Eur J Med Chem (1991) 26, 369–374

Naphthalenylsulfonyl-hydantoins as aldose reductase inhibitors

MS Malamas[1], K Sestanj[1], J Millen[2*]

[1]*Department of Medicinal Chemistry;*
[2]*Subdivision of Metabolic Disorders, Wyeth-Ayerst Research, CN 8000, Princeton, NJ 08543-8000, USA*

(Received 17 April 1990; accepted 28 September 1990)

Summary — Accumulation of intracellular sorbitol, formed from glucose by aldose reductase, is believed to play an important role in the development of certain chronic complications of diabetes mellitus. Several 1-(naphthalenylsulfonyl)hydantoins inhibit aldose reductase isolated from bovine lens *in vitro*, and decrease galactitol formation in sciatic nerves of galactosemic rats *in vivo*. The 5-bromo analogue (entry **12**, table I) was found to be the most orally active aldose reductase inhibitor of this series with an ED_{50} value of 8.1 mg/kg *po*. The 1-(naphthalenylsulfonyl)-2-thiohydantoin analogues with the exception of entry **11** (table I) which showed good *in vivo* activity, were either inactive or had only marginal activity.

Résumé — **Naphtalénylsylfonylhydantoïnes, inhibiteurs de l'aldose réductase.** *L'accumulation intracellulaire de sorbitol produit à partir du glucose par l'aldose réductase est supposée jouer un rôle important dans le développement de certaines complications chroniques du diabète mellitus. Plusieurs 1-(naphtalénylsulfonyl)hydantoïnes inhibent l'aldose réductase isolée du cristallin du bœuf* in vitro *et diminuent la formation de galacticol dans le nerf sciatique de rats galactosémiques* in vivo. *L'analogue 5-bromo (**12**, table I) s'est avéré l'inhibiteur d'aldose réductase le plus efficace de cette série avec une dose effective cinquante de 8,1 mg/kg par voie orale. Les 1-(naphtalénylsulfonyl)-2-thiohydantoïnes analogues, à l'exception de **11** qui a montré une bonne activité* in vivo, *sont inactives ou ne possèdent qu'une activité marginale.*

aldose reductase inhibitor / diabetic complications / anticonvulsant activity / galactosemic rat model

Introduction

During hyperglycemia, nerve, ocular, and renal tissues are exposed to a high concentration of glucose which enters the sorbitol pathway and is reduced by aldose reductase to sorbitol. The intracellular accumulation of sorbitol and its metabolite fructose can eventually result in a loss of osmotic integrity and cellular damage. These events have been linked to the development of certain complications of diabetes mellitus, such as cataracts, neuropathy or retinopathy [1–4]. If this hypothesis is correct, inhibition of the enzyme aldose reductase should provide a pharmacological approach to the prevention or treatment of these complications.

Over the past decade, several aldose reductase inhibitors of diverse structures have proven to be effective in delaying or even preventing pathologies associated with chronic diabetes in animals and humans [5, 6]. The compounds able to inhibit this enzyme *in vitro* are known in large numbers. Potent, orally active aldose reductase inhibitors, however, are relatively rare; only a few structural types are known which can yield therapeutically significant drug candidates [21]. Our interest is primarily directed toward such compounds and their structure-activity relationships.

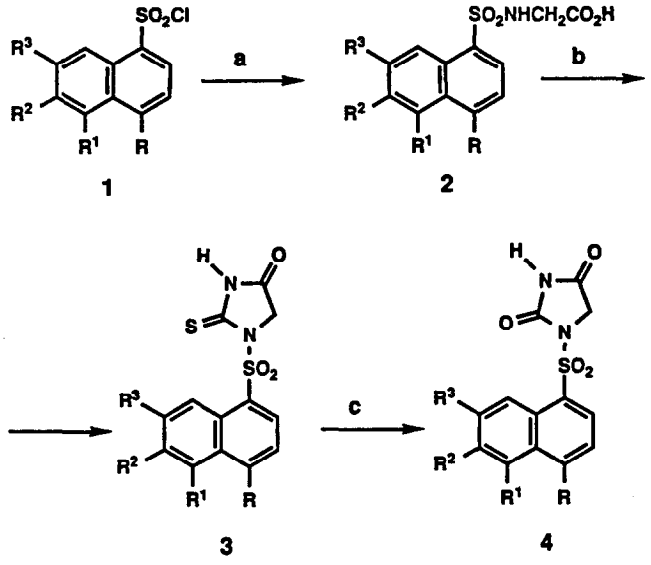
In this paper, we present the inhibitory activity of 1-(napthalenylsulfonyl) hydantoins on bovine lens aldose reductase *in vitro* and their evaluation in the galactosemic rat model by measuring effects on galactitol accumulation in sciatic nerves *in vivo*. (Details of these test procedures have been published previously [7–9].)

We have found in this study that 1-[(5-bromo-1-naphthalenyl)sulfonyl]hydantoin represents a very potent, orally active aldose reductase inhibitor. Its potency is equivalent to that of tolrestat, an aldose reductase inhibitor (developed in our laboratories [10, 11]) presently being marketed under the proprietary name Alredase for treatment of diabetic complications.

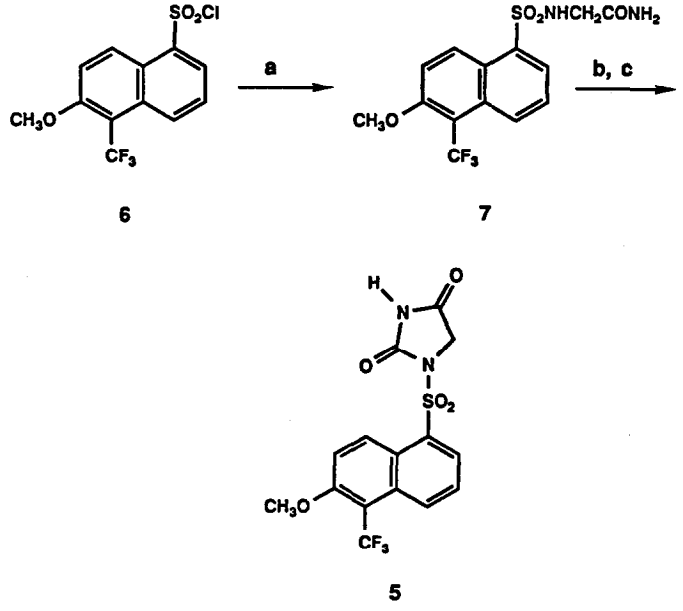
*Present address: School of Pharmacy, University of North Carolina, Chapel Hill, NC 27599-7360, USA

Chemistry

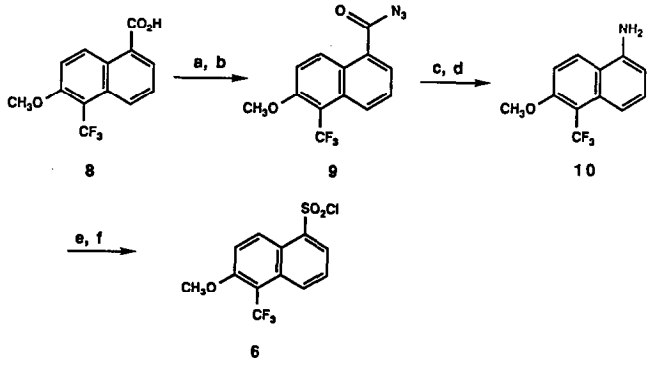
The 1-(naphthalenylsulfonyl)hydantoins and their 2-thioxo analogues were prepared by the following general synthetic scheme 1, wherein R, R^1, R^2 and R^3 represent the appropriate substituents as shown in table I.



Scheme 1. General synthetic. Reagents: a) $NH_2CH_2CO_2H$, aq Na_2CO_3, dioxane, b) Ac_2O, NH_4SCN, pyridine, c) Cl-CH_2CO_2H, H_2O.



Scheme 2. Reagents: a) $NH_2CH_2CONH_2$, aq Na_2CO_3, dioxane, b) NaH, $ClCO_2Me$, DMF, c) NaH, DMF.



Scheme 3. Reagents: a) $SOCl_2$, b) NaN_3, acetone, c) $C_6H_5CH_3$, D, d) 40% KOH, e) $NaNO_2$, HCl, f) SO_2, g), AcOH, CuCl.

Acylation of glycine with sulfonyl chloride **1** in the presence of aqueous Na_2CO_3 gave sulfonyl glycine **2**. Treatment of **2**, according to the process of J Okuda *et al* [12], with NH_4SCN and Ac_2O in the presence of anhydrous pyridine at 110°C, gave the sulfonyl-2-thiohydantoins **3**, which were hydrolyzed with Cl-CH_2CO_2H/H_2O at temperatures of 100 to 140°C to give sulfonyl hydantoins **4**.

Due to the drastic conditions required for the hydrolysis of the 2-thiohydantoins, compound **5**, carrying an acid sensitive substituent (-OCH_3) was prepared through an alternate route (scheme 2).

Acylation of glycinamide hydrochloride with sulfonyl chloride **6** in the presence of aqueous Na_2CO_3 gave compound **7** which was cyclized through acyl carbamate formation (NaH, $ClCO_2Me$) and NaH/DMF treatment to give compound **5**.

The 5-methyl and 5,5-dimethyl-1-(naphthalenylsulfonyl)hydantoins were prepared according to the general synthetic scheme 1 by utilizing DL-alanine and 2-aminoisobutyric acid, respectively.

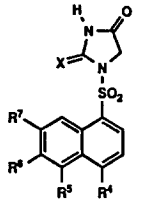
The required naphthalenylsulfonylchlorides are commercially available or can be prepared by known methods [13, 14]. One such method is illustrated in scheme 3.

Refluxing naphthoic acid **8** [11] with $SOCl_2$ and subsequent treatment of the acid chloride with NaN_3 in acetone gave azide **9**. Thermal decomposition of **9** (Curtius rearrangement) [15, 16] in refluxing toluene, followed by hydrolysis with KOH (40%) gave naphthylamine **10**. Conversion of **10** to sulfonyl chloride **6** was accomplished by the Meerwein reaction upon treatment of the diazonium salt with SO_2 (gas) in the presence of CuCl [17].

Results and Discussion

The test compounds were evaluated as inhibitors of bovine lens aldose reductase using a partially purified

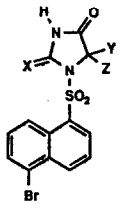
Table I. Chemical and biological data of 1-(naphthalenylsulfonyl)hydantoins. NS = not significant. ND = not determined. Recrystallization solvents. A: acetone/H_2O; B: DMF/H_2O; C: MeOH/H_2O; D: MeOH.



						% Inhibition of aldose reductase in vitro			% Lowering galactitol accumulation in vivo				
Compd	R^4	R^5	R^6	R^7	*X*	10^{-5}	10^{-6}	$10^{-7}M$	*Dose mg/kg per d*	*Sciatic nerve*	*Recryst*	mp °C	*Synthetic scheme*
11	H	Br	H	H	S	67	17	–	24	56	B	235–237	I
12	H	Br	H	H	O	93	89	43	10.2	57	A	227–228	I
13	Br	H	H	H	S	53	15	–	24	NS	B	239(dec)	I
14	Br	H	H	H	O	92	81	31	24	59	A	234–236	I
15	H	CF_3	OCH_3	H	S	40	15	–	23	NS	A	260(dec)	I
5	H	CF_3	OCH_3	H	O	86	84	43	25	35	C	273–274	II
16	H	NMe_2	H	H	S	58	12	–	96	NS	A	220(dec)	I
17	H	NMe_2	H	H	O	96	83	38	25	NS	D	185–186	II
18	H	H	H	H	S	17	–	–	ND	ND	A	253–255	I
19	H	H	H	H	O	89	59	14	23	22	A	210–212	I
20	H	H	Br	H	S	10	9	–	ND	ND	A	235(dec)	I
21	H	H	Br	H	O	89	70	23	24	NS	A	228–230	I
22	H	H	H	Br	S	46	16	–	ND	ND	A	270(dec)	I
23	H	H	H	Br	O	93	79	36	23	40	A	253–255	I
24	H	Cl	H	H	S	43	14	–	ND	ND	A	230(dec)	I
25	H	Cl	H	H	O	85	79	36	25	81	A	223–225	I
26	H	I	H	H	S	58	24	–	26	NS	A	242–244(dec)	I
27	H	I	H	H	O	94	89	59	24	63	A	226–228	I
28	N-[(6-methoxy-5-(trifluoromethyl)-1-naphthalenyl]thioxomethyl]-N-methylglycine(tolrestat)					98	94	65	9.4	58			

enzyme by a procedure similar to that previously described [9] (the final chromatographic step was omitted in the preparation of the enzyme). The inhibition of aldose reductase *in vivo* was assessed in rats fed 20% galactose for 4 days [7]. The test compounds were administered in the diet. The galactitol determination was performed by a modification of the method of Kraml and Cosyns [8]. Only two minor reagent changes were made: (a) the rinsing mixture was an aqueous 5% (w/v) trichloroacetic acid solution and (b) the stock solution was prepared by dissolving 25 mg of galactitol in 100 ml of the 5% aqueous trichloroacetic acid. The results are shown in tables I and II. In the bovine lens assay, all 1-(naphthalenylsulfonyl) hydantoins showed a high level of inhibition at very low concentrations (10^{-6} M). In contrast, the 2-thiohydantoin analogues were substantially less active. The 5-methyl analogue (entry **29**, table II) exhibited a dramatic decrease in activity and the 5,5-dimethyl analogue (**31**, table II) was found inactive. Such a decrease in inhibitory activity is possibly due to the introduction of steric hindrance which interferes with interaction between the inhibitor and the enzymatic receptor site. All the compounds which inhibited aldose reductase activity by more than 50% at 10^{-6} M were further evaluated in the 4-day galactose-

Table II. Chemical and biological data of 5-methyl and 5,5-dimethylnaphthalenylsulfonylhydantoins. NS = not significant. ND = not determined. Recrystallization solvents: A: acetone/H_2O; D: MeOH; E: EtoAc/pet ether.



				% Inhibition of aldose reductase in vitro		% lowering galactitol accumulation in vivo				
Compd	*X*	*Y*	*Z*	*10^{-5}*	*10^{-6} M*	*Dose mg/kg per d*	*Sciatic nerve*	*Recryst*	mp °C	*Synthetic scheme*
29	O	CH_3	H	86	50	25	NS	D	201–202	I
30	S	CH_3	H	51	13	ND	ND	E	207–208	I
31	O	CH_3	CH_3	NS	NS	ND	ND	A	221–223	I
32	S	CH_3	CH_3	NS	NS	ND	ND	A	211–213	I

mic rat model *in vivo*. It was determined that the *in vivo* potency was closely related to the naphthalene substitution. Electron withdrawing groups with lipophilic character, such as halogens, were the best substituents. The 5-bromo- or 5-chloronaphthalene analogues represent the most potent oral inhibitors. The 5-bromo analogue (**12**, table I) showed comparable results to that of tolrestat (**28**, table I) with ED_{50} values of 8.1 and 7.3 [10] mg/kg *po*, respectively. From the 2-thiohydantoin series only the 5-bromo analogue (**11**, table I) showed good *in vivo* activity with an ED_{50} value of 22 mg/kg *po*. The 5-methyl substituted hydantoin (**29**, table II) was found to be inactive. The *in vitro* activity of the sulfonylhydantoins **5**, **12**, **14**, **19**, **21**, **23** and **25** (table I) is almost identical to the similar substituted tolrestat analogues (**1**, **3–6**, **24**, table **8–12**, in [21]). Halogen or trifluoromethyl naphthalene substitution enhanced the intrinsic activity for both series with the 5-position representing the optimal substituted analogues. These similarities suggest that the aromatic region of the inhibitors for both series, binds to the lipophilic region of the enzyme with the same specificity (hydrophobic interaction) and further suggests that the sulfonylhydantoin and acylsarcosine moieties may act bioisosterically.

Sulfonylhydantoins similar to those reported herein have been described by Okuda *et al* [12, 18] and these authors have synthesized and tested one of the compounds we describe, *viz* 1-naphthalenylsulfonylhydantoin **19**. Consistent with our findings, they report that while **19** showed good *in vitro* activity inhibiting aldose reductase, it was inactive *in vivo* at doses up to 50 mg/kg *po*.

Anticonvulsant activity in mice

Phenytoin is a known anticonvulsant agent, and sorbinil (an aldose reductase inhibitor) has also been reported to possess anticonvulsant activity [19]. This common anticonvulsant property indicated that the hydantoin moiety was possibly responsible for this effect. Thus, the 1-(naphthalenylsulfonyl)hydantoins were tested for such an undesirable property, by determining their ability to prevent electroshock induced tonic seizures in mice. All 1-(naphthalenylsulfonyl)-hydantoins were found to be devoid of anticonvulsant activity at doses of up to 150 mg/kg *po*. In contrast, phenytoin and sorbinil exhibited anticonvulsant activity with ED_{50} of 11 and 103 mg/kg, respectively (table III).

This study has revealed that 1-(5-halogen-1-naphthalenylsulfonyl)hydantoins are very potent, orally active aldose reductase inhibitors, with the 5-bromo analogue being equipotent to tolrestat.

Experimental protocols

Melting points were determined in open capillary tubes on a Thomas-Hoover apparatus and are uncorrected. ^1H NMR spec-

tra were determined in the cited solvent on a Varian XL-200 (200 MHz) instrument, with tetramethylsilane as an internal standard. Chemical shifts are given in ppm and coupling constants are in hertz. Splitting patterns are designated as follows: s, singlet; brs, broad singlet; d, doublet; t, triplet; q, quarter; m, multiplet. IR spectra were recorded on a Perkin-Elmer 781 spectrophotometer as KBr pellets or as solutions in chloroform. Mass spectra were recorded on either a Finnigan model 8230 or a Hewlett-Packard model 5995A spectrometer. Elemental analyses (C, H, N) were performed on a Perkin-Elmer 240 analyzer and all compounds are within ± 0.4% of theory unless otherwise indicated. All products, unless otherwise noted, were purified by 'flash column chromatography' [22] using 220–400 mesh silica gel. Thin-layer chromatography was done on silica gel 60 F-254 (0.25 mm thickness) plates. Visualization was accomplished with UV light and/or 10% phosphomolybdic acid in ethanol.

The starting naphthalenylsulfonylchlorides were either commercially available or readily prepared by previously described methods [13 ,14].

General procedure for the synthesis of ***11–16, 18–27, 29–32***

Compounds **11–16**, **18–27**, **29–32** were synthesized from the appropriately substituted naphthalenylsulfonylchlorides by the representative procedures illustrated for the 5-bromo analog **12**.

*N-[(5-Bromo-1-naphthalenyl)sulfonyl]glycine (**2**, R^1 = Br, R, R^2, R^3 = H)*

To a mixture of [5-bromo-1-naphthanlenyl)sulfonyl]chloride (5 g, 16.36 mmol) and glycine (1.23 g, 16.36 mmol) in dioxane (25 ml) aqueous saturated Na_2CO_3 was added dropwise until pH ≈ 7.5–8. After stirring for 30 min, the mixture was acidified with HCl (1 N) and the precipitated solid was filtered and washed with H_2O. The crude product was recrystallized from hot H_2O to yield a white solid (**2**, 4.2 g, 74.6%, *mp* = 215–216°C). ^{1}H NMR (DMSO-d_6, 200 MHz): δ 3.67 (d, *J* = 6.0 Hz, 2H, -NH*CH*$_2$CO$_2$H), 7.63 (t, *J* = 8.4 Hz, 1H, Ar-*H*), 7.79 (t, *J* = 7.9 Hz, 1H, Ar-*H*), 8.06 (d, *J* = 7.8 Hz, 1H, Ar-*H*), 8.82 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 8.46 (d, *J* = 8.6 Hz, 1H, Ar-*H*); 8.55 (t, *J* = 6.0 Hz, 1H, -1*NH*CH$_2$CO$_2$H), 8.73 (d, *J* = 8.4 Hz, 1H, Ar-*H*). IR (KBr, cm^{-1}): 3340 (NH), 3000–2200 (CO$_2$H), 1715 (CO). M/S (m/e): 343 (10, M$^+$), 269 (10, M$^+$ -NHCH$_2$CO$_2$H), 205 (34, M$^+$ -SO$_2$NHCH$_2$CO$_2$H). Anal $C_{12}H_{10}BrNO_4S$ (C, H, N).

*1-[(5-Bromo-1-naphthalenyl)sulfonyl]-2-thioxo-4-imidazolinone (**11**)*

To a mixture of [(5-bromo-1-naphthalenyl)sulfonyl]glycine (**2**, 9.25 g, 26.89 mmol) and acetic anhydride (6.34 ml, 67.21 mmol) in anhydrous pyridine (30 ml) NH_4SCN (2.66 g, 34.95 mmol) was added and the suspension was heated to 110°C (bath) for 1 h. The volatiles were removed *in vacuo*, and the residue was suspended in H_2O (150 ml) and stirred for 1 h. The brown solid was filtered, washed with H_2O and dried. Recrystallization from DMF/H_2O (after cooling to 0°C), afforded a white solid (**11**, 6.9 g, 66.7%, *mp* = 235–237°C): ^{1}H NMR (DMSO-d_6, 200 MHz): d 5.02 (s, 2H, -NC*H*$_2$CO-), 7.7 (t, *J* = 7.8 Hz, 1H, Ar-*H*), 7.91 (t, *J* = 7.8 Hz, 1H, Ar-H), 8.13 (d, *J* = 7.2 Hz, 1H, Ar-*H*), 8.45 (d, *J* = 8.6 Hz, 1H, Ar-*H*), 8.62 (d, 7.8 Hz, 2H, Ar-*H*). IR (KBr, cm^{-1}): 3210 (NH), 1750 (C=O). M/S (CI): 385 (17, M$^+$ + H), 271 (4, M$^+$ – 2-thioxo-4-imidazolidinone), 117 (100, M$^+$ – Br-[(sulfonyl)-2-thioxo-4-imidazolinone). Anal $C_{13}H_9BrN_2O_3S_2$ (C, H, N).

*1-[(5-Bromo-1-naphthalenyl)sulfonyl]-2,4-imidazolidinedione (**12**)*

A mixture of 1-[(5-bromo-1-naphthalenyl)sulfonyl]-2-thioxo-4-imidazolidinone (**11**, 1.7 g, 4.41 mmol), ClCH$_2$CO$_2$H (10 g, 105.8 mmol) and H_2O (0.3 ml) was heated to 120°C for 24 h. The mixture was diluted with H_2O (100 ml) and cooled to 0°C for 1 h. The precipitated solid was filtered, washed with H_2O and dried. Recrystallization from acetone/H_2O (at 0°C) afforded a white solid (**12**, 1.52 g, 85.9%, *mp* = 227–228°C). ^{1}H NMR (DMSO-d_6, 200 MHz): δ 4.66 (s, 2H, -NC*H*$_2$CO-), 7.69 (t, *J* = 7.6 Hz, 1H, Ar-*H*), 7.91 (t, *J* = 7.6 Hz, 1H, Ar-*H*), 8.12 (d, *J* = 7.4 Hz, 1H, Ar-*H*), 8.54 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 8.63 (m, 2H, Ar-*H*), 11.67 (s, 1H, -CO*NH*CO-). R (KBr, cm^{-1}): 3170 (NH), 1800 (C=O), 1750 (C=O). M/S (CI): 369 (5, M$^+$ + H). Anal $C_{13}H_9BrN_2O_4S$ (C, H, N).

Table III. Antagonism to electroshock-induced seizures in mice. All test compounds were administered orally 60 min prior to shock except phenytoin which was given 2 h before ECS.

Treatment	*Dose mg/kg po*	*% Protection from tonus*	*ED_{50} mg/kg po*
Phenytoin	–	–	11
Sorbinil	–	–	103
12	150	inactive	–
5	150	inactive	–
29	150	inactive	–

General procedure for the synthesis of ***5*** *and* ***17***

Compounds **5** and **17** were prepared from the appropriate substituted naphthalenylsulfonylchlorides by the representative procedures illustrated for the 6-methoxy-5-trifluoromethyl analog **5**.

*2-[[[6-Methoxy-5-(trifluoromethyl)-1-naphthalenyl]sulfonyl]-amino]acetamide (**7**)*

To a suspension of [[6-methoxy-5-(trifluoromethyl)-1-naphthalenyl]-sulfonyl]chloride (**6**, 5.5 g, 16.9 mmol) and glycinamide hydrochloride (2.5 g, 33.7 mmol) in dioxane (30 ml) dropwise aqueous saturated Na_2CO_3 (approx 3 ml) was added until pH ≈ 7.5–8. After stirring for 1 h at ambient temperature, the volatiles were removed *in vacuo* and the solid mass was suspended in H_2O (50 ml). The precipitated solid was filtered, washed with H_2O and dried. Recrystallization from acetone/H_2O at 0°C gave a white solid (**7**, 5.98 g, 97.8%, *mp* = 213–215°C. ^{1}H NMR (DMSO-d_6, 200 MHz): δ 3.5 (d, *J* = 6.5 Hz, 2H, -NH*CH*$_2$CO-) 4.05 (s, 3H, -O*CH*$_3$), 7.1 (brs, 1H, -CO*NH*-), 7.25 (brs, 1H, CO*NH*), 7.78–7.95 (m, 2H, Ar-*H*), 8.09 (d, *J* = 7.8 Hz, 1H, Ar-*H*), 8.38 (m, 1H, Ar-*H*), 8.43 (t, *J* = 6.5 Hz, 1H, -*NH*CH$_2$CO-), 8.98 (d, *J* = 9.4 Hz, 1H, Ar-*H*). IR (KBr, cm^{-1}): 3450 (NH), 3320 (NH), 1675 (C=O). M/S (CI): 363 (19, M$^+$ + H), 289 (9, M$^+$ -NHCH$_2$CONH$_2$). Anal $C_{14}H_{13}F_3N_2O_4S$ (C, H, N).

*1-[[6-Methoxy-5-(trifluoromethyl)-1-naphthalenyl]sulfonyl]-2,4-imidazolidinedione (**5**)*

To a solution of [[[6-methoxy-5-trifluoromethyl)-1-naphthalenyl]sulfonyl]amino]acetamide (**7**, 5.5 g, 15.1 mmol) in anhydrous DMF (50 ml) was added NaH 50% dispersion in oil (500 mg, 16.6 mmol) portionwise over a 15 min period. After stirring for 2 h at ambient temperature, under a nitrogen atmo-

sphere, methyl chloroformate (1.16 ml, 15.1 mmol) was added and the mixture was stirred for 30 min. The volatiles were removed *in vacuo* and the residue was taken in anhydrous DMF (50 ml) and NaH (50% dispersion in oil, 400 mg, 16.6 mmol) was added dropwise. The mixture was heated at 75°C for 2 h and cooled to 20°C. The reaction was quenched with H_2O and acidified with HCl (1 N). The precipitated solid was filtered, washed with H_2O and dried. Recrystallization from MeOH-H_2O gave a white solid (**5**, 2.0 g, 34%, *mp* = 273°C). ^{1}H NMR (DMSO-d_6, 200 MHz): δ 4.04 (s, 3H, -O*CH*$_3$), 4.60 (s, 2H, -N*CH*$_2$CO-) 7.8–7.9 (m, 2H, Ar-*H*), 8.32 (d, *J* = 7.8 Hz, 1H, Ar-*H*), 8.43 (m, 1H, Ar-*H*), 8.87 (d, *J* = 9.3 Hz, 1H, Ar-*H*), 12.35 (s, 1H, -CO*NH*CO-). IR (KBr, cm^{-1}): 3400 (NH), 3200 (NH), 1800 (C=O), 1765 (C=O). M/S (CI): 389 (M+H)$^+$. Anal $C_{15}H_{11}F_3N_2O_5S$ (C, H, N).

*6-Methoxy-5-(trifluoromethyl)-1-naphthylamine (**10**)*
A mixture of 6-methoxy-5-(trifluoromethyl)-1-naphthoic acid (**8** [10], 30.0 g, 111.1 mmol), thionyl chloride (120 ml) and anhydrous DMF (0.75 ml) was refluxed for 4 h. The volatiles were removed *in vacuo* and the acid chloride (white solid) was dissolved in acetone (300 ml). The mixture was cooled to 0°C (ice bath) and sodium azide (7.8 g, 119.11 mmol) in H_2O (25 ml) was added dropwise (precipitate formation). After stirring at 0°C for 30 min, the suspension was diluted with H_2O (300 ml), stirred for 1 h at 0°C and the precipitated solid filtered and washed with H_2O (2 x 200 ml). The damp solid was dissolved in toluene (400 ml), concentrated under reduced pressure to 280 ml, refluxed for 1 h, and cooled to 20°C. Aqueous potassium hydroxide (40%, 200 ml) was added and the mixture was refluxed for 1 h, cooled to 0°C and the precipitated solid filtered and washed with H_2O (200 ml) and toluene (200 ml). The filtrate and washings were combined and the organic layer was separated, washed with H_2O (200 ml) and dried over $MgSO_4$. Evaporation gave a white solid (**10**, 19.09, 84%, *mp* = 120°C). ^{1}H NMR (DMSO-d_6, 200 MHz) δ 4.05 (s, 3H, -O*CH*3), 5.8 (s, 2H, -*NH*$_2$), 6.75–8.50 (m, 5H, Ar-*H*). IR (KBr, cm^{-1}): 3450 (NH). M/S (m/e): 241 (M$^+$).

*[[6-Methoxy-5-(trifluoromethyl)-1-naphthalenyl]-sulfonyl]chloride (**6**)*
To a mixture of concentrated HCl (10 ml) and glacial acetic acid (5 ml), under mechanical stirring, 6-methoxy-5-(trifluoromethyl)-1-naphthylamine (**10**, 2.7 g, 11.2 mmol) was added in one portion. The formed hydrochloride salt (white) was cooled with a dry ice-ethanol bath to – 10°C. An aqueous solution of $NaNO_2$ (1.0 g, 14.5 mmol) in H_2O (5 ml) was added dropwise at such a rate that the temperature did not exceed – 5°C. After the addition, the mixture was stirred for 1 h while the temperature was maintained between – 10°C and – 5°C. To a second mixture of glacial acetic acid (30 ml) and cuprous chloride (440 mg, 4.44 mmol), SO_2 (gas) was introduced until a blue-green suspension formed. The mixture was cooled to 0°C and the contents of the diazotization reaction were added slowly. The reaction temperature was allowed to rise to 50°C. After stirring for 1 h, the mixture was poured into ice water (300 ml), extracted with ether and the organic extracts were washed successively with H_2O (3 x 100 ml), $NaHCO_3$ (3 x 100 ml), H_2O (2 x 100 ml), and dried over $MgSO_4$. The crude product was purified initially by flash chromatography (6% EtOAc/hexane), and recrystallized from ether/hexane to give a white solid (**6**, 1.89 g, 50%, *mp* = 60–62°C), ^{1}H NMR ($CDCl_3$, 200 MHz): δ 4.08 (s, 3H, -O*CH*$_3$), 7.6–9.1 (m, 5H, Ar-*H*). IR (KBr, cm^{-1}): 1610 (C=O), 1590 (C=C). M/S (m/e): 324 (M$^+$). Anal $C_{12}H_8ClF_3O_3S$ (C, H, N).

Antagonism to electroshock-induced tonus in mice
The unit used to induce convulsive electroshock (ECS) to mice was manufactured by Ugo Basile (ECT No. 7801). A constant current output was used as a square-wave DC stimulus and set at a frequency of 200 Hz, the pulse duration 1 ms, shock intensity was 30 mA, and shock duration 0.3 s. Corneal electrodes were used, and a supramaximal intensity ECS induced tonic convulsions in all control animals, similar to the work of others [20]. Groups of eight mice were injected orally with selected compounds, or the vehicle solution 60 min before being subjected to an electroshock. The results were expressed as the percentage of mice protected from the tonic extensor component of the seizure. Graded doses of active compounds were tested and the results were summarized by the ED_{50} value (table III).

Acknowledgments

We wish to express our thanks to KL Keim *et al* for their contributions to the anticonvulsant study of the naphthalenylsulfonylhydantoins; to A Verwijs and his staff for the analytical data; to M Harrison for the *in vivo* and *in vitro* studies and to C Delfino for typing the manuscript.

References

1 Kador PF, Robinson WG, Kinoshita JH (1985) *Ann Rev Pharmacol* 25, 691
2 Benfield P (1986) *Drugs* 32 (suppl 2) 43
3 Sarges R (1986) *Trends in Medicinal Chemistry*, Proceedings of the 9th Int Symp on Medicinal Chemistry, Berlin (Mutschler E, Winterfeldt E, eds) Weinheim 1987, pp 551–564
4 Dvornik D (1987) *Aldose Reductase Inhibition. An Approach to the Prevention of Diabetic Complications* (Porte D, ed) McGraw-Hill, New York, pp 368
5 Lipinski CA, Hutson NJ (1984) *Ann Rep Med Chem* 19, 169
6 Kador PF, Kinoshita JH, Shrapless NE (1985) *J Med Chem* 28, 841
7 Dvornik D, Simard-Duquesne N, Kraml M, Sestanj K, Gabbay KH, Kinoshita JH, Varma SD, Merola LO (1973) *Science* 182, 1146
8 Kraml M, Cosyns L (1969) *Clin Biochem* 2, 373
9 Hayman S, Kinoshita JH (1965) *J Biol Chem* 240, 877
10 Sestanj K, Bellini F, Fung S, Abraham N, Treasurywala A, Humber L, Simard-Duquesne N, Dvornik D (1984) *J Med Chem* 27, 255
11 Sestanj K, Abraham NA, Bellini F, Treasurywala A (1986) US Patent 4, 439, 617
12 Okuda J, Inagaki K, Miwa I, Yashiro T (1982) *Chem Pharm Bull* 30, 3244
13 Cohen A, Huett JW (1934) *J Chem Soc* 656
14 Mercanton R (1945) *Helv Chim Acta* 28, 533
15 Smith PAS (1946) *Org React* 3, 337
16 Smith PAS (1966) *Open Chain Nitrogen Compounds* vol 2 (Benzamin WA, ed) New York, pp 219–221
17 Gilbert EE (1969) *Synthesis* 1, 1
18 Miwa I, Hirano M, Inagaki K, Belbeoc'h C, Okuda J (1987) *Biochem Pharm* 36, 2789
19 European Patent Application No. 84115873.4, pp 13–14
20 Swinyard EA, Brown WC, Goodman LS (1952) *J Pharmacol Exp Ther* 109, 319
21 Humber LG (1987) *Prog Med Chem* 24, 299
22 Still WC, Kahn M, Mitra A (1978) *J Org Chem* 43, 2923