7.95 (d, 1H). ^{13}C-NMR (DMSO-d_6): δ = 15.59, 15.89, 87.68, 88.71, 124.84, 125.99, 131.32, 133.11, 137.62, 151.07, 155.56, 197.78. Anal. Calcd for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.79; N, 10.14. Found C, 60.78; H, 5.83; N, 10.25.

1,3,3a,8a-Tetrahydro-3a,8a-dihydroxy-1,3-di-*n*-propylindeno[1,2-*d*]imidazole-2,8-dione (5b)

Di-*n*-propylurea,(7.9 g ,50.0 mmol) was reacted with ninhydrin,(8.9 g , 50.0 mmol). The product was recrystallized two times from aqueous MeOH and resulted in **5b** as white crystals. Yield: 72.0 %, mp 139-141 ºC. TLC (70% toluene: 30% MeCN) R_f = 0.53. IR (KBr) *v*: 3435, 2973, 2931, 1720, 1685 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ = 0.821 (dt, 6H), 1.46-1.65 (m, 4H), 3.21-3.32 (m, 4H), 6.77 (s, 1H), 6.92 (s, 1H), 7.64 (t, 1H), 7.81 (d, 1H), 7.88 (t, 1H), 7.93 (d, 1H). ^{13}C-NMR (DMSO-d_6) δ = 11.35, 11.40, 22.17, 22.53, 41.03, 41.11, 86.90, 87.91, 123.96, 125.25, 130.42, 132.41, 136.63, 150.24, 155.12, 196.95. Anal. Calcd for $C_{16}H_{20}N_2O_4$: C, 63.17; H, 6.58; N, 9.21. Found C, 63.29; H, 6.65; N, 9.35.

1,3,3a,8a-Tetrahydro-3a,8a-dihydroxy-1,3-dibenzylindeno[1,2-*d*]imidazole-2,8-dione (5c):

N,*N*'-Dibenzylurea, (3.67 g ,20.64 mmol) was reacted with ninhydrin, (4.96 g , 20.64 mmol). The product was recrystallized two times from aqueous MeOH yielding **5c** as white crystals. Yield: 41.5 %, mp 180-182 ºC. TLC (70% toluene: 30% MeCN) R_f = 0.57. IR (KBr) *v*: 3340, 1730, 1665 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ = 4.50 (s, 1H), 4.58 (s, 1H), 4.60 (s, 1H), 4.71 (s, 1H), 7.07 (s, 1H), 7.16 (d, 7H), 7.24 (d, 4H), 7.51-7.63 (multiplet, J = 8.0, 3H), 7.72 (d, 1H). ^{13}C-NMR (DMSO-d_6): δ = 36.12, 42.46, 87.11, 88.29, 123.84, 125.61, 126.42, 126.61, 127.02, 127.26, 127.37, 128.00, 130.46, 132.26, 136.30, 138.89, 139.07, 150.03, 155.72, 196.67. Anal. Calcd for $C_{24}H_{20}N_2O_4$: C, 71.98; H, 5.03; N, 6.99. Found C, 71.94; H, 5.08; N, 6.96.

3-Ethyl-3a,8a-dihydroxy-1-methyl-1,3,3a,8a-tetrahydroindeno[1,2-*d*]imidazole-2,8-dione (5d):

N-1-Ethyl-*N*-3-methylurea, (5.1 g ,50.0 mmol) was reacted with ninhydrin, (8.9 g ,50.0 mmol). The product was recrystallized two times from aqueous MeOH to give **5d** as white crystals. Yield: 76.3 %, mp 258-262 ºC. TLC (95% EtOAc: 5% MeOH) R_f = 0.41. IR (KBr) *v*: 3436, 1727, 1678 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ = 1.08 (t, 3H), 3.37-3.44 (multiplet, J = 7.0 Hz, 2H), 6.81 (s, 1H), 6.98 (s, 1H), 7.63 (t, 1H), 7.80 (d, 1H), 7.87 (t, 1H), 7.94 (t, 1H). ^{13}C-NMR (DMSO-d_6): δ = 15.91, 25.56, 34.86, 87.50, 88.69, 124.83, 126.00, 131.29, 133.18, 137.56, 151.22, 156.52, 197.03. Anal. Calcd for $C_{13}H_{14}N_2O_4$: C, 59.54; H, 5.38; N, 10.68. Found C, 59.47; H, 5.41; N, 10.84.

3-Ethyl-3a,8a-dihydroxy-1-phenyl-1,3,3a,8a-tetrahydroindeno[1,2-*d*]imidazole-2,8-dione (5e):

N-1-Ethyl-*N*-3-phenylurea, (6.0 g ,36.0 mmol) was reacted with ninhydrin, (6.51 g ,36.0 mmol). The product was recrystallized two times from aqueous MeOH, resulting in **5e** as white crystals. Yield: 52.7 %, mp 159-162 ºC. TLC (70% toluene: 30% MeCN) R_f = 0.41. IR (KBr) *v*: 3385, 2936, 1735, 1679 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ = 1.17 (t, 3H), 3.16 (sextet, 1H), 3.39 (sextet, 1H), 7.13 (s, 1H), 7.22 (t, 1H), 7.35 (t, 2H), 7.42 (s, 1H), 7.49 (d, 2H), 7.65 (t, 1H), 7.78 (d, 1H), 7.91 (t, 1H), 8.00 (t, 1H). ^{13}C-NMR (DMSO-d_6): δ = 14.96, 34.40, 87.94, 88.67, 124.14, 125.27, 125.73, 126.85, 128.14, 130.65, 132.45, 136.42, 150.00, 153.69, 195.31. Anal. Calcd for $C_{18}H_{16}N_2O_4$: C, 66.65; H, 4.97; N, 8.63. Found C, 66.85; H, 4.94; N, 8.65.

3-Ethyl-3a,8a-dihydroxy-1-(*o*-fluorophenyl)-1,3,3a,8a-tetrahydroindeno[1,2-*d*]imidazole-2,8-dione (5f):

N-1-Ethyl-*N*-3-(2-fluorophenyl)urea, (5.0 g ,27.47 mmol) was reacted with ninhydrin, (4.89 g ,27.47 mmol). The product was recrystallized from aqueous MeOH to give **5f** as white crystals. Yield: 74.8 %, mp 104-106 ºC. TLC (70% toluene: 30% MeCN) R_f = 0.36. IR (KBr) *v*: 3328, 3238, 1734, 1697 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ = 1.17 (t, 3H), 3.47-3.55 (multiplet, J = 7.2 Hz, 2H), 7.18 (s, 1H), 7.23 (d, 1H), 7.26 (d, 1H), 7.38 (s, 1H), 7.41 (t, 1H), 7.51 (t, 1H), 7.66 (t, 1H), 7.80 (d, 1H), 7.91 (t, 1H), 8.02 (d, 1H). ^{13}C-NMR (DMSO-d_6): δ = 15.00, 34.41, 87.79, 88.54, 115.69, 115.89, 123.26, 124.22, 125.28, 129.81, 130.72, 132.40, 136.88, 150.29, 153.31, 157.91, 160.38, 195.13. Anal. Calcd for $C_{18}H_{15}N_2O_4F$: C, 63.15; H, 4.41; N, 8.18. Found C, 63.25; H, 4.17; N, 8.03.

3-Ethyl-3a,8a-dihydroxy-1-(*m*-fluorophenyl)-1,3,3a,8a-tetrahydroindeno[1,2-*d*]imidazole-2,8-dione (5g):

N-1-Ethyl-*N*-3-(3-fluorophenyl)urea, (5.0 g ,27.47 mmol) was reacted with ninhydrin, (4.89 g ,27.47 mmol). The product was recrystallized from aqueous MeOH yielding **5g** as white crystals. Yield: 69.5 %, mp 169-172 ºC. TLC (70% toluene: 30% MeCN) R_f = 0.49. IR (KBr) *v*: 3355, 3241, 1734, 1694 cm^{-1}.

^{1}H-NMR (DMSO-d_6): δ = 1.15 (t, 3H), 3.47-3.58 (multiplet, J = 7.25 Hz, 2H), 7.03 (t, 1H), 7.23 (s, 1H), 7.37 (d, 1H), 7.50 (d, 1H), 7.54 (s, 1H), 7.60 (s, 1H), 7.67 (t, 1H), 7.79 (d, 1H), 7.92 (t, 1H), 8.02 (d, 1H). ^{13}C-NMR (DMSO-d_6): δ = 14.80, 34.43, , 87.79, 88.78, 111.89, 121.27, 124.28, 125.34, 129.44, 130.78, 132.41, 136.95, 138.43, 149.92, 153.20, 157.91, 160.43, 195.24. Anal. Calcd for $C_{18}H_{15}N_2O_4F$: C, 63.15; H, 4.41; N, 8.18. Found C, 63.32; H, 4.31; N, 8.24.

3-Ethyl-3a,8a-dihydroxy-1-(*p*-fluorophenyl)-1,3,3a,8a-tetrahydroindeno[1,2-*d*]imidazole-2,8-dione (5h):

N-1-Ethyl-*N*-3-(4-fluorophenyl)urea, (4.0 g ,22.0 mmol) was reacted with ninhydrin, (3.91 g ,22.0 mmol). The product was recrystallized from aqueous MeOH yielding **5h** as white crystals. Yield: 64.5 %, mp 173-175 ºC. TLC (70% toluene: 30% MeCN) R_f = 0.40. IR (KBr) *v*: 3385, 2936, 1735, 1679 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ = 1.16 (t, 3H), 3.13 (sextet, 1H), 3.37 (sextet, 1H), 7.16 (s, 1H), 7.19 (t, 2H), 7.45 (s, 1H), 7.47 (d, 2H), 7.66 (t, 1H), 7.81 (d, 1H), 7.91 (t, 1H), 8.01 (d, 1H). ^{13}C-NMR (DMSO-d_6): δ = 14.94, 34.40, 87.97, 88.47, 124.14, 125.73, 126.85, 128.14, 130.65, 132.45, 136.85, 150.08, 153.68, 159.01, 161.42, 195.36. Anal. Calcd for $C_{18}H_{15}N_2O_4F$: C, 63.15; H, 4.41; N, 8.18. Found C, 63.25; H, 4.17; N, 8.03.

3-Ethyl-3a,8a-dihydroxy-1-(*p*-nitrophenyl)-1,3,3a,8a-tetrahydroindeno[1,2-*d*]imidazole-2,8-dione (5i):

N-1-Ethyl-*N*-3-(4-nitrophenyl)urea, (5.0 g ,23.92 mmol) was reacted with ninhydrin, (4.16 g ,23.92 mmol). The product was recrystallized from aqueous MeOH to give **5i** as white crystals. Yield: 76.6 %, mp 217-219 ºC. TLC (70% toluene: 30% MeCN) R_f = 0.53. IR (KBr) *v*: 3352, 3180, 1731, 1680, 1595, 1338 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ = 1.14 (t, 3H), 3.39-3.63 (multiplet, J = 7.0, 2H), 7.36 (s, 1H), 7.69 (t, 1H), 7.81 (d, 1H), 7.85 (s, 2H), 7.95 (t, 1H), 8.04 (d, 1H), 8.15 (d, 2H), 8.25 (d, 2H). ^{13}C-NMR (DMSO-d_6): δ = 14.56, 34.59, 87.70, 89.21, 123.21, 123.65, 124.41, 125.39, 130.95, 132.27, 137.13, 143.07, 143.56, 149.60, 152.70, 195.13. Anal. Calcd for $C_{18}H_{15}N_3O_6$: C, 58.53; H, 4.09; N, 11.37. Found C, 58.50; H, 4.03; N, 11.26.

3-Ethyl-3a,8a-dihydroxy-1-(*p*-methoxyphenyl)-1,3,3a,8a-tetrahydroindeno[1,2-*d*]imidazole-2,8-dione (5j):

N-1-Ethyl-*N*-3-(4-methoxyphenyl)urea, (4.0 g ,20.60 mmol) was reacted with ninhydrin, (3.66 g ,20.60 mmol). The product was recrystallized from aqueous MeOH yielding **5j** as white crystals. Yield: 74.3 %, mp 170-172 ºC. TLC (70% toluene: 30% MeCN), R_f = 0.52. IR (KBr) *v*: 3298, 1729, 1604, 1447cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ = 1.16 (t, 3H), 3.41-3.51 (multiplet, J = 7.7, 2H), 6.90 (d, 2H), 6.97 (s, 1H), 7.18

(s, 1H), 7.26 (d, 2H), 7.64 (t, 1H), 7.77 (d, 1H), 7.89 (t, 1H), 7.98 (d, 1H). ^{13}C-NMR (DMSO-d_6): δ = 14.84, 34.22, 55.15, 87.85, 88.27, 113.39, 123.95, 125.12, 128.67, 129.11, 130.44, 132.46, 136.54, 149.96, 153.90, 157.58, 195.22. Anal. Calcd for $C_{19}H_{18}N_2O_5$: C, 64.40; H, 5.11; N, 7.90. Found C, 64.29; H, 5.08; N, 7.84.

1-Methyl -3a,8a-dihydroxy-3-propyl-1,3,3a,8a-tetrahydroindeno[1,2-*d*]imidazole-2,8-dione (5k):
N-1-Methyl-*N*-3-propylurea, (2.5 g ,21.55 mmol) was reacted with ninhydrin, (3.83 g ,21.55 mmol). The product was recrystallized two times from aqueous MeOH and resulted in **5k** as white crystals. Yield: 71.0 %, mp 205-207 ºC. TLC (70% toluene: 30% MeCN) R_f = 0.34. IR (KBr) *v*: 3301, 2967, 1713, 1686 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ = 0.83 (t, 3H), 1.46 (octet, 1H), 1.61 (octet, 1H), 2.79 (s, 3H), 3.21-3.46 (multiplet, J=5.32, 2H), 6.80 (s, 1H), 6.98 (s, 1H), 7.65 (t, 1H), 7.81 (d, 1H), 7.88 (t, 1H), 7.93 (d, 1H). ^{13}C-NMR (DMSO-d_6): δ = 11.39, 22.52, 24.80, 41.14, 86.66, 87.92, 123.99, 125.27, 130.45, 132.42, 136.66, 150.37, 154.93, 196.27. Anal. Calcd for $C_{14}H_{16}N_2O_4$: C, 60.71; H, 5.84; N, 10.14. Found C, 60.37; H, 6.03; N, 10.11.

1-Phenyl-3a,8a-dihydroxy-3-propyl-1,3,3a,8a-tetrahydroindeno[1,2-*d*]imidazole-2,8-dione (5l):
N-1-Phenyl-*N*-3-propylurea, (4.0 g ,22.30 mmol) was reacted with ninhydrin, (4.0 g ,22.30 mmol). The product was recrystallized two times from aqueous MeOH, resulting in **5l** as white crystals. Yield: 82.4 %, mp 184-186 ºC. TLC (60% n-hexane: 40% EtOAc) R_f = 0.30. IR (KBr) *v*: 3384, 3338, 2978, 1735, 1692 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ = 0.926 (t, 3H), 1.62 (octet, 1H), 1.77 (octet, 1H), 3.47 (sextet,1H), 3.52 (sextet, 1H), 7.12 (s, 1H), 7.28 (t, 1H), 7.36 (t, 2H), 7.40 (s, 1H), 7.42 (d, 2H), 7.64 (t, 1H), 7.83 (d, 1H), 7.88 (t, 1H), 7.96 (d, 1H). ^{13}C-NMR (DMSO-d_6): δ = 11.42, 22.43, 41.40, 88.00, 88.72, 124.16, 125.39, 125.73, 126.83, 128.15, 130.66, 132.56, 136.47, 136.74, 149.99, 153.96, 195.41. Anal. Calcd for $C_{19}H_{18}N_2O_4$: C, 67.44; H, 5.36; N, 8.27. Found C, 67.50; H, 5.28; N, 8.22.

3-Benzyl-3a,8a-dihydroxy-1-methyl-1,3,3a,8a-tetrahydroindeno[1,2-*d*]imidazole-2,8-dione (5m):
N-1-Benzyl-*N*-3-methylurea, (2.7 g ,16.4 mmol) was reacted with ninhydrin, (2.93 g ,16.4 mmol). The product was recrystallized two times from aqueous MeOH, resulting in **5m** as white crystals. Yield: 61.2 %, mp 166-167 ºC. (70% toluene: 30% MeCN) R_f = 0.31. IR (KBr) *v*: 3350, 3057, 1735, 1668 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ = 2.85 (s, 3H), 4.55 (d, 1H), 4.67 (d, 1H), 7.01 (s, 1H), 7.08 (s, 1H), 7.10 (d, 2H), 7.15 (t, 1H), 7.18 (t, 2H), 7.52-7.63 (multiplet, J= 7.63, 3H), 7.78 (d, 1H). ^{13}C-NMR (DMSO-d_6): δ = 24.99, 42.40, 87.03, 88.01, 123.85, 125.58, 126.47, 127.12, 127.93, 130.38, 132.32, 136.26, 139.13, 150.21, 155.35, 196.27. Anal. Calcd for $C_{18}H_{16}N_2O_4$: C, 66.65; H, 4.97; N, 8.63. Found C, 66.60; H, 4.98; N, 8.60.

3-Benzyl-3a,8a-dihydroxy-1-phenyl-1,3,3a,8a-tetrahydroindeno[1,2-*d*]imidazole-2,8-dione (5n):
N-1-Benzyl-*N*-3-phenylurea, (1.0 g ,4.58 mmol) was reacted with ninhydrin, (0.78 g ,4.58 mmol). The product was recrystallized two times from aqueous MeOH to give **5n** as white crystals. Yield: 73.8 %, m.p. 222-223 ºC. (70% toluene: 30% MeCN) R_f = 0.47. IR (KBr) *v*: 3343, 1736, 1665, 1644 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ = 4.65 (d, 1H), 4.78 (d, J = 16.35 Hz, 1H), 7.15-7.27 (multiplet, 6H), 7.31 (s, 1H), 7.35 (t, 2H), 7.51 (s, 1H), 7.52-7.57 (multiplet, J = 7.07, 3H), 7.62-7.66 (multiplet, 2H), 7.75 (d, 1H). ^{13}C-NMR (DMSO-d_6): δ = 42.70, 88.07, 89.07, 124.01, 125.69, 125.90, 126.58, 126.91, 127.18, 128.02, 128.22, 130.58, 132.45, 136.34, 136.38, 138.81, 149.77, 154.39, 195.31. Anal. Calcd for $C_{23}H_{18}N_2O_4$: C, 71.50; H, 4.69; N, 7.25. Found C, 71.72; H, 4.60; N, 7.27.

3-Benzyl-3a,8a-dihydroxy-1-(2'-phenylethyl)-1,3,3a,8a-tetrahydroindeno[1,2-*d*]imidazole-2,8-dione (5o):
N-1-Benzyl-*N*-3-(2'-phenylethyl)urea,(2.54 g ,10.0 mmol) was reacted with ninhydrin, (1.78 g ,10.0 mmol). The product was recrystallized two times from aqueous MeOH yielding **5o** as white crystals. Yield: 59.0 %, mp 182-184 ºC. TLC (70% toluene: 30% MeCN) R_f = 0.51. IR (KBr) *v*: 3384, 3130, 2945, 1725, 1682 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ = 2.90 (dt, 2H), 3.54 (t, 2H), 4.58 (d, 1H), 4.70 (d, 1H), 7.04 (s, 1H), 7.13-7.23 (multiplet, 9H), 7.28 (d, 2H), 7.55 (d, 2H), 7.60 (d, 1H), 7.77 (d, 1H). ^{13}C-NMR (DMSO-d_6): δ = 35.15, 41.14, 42.35, 87.20, 88.09, 123.90, 125.56, 126.17, 126.46, 127.14, 127.93, 128.43, 128.60,130.33, 132.25, 136.24, 139.09, 139.22, 150.07, 155.36, 196.88. Anal. Calcd for $C_{25}H_{22}N_2O_4$: C, 72.44; H, 5.35; N, 6.76. Found C, 72.41; H, 5.35; N, 6.73.

1-Ethyl-3a,8a-dihydroxy-3-isopropyl-1,3,3a,8a-tetrahydroindeno[1,2-*d*]imidazole-2,8-dione (5p):
N-1-Ethyl-*N*-3-isopropylurea, (2.0 g ,15.38 mmol) was reacted with ninhydrin, (2.73 g ,15.38 mmol). The product was recrystallized two times from aqueous MeOH to give **5p** as white crystals. Yield: 79.1 %, mp 221-222 ºC. TLC (70% toluene: 30% MeCN) R_f = 0.45. IR (KBr) *v*: 3420, 3279, 2998, 2973, 1719, 1684 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ = 1.07 (t, 3H), 1.44 (d, 6H), 3.30 (q, 2H), 4.08 (septet, 1H), 6.72 (s, 1H), 6.89 (s, 1H), 7.64 (t, 1H), 7.81 (d, 1H), 7.87 (t, 1H), 7.95 (d, 1H). ^{13}C-NMR (DMSO-d_6): δ = 14.87, 20.36, 21.43, 33.63, 43.21, 86.56, 87.75, 123.97, 124.87, 130.38, 132.25, 136.76, 150.47, 153.81, 196.93. Anal. Calcd for $C_{15}H_{18}N_2O_4$: C, 62.06; H, 6.25; N, 9.65. Found C, 61.96; H, 6.24; N, 9.56.

1-Ethyl-3a,8a-dihydroxy-3-neopentyl-1,3,3a,8a-tetrahydroindeno[1,2-*d*]imidazole-2,8-dione (5q):
N-1-Ethyl-*N*-3-neopentylurea, (4.0 g ,23.25 mmol) was reacted with ninhydrin, (4.13 g ,23.25 mmol). The product was recrystallized two times from aqueous MeOH yielding **5q** as white crystals. Yield: 75.0 %, mp 201-204 ºC. TLC (70% toluene: 30% MeCN) R_f = 0.59. IR (KBr) *v*: 3437, 3248, 2973, 1723,

1682 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ = 0.845 (s, 9H), 1.10 (d, 3H), 1.42 (d, 3H), 3.03 (d, 1H), 3.11 (d, 1H), 4.08 (septet, 1H), 6.71 (s, 1H), 6.87 (s, 1H), 7.63 (t, 1H), 7.78 (d, 1H), 7.87 (t, 1H), 7.953(d, 1H). ^{13}C-NMR (DMSO-d_6): δ = 20.25, 21.27, 28.69, 32.39, 43.29, 50.63, 87.39, 87.81, 123.79, 124.84, 130.35, 132.66, 136.58, 150.15, 155.48, 197.18. Anal. Calcd for $C_{18}H_{24}N_2O_4$: C, 65.04; H, 7.27; N, 8.42; Found C, 65.06; H, 7.31; N, 8.43.

3-Phenethyl-3a,8a-dihydroxy-1-phenyl-1,3,3a,8a-tetrahydroindeno[1,2-*d*]imidazole-2,8-dione (5r):
N-1-Phenethyl-*N*-3-phenylurea, (2.25 g ,12.5 mmol) was reacted with ninhydrin, (3.0 g ,12.5 mmol). The product was recrystallized two times from aqueous MeOH to give **5r** as white crystals. Yield: 82.5 %, mp 178-179 ºC. TLC (70% toluene: 30% MeCN) R_f = 0.30. IR (KBr) *v*: 3926, 3117, 1734, 1688, 1603 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ = 2.80 (sextet, 1H), 2.99 (sextet, 1H), 3.64 (dodecet, 2H), 7.19-7.32 (multiplet, 7H), 7.36 (t, 2H), 7.47, (s, 1H), 7.51 (d, 2H), 7.66 (t, 1H), 7.78 (d, 1H), 7.90 (t, 1H), 8.03 (d, 1H). ^{13}C-NMR (DMSO-d_6): δ = 35.34, 41.36, 87.99, 88.77, 124.16, 125.29, 125.79, 126.25, 126.85, 128.15, 128.47, 128.65, 130.67, 132.50, 136.34, 136.85, 139.12, 149.85, 153.82, 195.27. Anal. Calcd for $C_{24}H_{20}N_2O_4$: C, 71.98; H, 4.99; N, 6.99. Found C, 72.00; H, 4.97; N, 6.99.

3-(α,α-Dideutero-2-phenylethyl)-3a,8a-dihydroxy-1-phenyl-1,3,3a,8a-tetrahydroindeno[1,2-*d*]imidazole-2,8-dione (5s):
N-1-(α,α-Dideutero-2-phenylethyl)-*N*-3-phenylurea, (1.5 g ,6.20 mmol) was reacted with ninhydrin, (1.10 g ,6.20 mmol). The product was recrystallized two times from aqueous MeOH yielding **5s** as white crystals. Yield: 78.3 %, mp 177-178 ºC. TLC (70% toluene: 30% MeCN) R_f = 0.43. IR (KBr) *v*: 3306, 1735, 1686, 1603 cm^{-1}. ^{1}H-NMR (CD_3OD): δ = 2.86 (d, 1H), 3.02 (d, 1H), 4.88 (s, 2H), 7.14-7.19 (multiplet, 1H), 7.22-7.30 (multiplet, 5H), 7.37 (t, 2H), 7.45 (d, 2H), 7.61 (t, 1H), 7.80-7.85 (two doublets, 2H), 7.93 (d, 1H). ^{13}C-NMR (CD_3OD): δ = 36.55, 51.00, 89.86, 90.07, 125.60, 126.10, 127.41, 128.05, 129.28, 129.55, 129.56, 129.82, 131.92, 134.32, 136.81, 138.00, 140.35, 151.03, 156.84, 196.75. Anal. Calcd for $C_{24}H_{18}D_2N_2O_4$: C, 71.64; H, 4.97; N, 6.96. Found C, 71.48; H, 4.98; N, 6.93.

IV. ***General procedure for the synthesis of N-1',N-3'-disubstituted 2'H,3H,5'H-spiro[2-benzofuran-1,4'-imidazolidine]-2',3,5'-triones, 6.***
Sodium periodate, (5-20 mmol) in 50 mL of water was added dropwise to 100 mL of ethanol containing 5-20 mmol of the appropriate adduct **(5a-s)** and the mixture was stirred at room temperature for suitable amount of time (usually 12-24h) as determined by TLC monitoring. At the end of reaction inorganic precipitate was filtered off. The filtrate was concentrated to one-half of its volume, and the resultant precipitate filtered with suction and washed thoroughly with water. The crude product was allowed to air-

dry overnight and recrystallized from aqueous methanol to a constant melting point, except for compound **6b** which is an oil.

***N*-1',*N*-3'-Diethyl-2'*H*,3*H*,5'*H*-spiro[2-benzofuran-1,4'-imidazolidine]-2',3,5'-trione (6a):**

Product **5a**, 3 g (10.0 mmol) was reacted with sodium periodate, 2.11 g (10.0 mmol) for 20 h. Two recrystallizations from aqueous MeOH resulted in **6a** as white crystals. Yield: 58.2 %, mp 96-98 ºC. TLC (70% n-hexane: 30% EtOAc) R_f = 0.57. IR (KBr) *v*: 1803 1792, 1736 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ = 1.02 (t,3H), 1.25 (t, 3H), 3.06 (quintet, 1H), 3.34 (quintet, 1H), 3.65 (q, 2H), 7.68 (d, 1H), 7.79 (t, 1H), 7.87 (t, 1H), 8.01 (d, 1H). ^{13}C-NMR (DMSO-d_6): δ = 13.672, 14.875, 35.132, 35.686, 93.315, 124.410, 126.608, 127.294, 133.345, 136.855, 141.302, 155.610, 166.893, 167.716, MS: m/z 274 (M^+), 259, 230, 201, 175, 174, 160 (base peak), 104, 90, 76, 50. Anal. Calcd for $C_{14}H_{14}N_2O_4$: C, 61.31; H, 5.11; N, 10.22; Found C, 61.39; H, 5.03; N, 10.25.

***N*-1',*N*-3'-Di-*n*-propyl-2'*H*,3*H*,5'*H*-spiro[2-benzofuran-1,4'-imidazolidine]-2',3,5'-trione (6b):**

Product **5b**, 3 g (10.0 mmol) was reacted with sodium periodate, 2.11 g (10.0 mmol) for 20 h. Purification by flash chromatography (70% n-hexane/ 30% EtOAc) yielded pure **6b**, as an oil. Yield: 82.0%. TLC (70% n-hexane: 30% EtOAc) single spot, R_f = 0.76. IR (KBr) *v*: 2973, 2931, 1785, 1720 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ = 0.756 (t,3H), 0.883 (t, 3H), 1.298 (doublet of sextet, 2H), 1.64 (sextet, 2H), 2.90 (quintet, 1H), 3.29 (quintet, 1H), 3.521 (t, 2H), 7.85 (t, 1H), 7.92 (t, 1H), 7.94 (d, 1H), 8.07 (d, 1H). ^{13}C-NMR (DMSO-d_6): δ = 10.85, 10.90, 20.74, 21.84, 40.73, 41.54, 92.51, 135.89, 123.90, 125.81, 126.77, 132.44, 140.72, 155.16, 166.59, 167.04. MS: m/z 302 (M^+), 273, 258, 216, 188, 174, 160, 145, 130, 117, 104, 90, 76, 70, 56, 41 (base peak). Anal. Calcd for $C_{16}H_{18}N_2O_4$: C, 63.56; H, 6.00; N, 9.27; Found C, 63.86; H, 6.02; N, 9.14.

***N*-1',*N*-3'-Dibenzyl-2'*H*,3*H*,5'*H*-spiro[2-benzofuran-1,4'-imidazolidine]-2',3,5'-trione (6c):**

Product **5c**, 2 g (5.000 mmol) was reacted with sodium periodate, 1.321 g (5.000 mmol) for 24 h. Two recrystallizations from aqueous MeOH resulted in **6c** as white crystals. Yield: 71.0 %, mp 164-167 ºC. TLC (70% toluene: 30% MeCN) R_f = 0.80. IR (KBr) *v*: 1783, 1732, 1601 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ = 4.282 (d, 1H), 4.492 (d, 1H), 4.775 (s, 2H), 7.029 (s, 2H), 7.182 (s, 3H), 7.339 (d, 2H), 7.415(t, 3H), 7.711 (d, 3H), 7.975 (s, 1H). ^{13}C-NMR (DMSO-d_6): δ = 42.61, 43.32, 92.33, 124.14, 125.10, 125.61, 126.63, 127.34, 127.46, 127.84, 128.21, 128.81, 132.25, 135.47, 135, 64, 135.94, 140.19, 155.03, 166.31, 166.87. MS: m/z 398 (M^{-+}), 355, 293, 265, 222, 193, 174, 160, 132, 104, 91 (base peak), 77, 65, 51. Anal. Calcd for $C_{24}H_{18}N_2O_4$: C, 72.36; H, 4.52; N, 7.03; Found: C, 72.30; H, 4.59; N, 7.01.

***N*-1'-Methyl-*N*-3'-ethyl-2'*H*,3*H*,5'*H*-spiro[2-benzofuran-1,4'-imidazolidine]-2',3,5'-trione (6d):**

Product **5d**, 2.6 g (10.0 mmol) was reacted with sodium periodate, 2.14 g (10.0 mmol) at 50-60 ºC with stirring for 10 h. Two recrystallizations from MeOH-water (9:1) resulted in **6d** as white crystals. Yield: 77.4 %, mp 112-114 ºC. TLC (95% EtOAc: 5% MeOH) R_f = 0.54. IR (KBr) *v*: 1785, 1732cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ = 0.93 (t, 3H), 3.00 (sextet, 1H), 3.28 (sextet, 1H), 3.36 (s, 3H), 7.79 (d, 1H), 7.84 (t, 1H), 7.94 (t, 1H), 8.05 (d, 1H). ^{13}C-NMR (DMSO-d_6): δ = 15.20, 26.13, 35.65, 93.53, 125.10, 126.56, 127.67, 133.22, 136.61, 141.68, 155.85, 167.51, 167.87. MS: m/z 260 ($M^{+\cdot}$), 245, 231, 216, 201, 187, 160 (base peak), 104, 76. Anal. Calcd for $C_{13}H_{12}N_2O_4$: C, 60.00; H, 4.65; N, 10.76; Found C, 60.08, H, 4.59; N, 10.73.

***N*-1'-Phenyl-*N*-3'-ethyl-2'*H*,3*H*,5'*H*-spiro[2-benzofuran-1,4'-imidazolidine]-2',3,5'-trione, (6e):**

Product **5e**, 3 g (10 mmol) was reacted with sodium periodate, 2.07 g (10 mmol) for 18 h. Two recrystallizations from aqueous MeOH resulted in **6e** as white crystals. Yield: 67.0 %, mp 169-171 ºC. TLC (70% n-hexane: 30% EtOAc) R_f = 0.54. IR (KBr) *v*: 1797, 1783, 1735, 1598 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ = 1.019 (t, 3H), 3.12 (sextet, 1H), 3.38 (sextet, 1H), 7.48 (d, 5H), 7.86 (t, 1H), 7.98 (t, 1H), 8.09 (d, 1H), 8.19 (d, 1H). ^{13}C-NMR (DMSO-d_6): δ = 14.35, 35.16, 92.44, 124.50, 125.78, 127.65, 132.51, 135.87, 140.76, 153.65, 166.04, 166.59. MS: m/z 322 ($M^{+\cdot}$), 278, 249, 223, 174, 160, 131, 119 (base peak), 104, 76. Anal. Calcd for $C_{18}H_{14}N_2O_4$: C, 67.10; H, 4.37; N, 8.69; Found: C, 67.10; H, 4.35; N, 8.66.

***N*-1'-*o*-Fluorophenyl-*N*-3'-ethyl-2'*H*,3*H*,5'*H*-spiro[2-benzofuran-1,4'-imidazolidine]-2',3,5'-trione (6f):**

Product **5f**, 4 g (12.0 mmol) was reacted with sodium periodate, 2.53 g (12.0 mmol) for 16 h. Two recrystallizations from aqueous MeOH resulted in **6f** as white crystals. Yield: 72.8 %, mp 138-140 ºC. TLC (70% n-hexane: 30% EtOAc) R_f = 0.54. IR (KBr) *v*: 1800, 1788, 1744 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ = 1.018 (t, 3H), 3.127 (sextet, 1H), 3.381 (sextet, 1H), 7.402 (t, 1H), 7.634 (dd, 2H), 7.869 (t, 1H), 7.990, (t, 1H), 8.093 (d, 1H), 8.206 (d, 1H). ^{13}C-NMR (DMSO-d_6): δ = 14.23, 35.15, 92.40, 115.95, 124.54, 125.77, 127.21, 129.15, 132.51, 135.85, 140.75, 153.58, 160.38, 162.83, 166.02, 166.58. MS: m/z 340 ($M^{+\cdot}$), 241, 197, 174, 160, 137 (base peak), 131, 104, 76, 50. Anal. Calcd for $C_{18}H_{13}N_2O_4F$: C, 63.52; H, 3.85; N, 8.23; Found: C, 63.65; H, 3.84; N, 8.08.

***N*-1'-*m*-Fluorophenyl-*N*-3'-ethyl-2'*H*,3*H*,5'*H*-spiro[2-benzofuran-1,4'-imidazolidine]-2',3,5'-trione (6g):**

Product **5g**, 4 g (12.0 mmol) was reacted with sodium periodate, 2.53 g (12.0 mmol) for 16 h. Two

recrystallizations from aqueous MeOH resulted in **6g** as white crystals. Yield: 66.0 %, mp 139-141 ºC. TLC (70% toluene: 30% MeCN) R_f = 0.77**.** IR (KBr) *v*: 1799, 1782, 1745, 1601 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ = 1.020 (t, 3H), 3.132 (sextet, 1H), 3.376 (sextet, 1H), 7.350 (t, 1H), 7.445 (d, 1H), 7.751 (dt, 1H), 7.760, (t, 1H), 8.098 (d, 1H), 8.204 (d, 1H). ^{13}C-NMR (DMSO-d_6): δ = 14.23, 35.20, 92.32, 114.25, 115.62, 122.94, 124.61, 125.81, 126.77, 130.68, 132.47, 135.89, 140.71, 153.26, 160.48, 162.91, 165.80, 166.59. MS: m/z 340 (M^{+}), 241, 197, 175, 160 (base peak), 137, 131, 104, 76, 50. Anal. Calcd for $C_{18}H_{13}N_2O_4F$: C, 63.52; H, 3.85; N, 8.23; Found: C, 63.65; H, 3.84; N, 8.08.

_N_-1'-_p_-Fluorophenyl-_N_-3'-ethyl-2'_H_,3_H_,5'_H_-spiro[2-benzofuran-1,4'-imidazolidine]-2',3,5'-trione (6h):

Product **5h**, 4 g (12.0 mmol) was reacted with sodium periodate, 2.53 g (12.0 mmol) for 16 h. Two recrystallizations from aqueous MeOH resulted in **6h** as white crystals. Yield: 47.0 %, mp 131-133 ºC. TLC (70% n-hexane: 30% EtOAc) R_f = 0.54. IR (KBr) *v*: 1800, 1786, 1734 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ = 1.018 (t, 3H), 3.127 (sextet, 1H), 3.381 (sextet, 1H), 7.402 (t, 2H), 7.634 (dd, 2H), 7.869 (t, 1H), 7.990, (t, 1H), 8.093 (d, 1H), 8.206 (d, 1H). ^{13}C-NMR (DMSO-d_6): δ = 14.23, 35.15, 92.40, 115.95, 124.54, 125.77, 127.21, 129.15, 132.51, 135.85, 140.75, 153.58, 160.38, 162.83, 166.02, 166.58. MS: m/z 340 (M^{+}), 241, 197, 174, 160, 137 (base peak), 131, 104, 76, 50. Anal. Calcd for $C_{18}H_{13}N_2O_4F$: C, 63.52; H, 3.85; N, 8.23; Found: C, 63.41; H, 3.70; N, 8.01.

_N_-1'-_p_-Nitrophenyl-_N_-3'-ethyl-2'_H_,3_H_,5'_H_-spiro[2-benzofuran-1,4'-imidazolidine]-2',3,5'-trione (6i):

Product **5i**, 4 g (10.84 mmol) was reacted with sodium periodate, 2.319 g (10.84 mmol) for 16 h. Two recrystallizations from aqueous MeOH resulted in **6i** as white crystals. Yield: 63.0 %, mp 174-176 ºC. TLC (70% toluene: 30% MeCN) R_f = 0.85. The IR, ^{1}H-NMR, ^{13}C-NMR, MS and elemental analysis data of this compound have been reported in our earlier communication[1].

_N_-1'-_p_-Methoxyphenyl-_N_-3'-ethyl, 2'_H_,3_H_,5'_H_-spiro[2-benzofuran-1,4'-imidazolidine]-2',3,5'-trione (6j):

Product **5j**, 4 g (11.3 mmol) was reacted with sodium periodate, 2.41 g (11.3 mmol) for 16 h. Two recrystallizations from aqueous MeOH resulted in **6j** as white crystals. Yield: 71.0 %, mp 167-169 ºC. TLC (70% toluene: 30% MeCN) R_f = 0.68. IR (KBr) *v*: 1801, 1786, 1735 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ = 1.011 (t, 3H), 3.110 (sextet, 1H), 3.372 (sextet, 1H), 3.809 (s, 3H), 7.080 (d, 2H), 7.447 (d, 2H), 7.854 (t, 1H), 7.970 (t, 1H), 8.075 (d, 1H), 8.153 (d, 1H). ^{13}C-NMR (DMSO-d_6): δ = 14.15, 35.05, 55.34, 92.39, 114.17, 123.44, 125.65, 126.74, 128.20, 132.37, 135.74, 140.77, 153.85, 159.20, 166.13, 166.49. MS:

m/z 352 ($M^{+\cdot}$), 336, 253, 238, 160, 149 (base peak), 134, 104, 76, 50. Anal. Calcd for $C_{19}H_{16}N_2O_5$: C, 64.77; H, 4.58; N, 7.95; Found: C, 64.71; H, 4.53; N, 7.95.

***N*-1'-Methyl-*N*-3'-propyl-2'*H*,3*H*,5'*H*-spiro[2-benzofuran-1,4'-imidazolidine]-2',3,5'-trione (6k):**
Product, **5k**, 2.0 g (7.246 mmol) was reacted with sodium periodate, 1.551 g (7.246 mmol) with stirring for 18 h. Two recrystallizations from MeOH-water (9:1) resulted in **6k** as white crystals. Yield: 82.5 %, m.p. 142-144 ºC. TLC (70% toluene: 30% MeCN) R_f = 0.75. IR (KBr) *v*: 2986, 1792, 1784, 1734, 1604 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ = 0.748 (t, 3H), 1.310 (dodecet, 2H), 2.878 (quintet, 1H), 3.040 (s, 3H), 3.259 (quintet, 1H), 7.834 (t, 1H), 7.934 (t, 1H), 7.961 (d, 1H), 8.054 (d, 1H). ^{13}C-NMR (DMSO-d_6): δ = 10.97, 21.94, 25.48, 41.62, 92.78, 124.29, 125.85, 126.81, 132.55, 135.94, 140.87, 155.46, 166.80, 167.13. MS: m/z 274 ($M^{+\cdot}$), 259, 245, 230, 201, 189, 174, 160 (base peak), 145, 132, 130, 104, 76, 56. Anal. Calcd for $C_{14}H_{14}N_2O_4$: C, 61.30; H, 5.14; N, 10.21; Found C, 61.08, H, 5.09; N, 10.11.

***N*-1'-Phenyl-*N*-3'-propyl-2'*H*,3*H*,5'*H*-spiro[2-benzofuran-1,4'-imidazolidine]-2',3,5'-trione, (6l):**
Product **5l**, 4 g (11.23 mmol) was reacted with sodium periodate, 2.40 g (11.23 mmol) for 12 h. Two recrystallizations from hexane: EtOAc (6:4) resulted in **6l** as white crystals. Yield: 50.0 %, mp 122-124 ºC. TLC (60% n-hexane: 40% EtOAc) R_f = 0.54. IR (KBr) *v*: 2970, 1780, 1736, 1598 cm^{-1}. ^{1}H-NMR (CD_3OD): δ = 0.826 (t, 3H), 1.446 (nonet, 2H), 2.996 (sextet, 1H), 3.356 (sextet, 1H), 7.434 (t, 1H), 7.494 (d, 4H), 7.78-7.91 (m, 3H), 8.023 (d, 1H). ^{13}C-NMR (DMSO-d_6): δ =10.93, 21.81, 41.80, 92.46, 124.46, 125.82, 126.76, 126.83, 128.71, 129.01, 131.05, 132.55, 135.91, 140.75, 154.02, 166.05, 166.62. MS: m/z 336 ($M^{+\cdot}$), 307, 292, 263, 236, 188, 174, 160 (base peak), 132, 119, 104, 91, 76, 50. Anal. Calcd for $C_{19}H_{16}N_2O_4$: C, 67.72; H, 4.78; N, 8.31; Found: C, 67.51; H, 4.73; N, 8.29.

***N*-1'-Methyl-*N*-3'-benzyl-2'*H*,3*H*,5'*H*-spiro[2-benzofuran-1,4'-imidazolidine]-2',3,5'-trione (6m):**
Product **5m**, 2 g (6.173 mmol) was reacted with sodium periodate, 1.321 g (6.173 mmol) for 16 h. Two recrystallizations from aqueous MeOH resulted in **6m** as white crystals. Yield: 71.0 %, mp 134.5
136 ºC. TLC (70% toluene: 30% MeCN) R_f = 0.77. IR (KBr) *v*: 1785, 1725, 1598 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ = 3.07 (s, 3H), 4.24 (d, 1H), 4.46 (d,1H), 7.04 (m, 2H), 7.18 (t, 3H), 7.74 (m, 3H), 7.96(m, 1H). ^{13}C-NMR (DMSO-d_6): δ = 25.51, 43.14, 92.43, 124.37, 125.47, 126.65, 127.39, 127.80, 128.16, 132.14, 135.33, 136.09, 140.48, 155.43, 166.48, 167.02. MS: m/z 322 ($M^{+\cdot}$), 279, 265, 237, 217, 193, 165, 160, 132 (base peak), 105, 104, 91, 76, 65. Anal. Calcd for $C_{18}H_{14}N_2O_4$: C, 67.07; H, 4.37; N, 8.69; Found: C, 67.00; H, 4.32; N, 8.66.

***N*-1'-Phenyl-*N*-3'-benzyl-2'*H*,3*H*,5'*H*-spiro[2-benzofuran-1,4'-imidazolidine]-2',3,5'-trione (6n):**

Product **5n**, 2 g (6.173 mmol) was reacted with sodium periodate, 1.321 g (6.173 mmol) for 16 h. Two recrystallizations from aqueous MeOH resulted in **6n** as white crystals. Yield: 77.8 %, mp 147-148 ºC. TLC (70% toluene: 30% MeCN) R_f = 0.82. IR (KBr) *v*: 1782, 1738, 1597 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ = 4.34 (d, 1H), 4.57 (d, 1H), 7.09 (dd, 2H), 7.21 (t, 3H), 7.49 (t, 1H), 7.56 (m, 4H), 7.78 (dt, 2H), 7.96 (d, 1H), 7.99 (d, 1H). ^{13}C-NMR (DMSO-d_6): δ = 43.49, 92.22, 124.65, 125.56, 126.66, 126.89, 127.48, 127.94, 128.20, 128.78, 129.02, 131.04, 132.31, 135.46, 135.85, 140.39, 154.16, 166.05, 166.43. MS: m/z 384 (M^{+}), 279, 265, 249, 237, 224, 193,174, 165, 160, 132 (base peak), 119, 104, 91, 76, 65. Anal. Calcd for $C_{23}H_{16}N_2O_4$: C, 71.49; H, 4.69; N, 7.25; Found: C, 71.14; H, 4.40; N, 7.27.

***N*-1'-Phenethyl-*N*-3'-benzyl-2'*H*,3*H*,5'*H*-spiro[2-benzofuran-1,4'-imidazolidine]-2',3,5'-trione (6o):**
Product **5o**, 0.9 g (2.17 mmol) was reacted with sodium periodate, 0.4652 g (2.17 mmol) with stirring for 18 h. Two recrystallizations from MeOH-water (9:1) resulted in **6o** as white crystals. Yield: 67.7 %, mp 112-114 ºC. TLC (70% toluene: 30% MeCN) R_f = 0.75. IR (KBr) *v*: 1798, 1787, 1722, 1603 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ = 3.00 (t, 3H), 3.86 (t, 3H), 4.22 (d, 1H), 4.36 (d, 3H), 6.92 (t, 2H), 7.15-7.20 (multiplet, 4H), 7.23 (d, 2H), 7.27 (d, 1H), 7.33 (t, 2H), 7.68 (two triplets, 2H), 7.93 (d, 1H). ^{13}C-NMR (DMSO-d_6): δ = 32.66, 40.31, 42.87, 91.94, 123.68, 125.49, 126.47, 126.58, 127.34, 127.58, 128.12, 128.49, 128.83, 132.09, 135.20, 136.10, 137.65, 140.27, 154.87, 166.34, 166.66. MS: m/z 412 (M^{+}), 307, 217, 193, 174 (base peak), 165, 160, 132, 105, 104, 91, 77, 65. Anal. Calcd for $C_{25}H_{20}N_2O_4$: C, 72.80; H, 4.88; N, 6.79; Found C, 72.73, H, 4.77; N, 6.81.

***N*-1'-Ethyl-*N*-3'-isopropyl-2'*H*,3*H*,5'*H*-spiro[2-benzofuran-1,4'-imidazolidine]-2',3,5'-trione (6p):**
Product **5p**, 3.0 g (10.345 mmol) was reacted with sodium periodate, 2.213 g (10.345 mmol) for 15 h. Two recrystallizations from MeOH-water (9:1) resulted in **6p** as white crystals. Yield: 74.0 %, m.p. 105-107 ºC. TLC (70% toluene: 30% MeCN) R_f = 0.45. IR (KBr) *v*: 2989, 2945, 1780, 1732cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ = 1.19 (d and t superimposed, 9H), 3.38 (septet, 1H), 3.56 (quartet, 1H), 7.84 (t, 1H), 7.93 (d, 1H), 7.96 (t, 1H), 8.06 (d, 1H). ^{13}C-NMR (DMSO-d_6): δ = 13.08, 20.44, 21.00, 34.04, 92.69, 124.02, 125.73, 126.83, 132.37, 135.83, 141.24, 153.85, 166.62, 166.67. MS: m/z 288 (M^{+}), 287, 273, 245, 230, 189, 174 (base peak), 160, 145, 132, 130, 104, 76, 56. Anal. Calcd for $C_{15}H_{16}N_2O_4$: C, 62.48; H, 5.59; N, 9.71; Found C, 62.67, H, 5.57; N, 9.73.

***N*-1'-Neopentyl-*N*-3'-isopropyl-2'*H*,3*H*,5'*H*-spiro[2-benzofuran-1,4'-imidazolidine]-2',3,5'-trione (6q):**
Product **5q**, 3.0 g (9.036 mmol) was reacted with sodium periodate, 1.933 g (9.036 mmol) for 15 h. Two recrystallizations from MeOH-water (9:1) gave **6q** as white crystals. Yield: 68.3 %, mp 86-88 ºC. TLC

(70% toluene: 30% MeCN) R_f = 0.82. IR (KBr) *v*: 2974, 2935, 1782, 1736cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ = 0.90 (s, 9H), 1.18 (d,6H), 3.32 (s, 2H), 3.37 (septet, 1H), 7.82 (t, 1H), 7.90 (d, 1H), 7.94 (t, 1H), 8.05 (d, 1H). ^{13}C-NMR (DMSO-d_6): δ = 20.41, 20.89, 27.67, 33.34, 45.41, 49.73, 92.74, 123.78, 125.78, 126.87, 132.38, 135.93, 141.29, 154.47, 166.66, 167.51. MS: m/z 330 ($M^{\cdot+}$), 315, 274, 203, 189, 174 (base peak), 160, 132, 130, 104, 90, 76, 57, 41. Anal. Calcd for $C_{18}H_{22}N_2O_4$: C, 65.32; H, 6.70; N, 8.46; Found C, 65.25, H, 6.72; N, 8.57.

***N*-1'-Phenyl-*N*-3'-phenethyl-2'*H*,3*H*,5'*H*-spiro[2-benzofuran-1,4'-imidazolidine]-2',3,5'-trione (6r):**
Product **5r**, 2.0 g (5.00 mmol) was reacted with sodium periodate, 1.07 g (5.00 mmol) with stirring for 19 h. Two recrystallizations from MeOH-water (9:1) resulted in **6r** as white crystals. Yield: 60.0 %, mp 173-176 ºC. TLC (70% toluene: 30% MeCN) R_f = 0.62. IR (KBr) *v*: 1785, 1738, 1596 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ = 2.74 (sextet, 1H), 2.83 (sextet, 1H), 3.28 (septet, 1H), 3.60 (septet, 1H), 7.08 (d, 2H), 7.17-7.26 (multiplet, 3H), 7.48 (multiplet, 1H), 7.54 (multiplet, 4H), 7.86 (t, 1H), 7.94 (t, 1H), 8.09 (t, 2H). ^{13}C-NMR (DMSO-d_6): δ = 35.37, 42.49, 93.31, 125.27, 126.68, 127.32, 127.61, 127.76, 129.29, 129.37, 129.60, 129.90, 131.87, 133.37, 136.71, 138.75, 141.34, 154.73, 166.68, 167.39. MS: m/z 398 ($M^{\cdot+}$), 353, 307, 294, 266, 263, 206, 174, 160 (base peak), 119, 104, 91, 77, 76. Anal. Calcd for $C_{24}H_{18}N_2O_4$: C, 72.35; H, 4.55; N, 7.03; Found C, 72.18, H, 4.47; N, 7.00.

***N*-1'-(α,α-Dideutero-2-phenylethyl)-*N*-3'-benzyl-2'*H*,3*H*,5'*H*-spiro[2-benzofuran-1,4'-imidazolidine]-2',3,5'-trione (6s):**
Product **5s**, 2.0 g (4.95 mmol) was reacted with sodium periodate, 1.05 g (4.95 mmol) with stirring for 18 h. Two recrystallizations from MeOH-water (9:1) resulted in **6s** as white crystals. Yield: 72.5 %, mp 172-174 ºC. TLC (70% toluene: 30% MeCN) R_f = 0.73. IR (KBr) *v*: 1782, 1738, 1599 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ = 2.71 (d, 1H), 2.80 (d, 1H), 7.07 (d, 2H), 7.16-7.26 (multiplet, 3H), 7.45-7.57 (multiplet, 5H), 7.86 (t, 1H), 7.94 (t, 1H), 8.08 (d, 1H), 8.10 (d, 1H). ^{13}C-NMR (DMSO-d_6): δ = 34.31, 40.88, 92.42, 124.45, 125.83, 126.46, 126.78, 126.89, 128.44, 128.52, 128.76, 129.05, 130.97, 132.52, 135.87, 137.87, 140.46, 153.87, 166.04, 166.56. MS: m/z 400 ($M^{\cdot+}$), 309, 294, 266, 238, 174, 162 (base peak), 119, 104, 91, 76. Anal. Calcd for $C_{24}H_{16}D_2N_2O_4$: C, 71.63; H, 4.50; N, 6.96; Found C, 71.83, H, 4.50; N, 7.00.

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