Synthesis and Characterization of Novel Hydantoins as Potential COX-2 Inhibitors: 1,5-Diarylhydantoins

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To develop new COX-2 inhibitors, 1,5-diarylhydantoins and 1,5-diaryl-2-thiohydantoins were synthesized from phenylacetic acids by esterification, bromination, C-N bond formation and cyclization. Esters **1-3** were efficiently synthesized from the starting materials by reflux in absolute methanol for 3 h containing concentrated sulfuric acid as catalyst. Bromination was carried out with *N*-bromosuccinimide at rt in dichloromethane. Bromides **4-6** were reacted with aniline, *p*-anisidine, sulfanilamide in ethanol (or *N,N*-dimethylformamide) to provide the amines **7-15**. Hydantoins and 2-thiohydantoins **16-46** were synthesized from amines **7-15** by treating them with potassium isocyanate (or potassium thiocyanate) and triethylamine. The synthetic process from alkyl *α*-anilinophenylacetate **7-15** to 3-alkylhydantoins was carried out in a one-pot reaction using alkyl isocyanate (alkyl isothiocyanate).

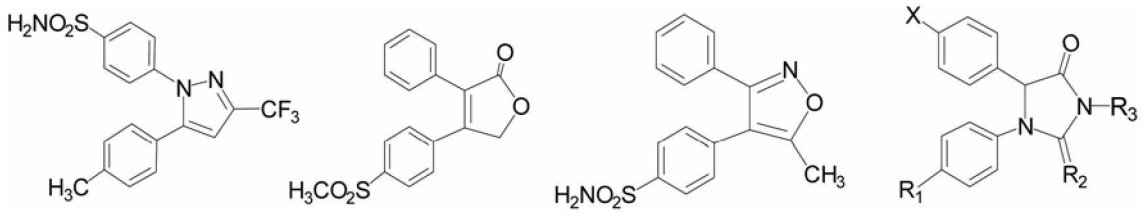
Key Words : Diarylhydantoins, Diaryl-2-thiohydantoins, Hydantoins, Synthesis, COX-2 inhibitors

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely utilized for the treatment of inflammation, pain, and fever, but their use is often accompanied by gastrointestinal (GI) ulcerations and bleeding.[1] Inflammatory processes are provoked by different chemicals/biospecies including proinflammatory enzymes/cytokines, small molecular species, such as eicosanoids, and tissue degrading enzymes. Of these factors, cyclooxygenase (COX) catalyzes the conversion of arachidonic acid to prostaglandins (PGs) – key proinflammatory eicosanoids. All NSAIDs are believed to disrupt the biosynthesis of PGs by inhibiting the COX.[2] In 1990s, Fu *et al.* discovered the existence of two isoforms of this enzyme.[3] COX-1 a constitutive form and COX-2 an inducible form. COX-1 is expressed in normal tissues and is physiologically important for GI and renal functions, while the COX-2 isoform is located primarily in inflamed tissues.[4-7] It seems reasonable that a selective COX-2 inhibitor could block PGs production at a site of inflammation without affecting beneficial PGs in normal tissues, such as, in the stomach and kidney.

The above hypothesis was partially proven when the first selective compounds, NS-398 and DuP-697, were tested in animal models. Both compounds showed anti-inflammatory, analgesic and antipyretic activities, but they did not cause gastrointestinal lesions at high doses.[8-10] Also, a new generation of anti-inflammatory drugs, celecoxib (Celebrex®),[11] rofecoxib (Vioxx®)[12] and valdecoxib (Bextra®)[13] are being widely prescribed to treat acute or chronic inflammation by providing symptomatic pain relief. COX-2 versus COX-1 selectivity demonstrated the superiority of these compounds over other NSAIDs in terms of reducing GI side effects.[14]

However, emerging evidence suggests that adverse reactions such as GI irritation or ulceration and renal complications are associated with the prolonged use of COX-2 selective inhibitors. These adverse reactions have been attributed, at least in part, to COX-1 inhibition during long-term exposure or at higher doses.[15] COX-2 selective inhibitors are also known to suppress the synthesis of prostacyclin, a potent vasodilator, gastroprotectant, and platelet inhibitor, by inhibiting endothelial COX-2. Moreover, COX-2 selective inhibitors do not inhibit the production of thromboxane, a vasoconstrictor, and promoter of platelet aggregation, which is synthesized in platelets by COX-1.[16] Therefore, COX-2 selective inhibitors intrinsically lack antithrombotic activity, and some cardiovascular complications were associated with their use preclinically.[17] Thus, there is still a need for novel, selective, potent COX-2 inhibitors with a better pharmacologic profile than the current COX-2



Celecoxib Rofecoxib Valdecoxib 1,5-Diarylhydantoins

inhibitors.

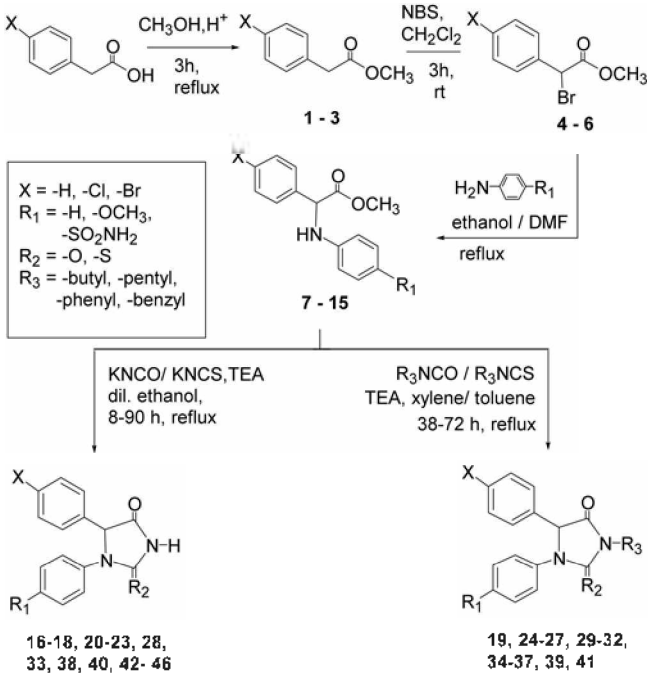
Due to the NSAIDs exhibited by selective COX-2 inhibitors, many researchs were reported during last several years. Very recently, Hwang *et al.*,[18] reported the indole derivatives as potential COX-2 inhibitors.

Here, we describe the synthesis of a novel series of hydantoin containing a 5-membered heterocyclic ring. In this study, we introduced a *p*-substituted phenyl group onto the 1- and 5-positions of the hydantoin ring in the hope of producing a selective COX-2 inhibitory effect. This study describes the syntheses of novel 1,5-diarylhydantoin derivatives with a phenyl group at the 5-position and a phenyl group (or *p*-sulfamylphenyl, *p*-methoxyphenyl group) at the 1-position (Scheme 1).

Results and Discussion

In Table 1, we summarized the physical properties and the optimal condition for the compounds **16-46**. Two synthetic routes were classified as follows.

Production of hydantoin ring using KNCO/KNCS (Class I). We have previously reported some preliminary



Scheme 1. Synthesis of diaryl hydantoin derivatives **16-46**.

Table 1. Target Compounds **16-46** and Optimal Conditions for Synthesis

Comp	Class/ I[a], II[b]	R_1	R_2	R_3	X	Molar Ratio[c] Reag./Subs.	Time /hr	mp/°C	Yield/%[d]
16	I	H	O	H	H	1	8	190	59.1
17	I	H	O	H	Cl	1.5	67	203.2-204.9	81.0
18	I	H	O	H	Br	1.5	48	209	79.8
19	II	H	O	*n*-butyl	H	1	38	oil	–
20	I	H	S	H	H	1.8	32	189	59.7
21	I	H	S	H	Cl	1	74	205.1-205.9	68.2
22	I	H	S	H	Br	1	90	205	75.2
23	I	CH_3O	O	H	H	1.5	8	193.7-195.5	77.9
24	II	CH_3O	O	*n*-butyl	H	2	48	101.8-103.7	62.3
25	II	CH_3O	O	*n*-pentyl	H	2	48	122.4-125.3	41.3
26	II	CH_3O	O	phenyl	H	2	48	145.8-148.0	32.3
27	II	CH_3O	O	benzyl	H	2	48	118.9-121.6	55.2
28	I	CH_3O	O	H	Cl	2	24	197.6-200.4	90.4
29	II	CH_3O	O	*n*-butyl	Cl	2	72	93.6-95.2	67.2
30	II	CH_3O	O	*n*-pentyl	Cl	2	48	97.4-98.6	79.4
31	II	CH_3O	O	phenyl	Cl	2	48	180.2-183.2	62.1
32	II	CH_3O	O	benzyl	Cl	2	48	147.6-148.8	89.6
33	I	CH_3O	O	H	Br	2	24	194.5-195.9	93.1
34	II	CH_3O	O	*n*-butyl	Br	2	72	102.7-104.5	56.7
35	II	CH_3O	O	*n*-pentyl	Br	2	48	91.7-93.9	54.8
36	II	CH_3O	O	phenyl	Br	2	48	189.5-190.1	30.4
37	II	CH_3O	O	benzyl	Br	2	48	139.5-141.0	87.7
38	I	CH_3O	S	H	H	2	16	197.7-200.5	92.7
39	II	CH_3O	S	benzyl	H	2	48	119.1-121.1	48.6
40	I	CH_3O	S	H	Br	2	60	184.6-186.8	93.3
41	II	CH_3O	S	benzyl	Br	2	48	188.7-191.0	27.2
42	I	SO_2NH_2	O	H	H	2	16	202.0-211.5	60.0
43	I	SO_2NH_2	O	H	Cl	2	16	212.4-225.0	68.1
44	I	SO_2NH_2	O	H	Br	2	18	221.2-226.0	95.8
45	I	SO_2NH_2	S	H	H	2	30	242.0-248.0	76.9
46	I	SO_2NH_2	S	H	Cl	2	50	200.9-204.2	69.3

[a,b]All reactions were performed in ethanol/xylene under reflux, except **19** (in toluene). [c]Reag./Subs. is the ratio of reagent (KNCO, KNCS, R_3NCO, and R_3NCS) to substrate (amine **7-15**). [d]Yields referred to isolated product.

results for a novel series of α-amino acids **7-15**[19] (Scheme 1). The classical method for the preparation of hydantoins involves the reaction of α-amino acids with potassium cyanate: this reaction was carried out in boiling aqueous solution. The free hydantoic acid produced may be isolated by acidification of the solution or it may be converted into the corresponding hydantoin by treatment with 25% HCl.

This cyclization was preferentially carried out by refluxing a solution in *dil*-ethanol. It should be noted that the production of analogues of 2-thiohydantoin needs additional mild base such as triethylamine, because of the different reactivity of sulfur versus oxygen containing analogs. The formation of hydantoin was generally faster than that of 2-thiohydantoins. In some cases (*e.g.*, R_1 = anilino group or *p*-methoxyanilino group), the reaction mixture was stirred for 1 h in order to increase the yield of Class I after adding c-HCl. In other case (*e.g.*, R_1 = *p*-sulfamylanilino group), the pH of the reaction mixture was optimized with respect to yield according to the presence of halogen (X = H, Cl, Br). For example, compounds **42** and **45** were obtained in maximal yields at pH 4, while compounds **43**, **44**, and **46** required a pH 1. Also, compounds containing a halogen (X = Cl, Br) required longer reaction times than those without a halogen (Table 1).

Identification of Class I products was performed by NMR, IR and GC-MS. In the ^{1}H-NMR, the NH peak disappeared whereas the CH peak appeared as a singlet at 5 ppm. In the IR spectra, the carbonyl absorption band was not present at 1700 cm^{-1} because of the tautomeric nature of the hydantoin ring (Figure 1). When R_1 was H or CH_3O, this band appeared clearly. We believed that the enol-form was more stable than keto-form because both of functional groups donated an electron to the hydantoin ring.

Production of hydantoin ring using RNCO/RNCS (one-pot reaction) (Class II). A large number of aryl and alkyl isocyanate and isothiocyanates have been employed in this reaction.[20] The *N*-aralkylhydantoin analogues containing a phenyl or methoxyphenyl at position 1 of the hydantoin ring (R3 = *n*-butyl, *n*-pentyl, phenyl, benzyl) were synthesized in a one-step process (Scheme 1) from α-amino acids **7-15** using aralkyl isocyanate or isothiocyanate in xylene using a mild base like triethylamine.[21] Molecular sieve (4 Å) was added to remove the methanol produced. Reaction rates were found to be highly dependent on the solvent system used.

The reactivity of aralkyl isothiocyanate was low versus isocyanate and it generated many side reactions. The success or failure of the reaction depended on the nature of the functional group (R1 = *p*-methoxy or *p*-sulfonamide). For example, when R1 was *p*-methoxy (an electron donating group), the reaction proceeded well to give the desired products in good yield (Table 1). On the other hand, when R1 was *p*-sulfonamide group (an electron withdrawing group), the reaction did not proceed well. Also, compounds with *p*-sulfonamide did not react regardless of solvent type (*e.g.* xylene, DMF, toluene, ethanol, etc.).

In the ^{1}H-NMR spectra, the -CH peak was shifted from 5 ppm to 6 ppm. Also in the IR spectra, two carbonyl absorption bands appeared at 1700 cm^{-1}, whereas they were absent in Class I (Table 1). We considered that the keto-form was more stable than the enol-form in the case of substitution aralkyl group at the 3-position of the hydantoin ring.

In conclusion, we have developed a new class of 1,5-diarylhydantoins, which is the hybrid type compound **16-46** by structural modification of celecoxib and rofecoxib. 1,5-Diarylhydantoins were synthesized by esterification, bromination, C-N-bond formation and cyclization.

Experimental Section

Chemicals. Chemicals were supplied by Aldrich, Sigma, Merck, and Tokyo Kasei. Melting points were determined in open capillary tubes on a Büchi 535 melting point apparatus and uncorrected. NMR spectra were recorded using a Bruker 300 MHz NMR spectrometer. Chemical shifts are reported in parts per million and were recorded in chloroform-d or dimethyl-d_6 sulfoxide with tetramethylsilane as the internal standard. NMR spin multiplicities are indicated by the symbols: s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). IR spectra were recorded on a Perkin-Elmer 16F PC FT-IR spectrometer using NaCl discs and pellets. Mass fragmentations were recorded using an Agilent 6890 GC and 5973 MS.

General procedure for the compounds 16-18, 23, 28, 33 and 42-44. Methyl α-anilinophenylacetate **7** (2.4 g, 10 mmol) was dissolved in ethanol (20 mL) by heating. KNCO (0.81 g, 10 mmol) in water (10 mL) was added quickly and then refluxed for 8 h. The reaction mixture was concentrated under reduced pressure to 3 mL and c-HCl was added to pH 1 in an ice-bath. The resulting solid was washed with ice-water and recrystallized in *dil*-ethanol.

1,5-Diphenylhydantoin (16): Yield: 1.49 g (59.1%), mp 190 °C. TLC [methylene chloride:methanol (9:1)] Rf 0.27. ^{1}H NMR (DMSO-d_6) δ 7.51 (d, J = 6.0 Hz, 2H, aromatic), 7.39-7.26 (m, 3H, aromatic), 7.03 (t, J = 9.0 Hz, 2H, aromatic), 6.65 (d, J = 6.0 Hz, 2H, aromatic), 6.54 (t, J = 9.0

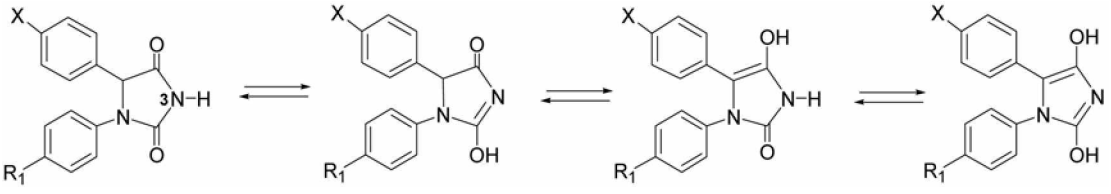


Figure 1. Keto-enol tautomerizations of hydantoin ring.

Hz, 1H, aromatic). 5.07 (s, 1H, CH), 3.34 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ 172.86 (C=O×2), 146.86, 138.45, 128.63, 128.34, 127.65, 127.40, 116.43, 112.93 (aromatic × 2), 59.57 (CH), 55.09 (CH_3). FT-IR (KBr) cm^{-1} 3408 (NH), 2991 (CH). GC-MS: m/z 252.32 (M^+), 180.1 (100.0), 181.1 (87.18), 77.1 (35.0), 182.1 (11.8), 51.1 (10.6).

1-Phenyl-5-(*p*-chlorophenyl)hydantoin (17): Yield: 81.0%, mp 203.2-204.9 °C, TLC [methylene chloride: methanol (9:1)] Rf 0.28. ^{1}H NMR (DMSO-d_6) δ 7.52 (d, J = 8.7 Hz, 2H, aromatic), 7.42 (d, J = 8.4 Hz, 2H, aromatic), 7.03 (t, J = 8.4 Hz, 2H, aromatic), 6.64 (d, J = 7.8 Hz, 2H, aromatic), 6.57 (t, J = 7.2 Hz, 1H, aromatic), 5.13 (s, 1H, CH), 3.35 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ 172.89 (C=O×2), 147.07, 138.16, 132.63, 129.69, 129.10, 128.75, 117.02, 113.47 (aromatic×2), 59.31(CH). FT-IR (KBr) cm^{-1} 3412 (NH), 2993 (CH), 770 (C-Cl). GC-MS: m/z 287.76 (M^+), 214.1 (100.0), 215.1 (94.5), 77.1 (47.1), 216.0 (43.6), 217.0 (32.0).

1-Phenyl-5-(*p*-bromophenyl)hydantoin (18): Yield: 79.8%, mp 209 °C, TLC [methylene chloride:methanol (9:1)] Rf 0.34. ^{1}H NMR (DMSO-d_6) δ 7.56 (d, J = 8.4 Hz, 2H, aromatic), 7.47 (d, J = 8.7 Hz, 2H, aromatic), 7.03 (t, J = 8.4 Hz, 2H, aromatic), 6.64 (d, J = 7.8 Hz, 2H, aromatic), 6.55 (t, J = 7.2 Hz, 1H, aromatic), 5.12 (s, 1H, CH), 3.36 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ 172.83 (C=O×2), 147.05, 138.56, 131.68, 130.05, 129.10, 121.22, 117.04, 113.48 (aromatic×2), 59.35 (CH). FT-IR (KBr) cm^{-1} 3406 (NH), 2992 (CH), 766 (C-Br). GC-MS: m/z 332.16 (M^-), 169.0 (100.0), 171.0 (99.2), 261.0 (73.4), 263.0 (69.7), 90.1 (30.8).

1-(*p*-Methoxyphenyl)-5-phenylhydantoin (23): Yield: 77.9%, mp 193.7-195.5 °C, TLC [*n*-hexane:ethyl acetate (2:1)] Rf 0.1, [methylene chloride:methanol (9:1)] Rf 0.29. ^{1}H NMR (DMSO-d_6) δ 7.50 (d, J = 7.2 Hz, 2H, aromatic), 7.37-7.25 (m+d, 3H, aromatic), 6.64 (d+d, J = 9.3 and 9 Hz, 4H, aromatic), 5.01 (s, 1H, CH), 3.60 (s, 3H, CH_3), 3.40 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ 173.00 (C=O×2), 151.04, 140.96, 138.75, 128.26, 127.51, 127.35, 114.27, 114.10 (aromatic×2), 60.42 (CH), 55.09 (CH_3). FT-IR (KBr) cm^{-1} 3402 (NH), 1514 (CO). GC-MS: m/z 282.30 (M^-), 196.1 (100.00), 211.1 (88.27), 167.1 (21.76), 210.2 (15.50), 197.1 (15.11).

1-(*p*-Methoxyphenyl)-5-(*p*-chlorophenyl)hydantoin (28): Yield: 90.4%, mp 197.6-200.4 °C, TLC [*n*-hexane:ethyl acetate (2:1)] Rf 0.1, [methylene chloride:methanol (9:1)] Rf 0.22. ^{1}H NMR (DMSO-d_6) δ 7.52 (d, J = 8.4 Hz, 2H, aromatic), 7.41 (d, J = 8.4 Hz, 2H, aromatic), 6.63 (d+d, J = 9 and 9 Hz, 4H, aromatic), 5.06 (s, 1H, CH), 3.60 (s, 3H, CH_3), 3.34 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ 172.62 (C=O×2), 151.14, 140.66, 137.87, 132.10, 129.22, 128.24, 114.25, 114.22 (aromatic×2), 59.59 (CH), 55.14 (CH_3). FT-IR (KBr) cm^{-1} 3401 (NH), 1514 (CO), 769 (C-Cl). GC-MS: m/z 316.74 (M^-), 230.0 (100.00), 245.0 (91.43), 232.0 (34.32), 247.0 (30.96), 246.0 (18.70).

1-(*p*-Methoxyphenyl)-5-(*p*-bromophenyl)hydantoin (33): Yield: 93.1%, mp 194.5-195.9 °C, TLC [*n*-hexane:ethyl acetate (2:1)] Rf 0.1, [methylene chloride:methanol (9:1)] Rf 0.17. ^{1}H NMR (DMSO-d_6) δ 7.55 (d, J = 8.4 Hz, 2H, aromatic), 7.45 (d, J = 8.4 Hz, 2H, aromatic), 6.63 (d+d, J = 9 and 9 Hz, 4H, aromatic), 5.06 (s, 1H, CH), 3.60 (s, 3H, CH_3), 3.36 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ 172.55 (C=O×2), 151.14, 140.63, 138.28, 131.16, 129.58, 120.67, 114.32, 114.24 (aromatic×2), 59.62 (CH), 55.06 (CH_3). FT-IR (KBr) cm^{-1} 3401 (NH), 1513 (CO), 765 (C-Br). GC-MS: m/z 361.20 (M^-), 291.0 (100.00), 289.0 (99.18), 274.0 (88.27), 275.9 (87.91), 290.0 (27.41).

5-Phenyl-1-(*p*-sulfamylphenyl)hydantoin (42): Yield: 60.0%, mp 202.0-211.5 °C, TLC [methylene chloride: methanol (9:1)] Rf 0.1. ^{1}H NMR (DMSO-d_6) δ 7.48 (d, J = 8.7 Hz, 4H, aromatic), 7.31-7.18 (m, 3H, aromatic), 6.79 (s, 2H, NH_2), 6.58 (d, J = 8.7 Hz, 2H, aromatic), 4.89 (s, 1H, CH), 3.24 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ 171.32 (C=O×2), 149.63, 140.05, 130.05, 127.89, 127.03, 126.94, 126.71, 111.63 (aromatic×2), 60.53 (CH). FT-IR (NaCl) cm^{-1} 3369 (NH), 3193 (NH_2), 1710 (C=O), 1301 (SO_2). GC-MS: m/z 331.35 (M^-), 180.1 (100.00), 181.1 (84.25), 77.1 (36.22), 51.1 (11.75), 182.1 (11.11).

5-(*p*-Chlorophenyl)-1-(*p*-sulfamylphenyl)hydantoin (43): Yield: 68.1%, mp 212.4-225.0 °C, TLC [methylene chloride: methanol (9:1)] Rf 0.1. ^{1}H NMR (DMSO-d_6) δ 7.80-7.43 (m, 6H, aromatic), 6.93 (s, 2H, NH_2), 6.75 (d, J = 8.7 Hz, 2H, aromatic), 5.29 (d, J = 7.2 Hz, 1H, CH), 3.45 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ 172.22 (C=O×2), 152.61, 150.92, 137.30, 132.93, 129.69, 129.19, 128.94, 126.81, 112.23 (aromatic×2), 58.72 (CH). FT-IR (NaCl) cm^{-1} 3332 (NH), 3160 (NH_2), 1712 (C=O), 1334 (SO_2), 722 (C-Cl). GC-MS: m/z 365.80 (M^+), 214.1 (100.00), 215.0 (95.39), 77.0 (46.56), 216.0 (44.66), 217.0 (32.02).

5-(*p*-Bromophenyl)-1-(*p*-sulfamylphenyl)hydantoin (44): Yield: 95.8%, mp 221.2-226.0 °C, TLC [methylene chloride :methanol (9:1)] Rf 0.1. ^{1}H NMR (DMSO-d_6) δ 7.60-7.44 (m, 6H, aromatic), 6.92 (s, 2H, NH_2), 6.74 (d, J = 9 Hz, 2H, aromatic), 5.27 (d, J = 7.2 Hz, 1H, CH), 3.43 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ 171.66 (C=O×2), 152.15, 150.45, 137.31, 131.39, 129.56, 128.72, 126.36, 121.03, 111.77 (aromatic×2), 58.35 (CH). FT-IR (NaCl) cm^{-1} 3337 (NH), 3159 (NH_2), 1711 (C=O), 1336 (SO_2), 721 (C-Br). GC-MS: m/z 410.25 (M^-), 221.1 (100.00), 281.0 (82.28), 147.1 (71.86), 207.0 (65.85), 73.1 (57.75).

General procedure for the compounds 20-22, 38, 40, 45-46. Methyl α-anilinophenylacetate **7** (1.2 g, 4.98 mmol) was dissolved in ethanol (10 mL) by heating. KNCS (0.87 g, 8.95 mmol) in water (5 mL) and triethylamine (1.26 mL, 9.04 mmol) were added and then refluxed for 8 h. The reaction mixture was then concentrated under reduced pressure to 3 mL and c-HCl was added to pH 1 in an ice-bath. The resulting solid was washed with ice-water and recrystallized in *dil*-ethanol.

1,5-Diphenyl-2-thiohydantoin (20): Yield: 0.8 g (59.7%), mp 189 °C. TLC [methylene chloride:methanol (9:1)] Rf 0.39. ^{1}H NMR (DMSO-d_6) δ 7.51 (d, J = 6.9 Hz, 2H, aromatic), 7.33 (m, 3H, aromatic), 7.03 (t, J = 7.9 Hz, 2H, aromatic), 6.65 (d, J = 7.8 Hz, 2H, aromatic), 6.54 (t, J = 7.2 Hz, 1H, aromatic), 5.07 (s, 1H, CH), 3.34 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ 172.80 (C=O, C=S), 146.86, 138.55,

128.61, 128.30, 127.58, 127.37, 116.39, 112.91 (aromatic×2), 59.65 (CH). FT-IR (NaCl) cm^{-1} 3275 (NH), 2928 (CH), 1714 (C=O). GC-MS: m/z 268.32 (M^+), 207.0 (100.0), 147.1 (73.1), 281.1 (68.8), 73.1 (607).

1-Phenyl-5-(*p*-chlorophenyl)-2-thiohydantoin (21): Yield: 68.2%, mp 205.1-205.9 °C, TLC [methylene chloride :methanol (9:1)] Rf 0.31. ^1H NMR (DMSO-d_6) δ 7.53 (d, J = 6.6 Hz, 2H, aromatic), 7.42 (d, J = 6.6 Hz, 2H, aromatic), 7.03 (t, J = 7.5 Hz, 2H, aromatic), 6.64 (d, J = 7.5 Hz, 2H, aromatic), 6.55 (t, J = 7.2 Hz, 1H, aromatic), 5.14 (s, 1H, CH), 3.38 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ 172.91 (C=O, C=S), 147.07, 138.11, 132.66, 131.55, 129.70, 129.11, 128.77, 117.04, 113.48 (aromatic×2), 59.29(CH). FT-IR (KBr) cm^{-1} 3407 (NH), 2993 (CH), 770 (C-Cl). GC-MS: m/z 303.82 (M^-), 125.0 (100.0), 217.1 (63.8), 127.0 (33.2), 219.1 (21.2), 216.1 (14.9).

1-Phenyl-5-(*p*-bromophenyl)-2-thiohydantoin (22): Yield: 75.2%, mp 205 °C, TLC [methylene chloride: methanol (9:1)] Rf 0.26. ^1H NMR (DMSO-d_6) δ 7.56 (d, J = 8.4 Hz, 2H, aromatic), 7.45 (d, J = 8.4 Hz, 2H, aromatic), 7.03 (t, J = 8.4 Hz, 2H, aromatic), 6.60 (d, J = 7.5 Hz, 2H, aromatic), 6.55 (t, J = 7.2 Hz, 1H, aromatic), 5.12 (s, 1H, CH), 3.36 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ 172.83 (C=O, C=S), 147.05, 138.58, 131.68, 130.05, 129.10, 121.21, 117.03, 113.48 (aromatic×2), 59.36 (CH). FT-IR (KBr) cm^{-1} 3407 (NH), 2992 (CH), 766 (C-Br). GC-MS: m/z 348.22 (M^-), 169.0 (100.0), 171.0 (97.1), 261.0 (72.4), 263.0 (70.4), 90.1 (29.2).

1-(*p*-Methoxyphenyl)-5-phenyl-2-thiohydantoin (38): Yield: 92.7%, mp 197.7-200.5 °C, TLC [*n*-hexane:ethyl acetate (2:1)] Rf 0.1, [methylene chloride:methanol (9:1)] Rf 0.29. ^1H NMR (DMSO-d_6) δ 7.50 (d, J = 6.9 Hz, 2H, aromatic), 7.37-7.28 (m+d, 3H, aromatic), 6.64 (d+d, J = 9.3 and 9.3 Hz, 4H, aromatic), 5.01 (s, 1H, CH), 3.60 (s, 3H, CH_3), 3.36 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ 172.96 (C=O, C=S), 151.03, 140.98, 138.82, 128.24, 127.48, 127.34, 114.27, 114.09 (aromatic×2), 60.46 (CH), 55.10 (CH_3). FT-IR (KBr) cm^{-1} 3403 (NH), 1514 (CO). GC-MS: m/z 298.37 (M^+), 196.1 (100.00), 211.1 (92.10), 167.1 (21.49), 210.2 (15.03), 197.1 (14.57).

1-(*p*-Methoxyphenyl)-5-(*p*-bromophenyl)-2-thiohydantoin (40): Yield: 93.3%, mp 184.6-186.8 °C, TLC [*n*-hexane :ethyl acetate (2:1)] Rf 0.1. ^1H NMR (DMSO-d_6) δ 7.55 (d, J = 8.4 Hz, 2H, aromatic), 7.45 (d, J = 8.4 Hz, 2H, aromatic), 6.63 (dd, J = 9.3 and 9 Hz, 4H, aromatic), 5.05 (s, 1H, CH), 3.60 (s, 3H, CH_3), 3.34 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ 172.54 (C=O, C=S), 151.13, 140.63, 138.30, 131.16, 129.58, 120.66, 114.24, 114.21 (aromatic×2), 59.62 (CH), 55.05 (CH_3). FT-IR (KBr) cm^{-1} 3413 (NH), 1513 (CO), 765 (C-Br). GC-MS: m/z 377.26 (M^+), 291.0 (100.00), 289.0 (97.51), 276.0 (87.35), 274.0 (86.73), 290.0 (27.00).

5-Phenyl-1-(*p*-sulfamylphenyl)-2-thiohydantoin (45): Yield: 76.9%, mp 242.0-248.0 °C, TLC [methylene chloride :methanol (9:1)] Rf 0.1. ^1H NMR (DMSO-d_6) δ 7.48 (d, J = 9 Hz, 4H, aromatic), 7.30-7.18 (m, 3H, aromatic), 6.77 (s, 2H, NH_2), 6.57 (d, J = 9 Hz, 2H, aromatic), 4.89 (s, 1H, CH), 3.25 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ 171.15 (C=O, C=S), 149.63, 140.09, 130.02, 127.88, 127.01, 126.95, 126.68, 111.61 (aromatic×2), 60.56 (CH). FT-IR (NaCl) cm^{-1} 3367 (NH), 3192 (NH_2), 1298 (SO_2). GC-MS: m/z 347.42 (M^-), 270.2 (100.00), 271.2 (52.55), 167.1 (37.52), 165.1 (21.69), 77.1 (16.51).

5-(*p*-Chlorophenyl)-1-(*p*-sulfamylphenyl)-2-thiohydantoin (46): Yield: 69.3%, mp 200.9-204.2 °C, TLC [methylene chloride:methanol (9:1)] Rf 0.1. ^1H NMR (DMSO-d_6) δ 7.44 (d+d, J = 8.7 and 8.4 Hz, 4H, aromatic), 7.23(d, J = 8.4 Hz, 2H, aromatic), 6.62 (s, 2H, NH_2), 6.52 (d, J = 8.7 Hz, 2H, aromatic), 4.94 (s, 1H, CH), 3.23 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ 171.84 (C=O, C=S), 149.34, 137.06, 132.35, 131.19, 129.22, 128.39, 126.95, 111.99 (aromatic×2), 58.38 (CH). FT-IR (NaCl) cm^{-1} 3340 (NH), 3215 (NH_2), 1716 (C=O), 1301 (SO_2), 721 (C-Cl). GC-MS: m/z 381.86 (M^-), 180.1 (100.00), 181.1 (86.85), 77.1 (36.71), 51.1 (13.17), 182.1 (11.41).

Procedure for the 3-butyl-1,5-diphenylhydantoin (19). Methyl α-anilinophenylacetate **7** (1.2 g, 4.98 mmol) and butyl isocyanate (0.56 mL, 4.98 mmol) were dissolved in toluene (10 mL). The reaction mixture was then refluxed at 90 °C for 38 h, cooled to room temperature and evaporated to remove the toluene. The residue obtained was purified by column chromatography to give compound **19**: TLC [*n*-hexane:ethyl acetate (4:1)] Rf 0.36. ^1H NMR (DMSO-d_6) δ 7.48 (d, J = 7.8 Hz, 2H, aromatic), 7.35-7.24 (m, 7H, aromatic), 7.08 (t, J = 7.5 Hz, 1H, aromatic), 5.43 (s, 1H, CH), 3.65-3.59 (m, 2H, CH_2), 1.70-1.61 (m, 2H, CH_2), 1.36 (q, J = 7.5 Hz, 2H, CH_2), 0.93 (t, J = 7.2 Hz, 3H, CH_3). ^{13}C NMR (DMSO-d_6) δ 170.03 (C=O×2), 154.76, 136.54, 133.03, 129.28, 129.09, 126.66, 124.58, 120.11, 113.36 (aromatic×2), 64.06 (CH), 39.04 (CH_2), 30.02 (CH_2), 19.92 (CH_2), 13.61 (CH_3). FT-IR (NaCl) cm^{-1} 2957 (CH), 1774 (C=O), 1712 (C=O). GC-MS: m/z 308.38 (M^-), 180.1 (100.0), 181.1 (100.0), 182.1 (100.0), 308.2 (100.0), 77.1 (54.3).

General procedure for the compounds 24-27, 29-32, and 34-37. Methyl α-(*p*-methoxyanilino)phenylacetate **10** (0.5 g, 1.84 mmol) and molecular sieve (4 Å) were added to xylene (10 mL) and then triethylamine (0.51 mL, 3.68 mmol), and butyl isocyanate (0.42 mL, 3.68 mmol) were added. The reaction mixture was refluxed 48 h, cooled to room temperature and evaporated under reduced pressure. The residue obtained was crystallized and recrystallized from ethanol to yield a white solid.

3-Butyl-1-(*p*-methoxyphenyl)-5-phenylhydantoin (24): Yield: 0.61 g (62.3%), mp 101.8-103.7 °C, TLC [*n*-hexane: ethyl acetate (2:1)] Rf 0.53. ^1H NMR (DMSO-d_6) δ 7.41-7.30 (m+d, 7H, aromatic), 6.86 (d, J = 9 Hz, 2H, aromatic), 5.93 (s, 1H, CH), 3.68 (s, 3H, CH_3), 3.53-3.47 (m, 2H, CH_2), 1.60-1.52 (m, 2H, CH_2), 1.33-1.26 (m, 2H, CH_2), 0.89 (t, J = 7.5 Hz, 3H, CH_3). ^{13}C NMR (DMSO-d_6) δ 170.45 (C=O×2), 156.21, 154.36, 133.84, 128.97, 128.85, 128.57, 127.27, 123.30, 113.92 (aromatic×2), 63.63 (CH), 55.06 (CH_3), 38.04 (CH_2), 29.44 (CH_2), 19.23 (CH_2), 13.39 (CH_3). FT-IR (KBr) cm^{-1} 1770 (C=O), 1710 (C=O), 1514 (CO). GC-MS: m/z 338.41 (M^-), 338.3 (100.00), 196.1 (78.65), 339.3 (53.26), 211.2 (49.11), 212.2 (39.49).

3-Pentyl-1-(*p*-methoxyphenyl)-5-phenylhydantoin (25): Yield: 41.3%. mp 122.4-125.3 °C. TLC [*n*-hexane:ethyl acetate (2:1)] Rf 0.55. ^{1}H NMR (DMSO-d_6) δ 7.41-7.30 (m+d, 7H, aromatic), 6.86 (d, J = 9.3 Hz, 2H, aromatic), 5.93 (s, 1H, CH), 3.68 (s, 3H, CH_3), 3.51-3.46 (m, 2H, CH_2), 1.61-1.56 (m, 2H, CH_2), 1.31-1.24 (m, 4H, CH_2×2), 0.85 (t, J = 6.9 Hz, 3H, CH_3). ^{13}C NMR (DMSO-d_6) δ 170.43 (C=O×2), 156.19, 154.34, 133.84, 128.98, 128.83, 128.57, 127.27, 123.27, 113.92 (aromatic×2), 63.61 (CH), 55.06 (CH_3), 38.29 (CH_2), 28.12 (CH_2), 26.96 (CH_2), 21.53 (CH_2), 13.72 (CH_3). FT-IR (KBr) cm^{-1} 1771 (C=O), 1711 (C=O), 1514 (CO). GC-MS: m/z 352.43 (M^-), 352.3 (100.00), 196.1 (70.30), 353.3 (55.57), 212.2 (44.00), 211.2 (42.03).

3-Phenyl-1-(*p*-methoxyphenyl)-5-phenylhydantoin (26): Yield: 32.3%. mp 145.8-148.0 °C. TLC [*n*-hexane:ethyl acetate (2:1)] Rf 0.4. ^{1}H NMR (DMSO-d_6) δ 7.56-7.35 (m+d, 12H, aromatic), 6.90 (d, J = 9 Hz, 2H, aromatic), 6.07 (s, 1H, CH), 3.69 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6) δ 169.61 (C=O×2), 156.44, 153.39, 133.76, 131.78, 128.86, 128.71, 128.38, 127.68, 127.05, 126.93, 123.80, 113.96 (aromatic×3), 63.94 (CH), 55.07 (CH_3). FT-IR (KBr) cm^{-1} 1778 (C=O), 1716 (C=O), 1512 (CO). GC-MS: m/z 358.40 (M^+), 358.2 (100.00), 211.2 (87.82), 196.1 (86.25), 359.2 (53.89), 167.1 (19.48).

3-Benzyl-1-(*p*-methoxyphenyl)-5-phenylhydantoin (27): Yield: 55.2%, mp 118.9-121.6 °C. TLC [*n*-hexane:ethyl acetate (2:1)] Rf 0.45. ^{1}H NMR (DMSO-d_6) δ 7.43-7.29 (m+d, 12H, aromatic), 6.87 (d, J = 9 Hz, 2H, aromatic), 6.05 (s, 1H, CH), 4.70 (s, 2H, CH_2), 3.68 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6) δ 170.31 (C=O×2), 156.30, 154.17, 136.25, 133.63, 128.86, 128.64, 128.50, 127.46, 127.30, 123.40, 113.94 (aromatic×3), 63.82 (CH), 55.07 (CH_3), 41.79 (CH_2). FT-IR (KBr) cm^{-1} 1777 (C=O), 1713 (C=O), 1515 (CO). GC-MS: m/z 372.42 (M^+), 372.1 (100.00), 196.1 (38.26), 211.1 (28.23), 373.1 (26.95), 91.1 (25.55).

3-Butyl-1-(*p*-methoxyphenyl)-5-(*p*-chlorophenyl)hydantoin (29): Yield: 67.2%, mp 93.6-95.2 °C. TLC [*n*-hexane: ethyl acetate (2:1)] Rf 0.30. ^{1}H NMR (DMSO-d_6) δ 7.44-7.38 (m, 6H, aromatic), 6.88 (d, J = 6.9 Hz 2H, aromatic), 5.98 (s, 1H, CH), 3.69 (s, 3H, CH_3), 3.52-3.45 (m, 2H, CH_2), 1.59-1.54 (m, 2H, CH_2), 1.33-1.28 (m, 2H, CH_2), 0.89 (t, J = 7.5 Hz, 3H, CH_3). ^{13}C NMR (DMSO-d_6) δ 170.56 (C=O×2), 156.72, 154.72, 133.74, 133.28, 129.68, 129.33, 129.25, 123.73, 114.42 (aromatic×2), 63.35 (CH), 55.52 (CH_3), 38.57 (CH_2), 29.86 (CH_2), 19.68 (CH_2), 13.84 (CH_3). FT-IR (NaCl) cm^{-1} 1771 (C=O), 1712 (C=O), 1514 (CO), 831 (Cl). GC-MS: m/z 372.85 (M^-) 230.1 (100.0), 245.1 (64.81), 246.1 (50.87), 149.1 (35.40), 232.1 (34.45).

3-Pentyl-1-(*p*-methoxyphenyl)-5-(*p*-chlorophenyl)hydantoin (30): Yield: 79.4%, mp 97.4-98.6 °C. TLC [*n*-hexane :ethyl acetate (2:1)] Rf 0.35. ^{1}H NMR (DMSO-d_6) δ 7.44-7.35 (m, 6H, aromatic), 6.88 (d, J = 6.9 Hz 2H, aromatic), 5.99 (s, 1H, CH), 3.69 (s, 3H, CH_3), 3.51-3.48 (m, 2H, CH_2), 1.61-1.56 (m, 2H, CH_2), 1.31-1.24 (m, 4H, CH_2+CH_2), 0.85 (t, J = 6.9 Hz, 3H, CH_3). ^{13}C NMR (DMSO-d_6) δ 170.09 (C=O×2), 156.26, 154.25, 133.29, 132.84, 129.23, 128.86, 128.81, 123.24, 113.97 (aromatic×2), 62.88 (CH), 55.07 (CH_3), 38.55 (CH_2), 28.13 (CH_2), 26.95 (CH_2), 21.53 (CH_2), 13.72 (CH_3). FT-IR (NaCl) cm^{-1} 1772 (C=O), 1712 (C=O), 1514 (CO), 828 (Cl). GC-MS: m/z 386.88 (M^+) 230.1 (100.0), 246.1 (65.19), 245.1 (62.04), 149.1 (40.78), 232.1 (33.94).

3-Phenyl-1-(*p*-methoxyphenyl)-5-(*p*-chlorophenyl)hydantoin (31): Yield: 62.1%. mp 180.2-183.2 °C, TLC [*n*-hexane: ethyl acetate (2:1)] Rf 0.48. ^{1}H NMR (DMSO-d_6) δ 7.56-7.42 (d+m, 11H, aromatic), 6.91 (d, J = 9 Hz, 2H, aromatic), 6.11 (s, 1H, CH), 3.70 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6) δ 169.74 (C=O×2), 156.98, 153.78, 133.91, 132.20, 130.12, 129.32, 127.49, 124.26, 114.48 (aromatic× 3), 63.70 (CH), 55.55 (CH_3). FT-IR (KBr) cm^{-1} 1777 (C=O), 1721 (C=O), 1513 (CO), 831 (Cl).

3-Benzyl-1-(*p*-methoxyphenyl)-5-(*p*-chlorophenyl)hydantoin (32): Yield: 89.6%, mp 147.6-148.8 °C. TLC [*n*-hexane:ethyl acetate (2:1)] Rf 0.37. ^{1}H NMR (DMSO-d_6) δ 7.69-7.24 (m, 9H, aromatic), 7.26 (d, J = 6.9 Hz 2H, aromatic), 6.85 (d, J = 6.9 Hz 2H, aromatic), 6.05 (s, 1H, CH), 4.74 (s, 2H, CH_2), 3.69 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6) δ 171.62 (C=O×2), 158.01, 154.32, 136.50, 135.63, 134.02, 128.94, 128.91, 128.52, 127.92, 127.80, 127.18, 114.27 (aromatic×3), 88.10 (CH), 55.50 (CH_3), 42.22 (CH_2). FT-IR (NaCl) cm^{-1} 1773 (C=O), 1713 (C=O), 1513 (CO), 828 (Cl). GC-MS: m/z 406.87 (M^+) 230.1 (100.0), 91.1 (93.79), 245.1 (83.25), 166.0 (61.75), 246.1 (38.77).

3-Butyl-1-(*p*-methoxyphenyl)-5-(*p*-bromophenyl)hydantoin (34): Yield: 56.7%, mp 102.7-104.5 °C. TLC [*n*-hexane:ethyl acetate (2:1)] Rf 0.30. ^{1}H NMR (DMSO-d_6) δ 7.55 (d, J = 6.6 Hz 2H, aromatic), 7.39 (d, J = 6.6 Hz 2H, aromatic), 7.30 (d, J = 6.6 Hz 2H, aromatic), 6.88 (d, J = 6.9 Hz 2H, aromatic), 5.97 (s, 1H, CH), 3.69 (s, 3H, CH_3), 3.52-3.49 (m, 2H, CH_2), 1.59-1.54 (m, 2H, CH_2), 1.30-1.27 (m, 2H, CH_2), 0.90 (t, J = 7.2 Hz, 3H, CH_3). ^{13}C NMR (DMSO-d_6) δ 170.49 (C=O×2), 156.71, 154.72, 133.70, 132.25, 129.98, 129.24, 123.70, 122.35, 114.42 (aromatic×2), 63.41 (CH), 55.52 (CH_3), 38.57 (CH_2), 29.86 (CH_2), 19.68 (CH_2), 13.84 (CH_3). FT-IR (NaCl) cm^{-1} 1771 (C=O), 1711 (C=O), 1514 (CO), 830 (Br). GC-MS: m/z 417.30 (M^-) 276.0 (100.0), 274.0 (99.63), 291.0 (65.28), 289.0 (61.55), 290.0 (52.65).

3-Pentyl-1-(*p*-methoxyphenyl)-5-(*p*-bromophenyl)hydantoin (35): Yield: 54.8%, mp 91.7-93.9 °C. TLC [*n*-hexane :ethyl acetate (2:1)] Rf 0.40. ^{1}H NMR (DMSO-d_6) δ 7.55 (d, J = 8.7 Hz 2H, aromatic), 7.38 (t, J = 8.7 Hz 2H, aromatic), 7.27 (q, J = 8.4 Hz 2H, aromatic), 6.86 (t, J = 9 Hz 2H, aromatic), 5.97 (s, 1H, CH), 3.69 (s, 3H, CH_3), 3.51-3.47 (m, 2H, CH_2), 1.61-1.58 (m, 2H, CH_2), 1.31-1.26 (m, 4H, CH_2+CH_2), 0.86 (t, J = 6.6 Hz, 3H, CH_3). ^{13}C NMR (DMSO-d_6) δ 171.65 (C=O), 170.09 (C=O), 156.70, 154.46, 133.70, 132.24, 129.98, 128.81, 127.64, 123.68, 114.42 (aromatic× 2), 63.40 (CH), 55.50 (CH_3), 28.58 (CH_2), 27.58 (CH_2), 27.40 (CH_2), 21.98 (CH_2), 14.17 (CH_3). FT-IR (NaCl) cm^{-1} 1772 (C=O), 1712 (C=O), 1514 (CO), 827 (Br). GC-MS: m/z 431.33 (M^+) 274.0 (100.0), 276.0 (98.20), 290.0 (69.05), 291.0 (67.19), 289.0 (60.88).

3-Phenyl-1-(*p*-methoxyphenyl)-5-(*p*bromophenyl)hydantoin (36): Yield: 30.4%, mp 189.5-190.1 °C, TLC [*n*-hexane: ethyl acetate (2:1)] Rf 0.48. ^{1}H NMR (DMSO-d_6) δ 7.60-

7.29 (m+d, 11H, aromatic), 6.91 (d, J = 8.9 Hz, 2H, aromatic), 6.10 (s, 1H, CH), 3.70 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6) δ 169.69 (C=O×2), 156.97, 153.79, 133.65, 132.25, 130.44, 129.34, 127.52, 124.22, 114.48 (aromatic ×3), 63.74 (CH), 55.55 (CH_3). FT-IR (KBr) cm^{-1} 1777 (C=O), 1721 (C=O), 1514 (CO), 831 (Br). GC-MS: m/z 437.29 (M^+) 256.1 (100.0), 120.1 (56.40), 228.1 (40.36), 258.1 (34.73), 92.1 (32.19).

3-Benzyl-1-(*p*-methoxyphenyl)-5-(*p*-bromophenyl)hydantoin (37): Yield: 87.7%, mp 139.5-141.0 °C. TLC [*n*-hexane:ethyl acetate (2:1)] Rf 0.40. ^1H NMR (DMSO-d_6) δ 8.24 (s, 1H, OH), 7.55 (d, J = 6.9 Hz 2H, aromatic), 7.39-7.35 (m, 7H, aromatic), 7.26 (d, J = 6.6 Hz 2H, aromatic), 6.85 (d, J = 6.9 Hz 2H, aromatic), 4.73 (s, 2H, CH_2), 3.69 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6) δ 171.57 (C=O×2), 158.01, 154.32, 136.49, 136.05, 131.84, 128.95, 128.82, 127.95, 127.91, 127.76, 127.18, 122.731, 114.27 (aromatic×3), 88.17 (CH), 55.50 (CH_3), 42.22 (CH_2). FT-IR (NaCl) cm^{-1} 1773 (C=O), 1713 (C=O), 1513 (CO), 828 (Br). GC-MS: m/z 451.32 (M^-) 248.1 (100.0), 171.1 (36.00), 77.1 (29.97), 105.1 (29.62), 115.1 (28.59).

General pocedure for the compounds 39, 41. Methyl α-(*p*-methoxyanilino)phenylacetate **10** (1.0 g, 3.69 mmol) and molecular sieve (4 Å) were added to xylene (10 mL) and then triethylamine (1.03 mL, 7.38 mmol), benzyl isothiocyanate (0.98 mL, 7.38 mmol) were added. The reaction mixture was refluxed for 48 h, cooled to room temperature and then evaporated under reduced pressure. The residue obtained was crystallized and recrystallized from ethanol to yield white solid.

3-Benzyl-1-(*p*-methoxyphenyl)-5-phenyl-2-thiohydantoin (39): Yield: 0.7 g (48.6%), mp 119.1-121.1 °C, TLC [*n*-hexane:ethyl acetate (2:1)] Rf 0.4. ^1H NMR (DMSO-d_6) δ 7.42-7.22 (m+d, 12H, aromatic), 6.89 (d, J = 9 Hz, 2H, aromatic), 6.12 (s, 1H, CH), 5.08 (d, J = 3.3 Hz, 2H, CH_2), 3.71 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6) δ 171.70 (C=O, C=S), 158.10, 136.04, 132.82, 129.69, 129.00, 128.47, 128.38, 128.19, 127.78, 127.63, 127.37, 113.86 (aromatic× 3), 68.00 (CH), 55.13 (CH_3), 44.70 (CH_2). FT-IR (KBr) cm^{-1} 1752 (C=O), 1513 (CO). GC-MS: m/z 388.49 (M^-), 388.2 (100.00), 212.2 (41.03), 387.2 (29.02), 389.2 (27.82), 91.1 (26.68).

3-Benzyl-1-(*p*-methoxyphenyl)-5-(*p*-bromophenyl-2-thiohydantoin (41): Yield: 27.2%, mp 188.7-191.0 °C, TLC [*n*-hexane:ethyl acetate (2:1)] Rf 0.35. ^1H NMR (DMSO-d_6) δ 7.56-7.42 (d+m, 11H, aromatic), 6.91 (d, J = 9 Hz, 2H, aromatic), 6.11 (s, 1H, CH), 5.08 (s, 2H, CH_2), 3.70 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6) δ 169.74 (C=O, C=S), 156.98, 153.78, 133.91, 132.20, 130.12, 129.32, 127.49, 124.26, 114.48 (aromatic×3), 63.70 (CH), 55.55 (CH_3), 44.50 (CH_2). FT-IR (KBr) cm^{-1} 1777 (C=O), 1720 (C=O), 1513 (CO), 831 (C-Br).

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References

1. (a) Hardman, J. G.; Limbird, L. E. In *Goodman and Gilman's The Pharmacological Basis of Therapeutics*. 10th ed.; McGraw-Hill: New York, 2001; pp 688-731. (b) Lombardino, G. *Nonsteroidal Antiinflammtory Drugs*; John Wiely & Sons: New York, 1985.
2. Allison, M. C.; Howatson, A. G.; Torrance, C. J.; Lee, F. D.; Russell, R. I. G. N. *Engl. J. Med.* **1992**, *327*, 749.
3. (a) Fu, J. Y.; Masferrer, J. L.; Seibert, K.; Raz, A.; Needleman, P. *J. Biol. Chem.* **1990**, *265*, 16737. (b) Vane, J.; Botting, J.; Botting, R. *Improved Non-steroid Anti-inflammatory Drugs COX-2 Enzyme Inhibitors*; Kluwer Academic Publishers and William Harvey Press: London, 1996.
4. Hla, T.; Neilson, K. *Proc. Natl. Acad. Sci. U.S.A.* **1992**, *89*, 7384.
5. Xie, W.; Chipman, J. G.; Robertson, D. L.; Erikson, R. L.; Simmons, D. L. *Proc. Natl. Acad. Sci. U.S.A.* **1991**, *88*, 2692.
6. Kujubu, D. A.; Fletcher, B. S.; Varnum, B. C.; Lim, R. W.; Herschman, H. R. *J. Biol. Chem.* **1991**, *266*, 12866.
7. Masferrer, J. L.; Seibert, K.; Zweifel, B.; Needleman, P. *Proc. Natl. Acad. Sci. U.S.A.* **1992**, *89*, 3917.
8. Futaki, N.; Yoshikawa, K.; Hamasaka, Y.; Arai, I.; Higuchi, S.; Iizuka, H.; Otomo, S. *Gen. Pharmacol.* **1993**, *24*, 105.
9. Futaki, N.; Takahashi, S.; Yokoyama, M.; Arai, I.; Higuchi, S.; Otomo, S. *Prostaglandins* **1994**, *47*, 55.
10. Gans, K. R.; Galnraith, W.; Romans, R. J.; Haber, S. B.; Kerr, J. S.; Schmidt, W. K.; Smith, C.; Hewes, W. E.; Ackerman, N. R. *J. Pharmacol. Exp. Ther.* **1990**, *254*, 180.
11. Penning, T. D.; Tally, J. J.; Bertenshaw, S. R.; Carter, J. S.; Collins, P. W.; Doctor, S.; Graneto, M. J.; Lee, L. F.; Veenhuizen, A. W.; Zhang, Y. Y.; Isakson, P. C. *J. Med. Chem.* **1997**, *40*, 1347.
12. Prasit, P.; Wang, Z.; Brideau, C.; Chan, C.-C.; Charleson, S.; Cromlish, W.; Ethier, D.; Evans, J. F.; Ford-Hutchinson, A. W.; Gauthier, J. Y.; Gordon, R.; Forrest, M.; Visco, D.; Patrick, D. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1773.
13. Talley, J. J.; Brown, D. L.; Carter, J. S.; Graneto, M. J.; Koboldt, C. M.; Masferrer, J. L.; Perkins, W. E.; Rogers, R. S.; Shaffer, A. F.; Zhang, Y. Y.; Zweifel, B. S.; Seibert, K. *J. Med. Chem.* **2000**, *43*, 775.
14. Kwon, S. K.; Jung, H. W.; Park, M. S. *Korean J. Med. Chem.* **1995**, *5*, 166.
15. Wolfe, M. M.; Lichtenstein, D. R.; Singh, G. *N. Engl. J. Med.* **1999**, *340*, 1888.
16. Mukherjee, D.; Nissen, S. E.; Topol, E. J. *JAMA* **2001**, *286*, 954.
17. Gaetano, G.; Donati, M. B.; Cerletti, C. *Trends Pharm. Sci.* **2003**, *24*, 245.
18. Hwang, K. J.; Lee, S. J.; Kim, B. T.; Raucher, S. *Bull. Korean Chem. Soc.* **2006**, *27*(6), 933.
19. Park, M. S.; Park, H. S. *Yakhak Hoeji* **2003**, *47*, 276.
20. Kirk-Othmer *Encyclopedia of Chemical Technology*, 2nd ed.; Interscience: New York-London-Sydney, 1966; Vol 11, pp 141-161.
21. (a) Ware, E. *Chem. Rev.* **1950**, 411. (b) Li, J. P. *Org. Chem.* **1975**, *40*, 3414. (c) Kirk-Othmer *Encyclopedia of Chemical Technology*, 3nd ed.; Interscience: New York-London Sydney, 1979; Vol 12, pp 692-708.