Structural and conformational studies of 5-(1*H*-pyrrol-2-ylmethylene)-substituted imidazolidine-2,4-diones and thiazolidine-2,4-diones

Alfonso de Dios, Maria Luz de la Puente, Alfonso Rivera-Sagredo, and Juan Felix Espinosa

Abstract: Some imidazolidine-2,4-dione (hydantoin) and thiazolidine-2,4-dione (TZD) derivatives with a 1*H*-pyrrol-2-ylmethylene substituent at the 5-position (**1**–**8**) have been synthesized via an aldol condensation reaction. A mixture of *Z*- and *E*- stereoisomers was obtained, as confirmed by HPLC and NMR studies. Assignment of the stereochemistry was achieved through chemical shift knowledge, NOE, and $^3J_{H,C}$ data. The conformation of the molecules depends on the configuration at the double bond. While the (NH,C *cis*) form is the most stable conformer for the *E*-isomer, the (NH,C *trans*) form is the preferred conformer for the *Z*-isomer. The temperature coefficients of the NH pyrrole protons reveal the existence of an intramolecular hydrogen bond for the *E*-isomers.

Key words: hydantoin, TZD, NMR spectroscopy, conformational analysis, temperature coefficient.

Résumé : Faisant appel à une réaction de condensation aldolique, on a réalisé la synthèse de dérivés de l'imidazolidine-2,4-dione (hydrantoïne) et de la thiazolidine-2,4-dione (TZD) portant un substituant 1*H*-pyrrol-2-ylméthylène en position 5 (**1**–**8**). La formation de mélanges de stéréoisomères *Z*- et *E*- a été confirmée par des études de CLHP et de RMN. L'attribution de la stéréochimie a été réalisée sur la base de connaissances chimiques et de données relatives aux valeurs $^3J_{H,C}$ et d'effet Overhauser nucléaire. La conformation des molécules dépend de la configuration de la double liaison. Alors que le forme NH,C *cis* correspond à la conformation la plus stable de l'isomère *E*, la forme NH,C *trans* correspond à la conformation la plus stable de l'isomère *Z*. Les coefficients de température des protons NH du pyrrole mettent en évidence l'existence d'une liaison hydrogène intramoléculaire pour les isomères *E*.

Mots clés : hydantoïne, TZD, spectroscopie RMN, analyse conformationnelle, coefficient de température.

[Traduit par la Rédaction]

Introduction

Imidazolidine-2,4-dione (hydantoin) (1) and thiazolidine-2,4-dione (TZD) (2) derivatives are good examples of compounds that exhibit a wide range of interesting biological properties. The hydantoin scaffold is a common feature present in orally active fibrinogen (1(*a*)) and angiotensin II (1(*b*)) receptor antagonists, anticonvulsant sodium channels (1(*c*)), and muscarinic receptor ligands (1(*d*)). The synthesis of combinatorial libraries of hydantoins for biological screening (1(*e*)) is a clear indication of their pharmaceutical relevance. On the other hand, some TZD derivatives that show high affinity for peroxisome proliferator-activated receptor γ (PPARγ) are very well known hypoglycemic drugs (2(*a*)).

As these two scaffolds are usually responsible for key interactions in the receptor binding sites, Structure-activity relationship studies (SAR) techniques have been employed to correlate biological activity with differences in steric and electrostatic parameters (1(*c*)). In this context, structural and conformational analysis of the aforementioned derivatives may be a very powerful tool to understanding possible binding modes, thus facilitating SAR studies.

As part of a medicinal chemistry project developed in our laboratories, we have synthesized several hydantoin and TZD derivatives (**1**–**8**, Fig. 1). *E*- and *Z*- isomers were isolated by preparative HPLC and their configuration assigned by NMR spectroscopy. The conformational preferences were investigated to gain insight into the influence of the geometry on the pharmacological properties of the compounds.

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Results and discussion

Synthesis

Aldol condensations of commercially available or easily accessible starting materials with pyrrole-2-carboxaldehyde and using standard thermodynamic control conditions were carried out (3). An excess of aldehyde, a catalytic amount of amine base in THF, and long refluxing times were employed to afford mixtures of *E*–*Z* compounds (Scheme 1). Attempts to isolate the stereoisomers by silica gel chromatography were unsuccessful; thus purification was performed by HPLC.

An efficient system capable of baseline resolving the two *E*–*Z* isomers was developed. A series of parameters (composition of the mobile phase, column packing, and additives)

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Scheme 1. Preparation of compounds **1**–**8**.

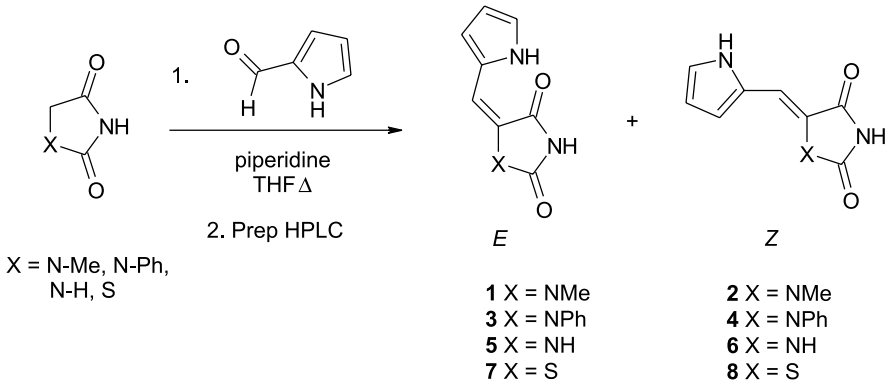


Fig. 1. Structure of compounds **1**–**8** showing the atomic numbering.

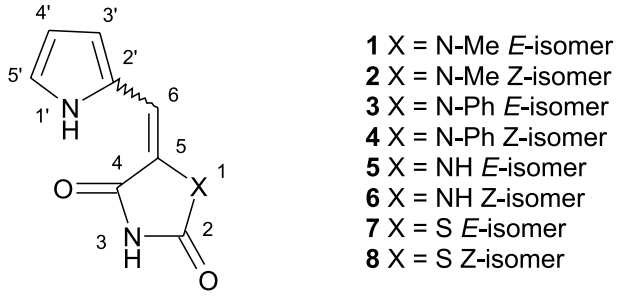
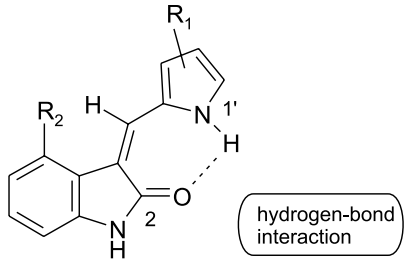


Fig. 2. Preferred configuration for 3-(1*H*-pyrrol-2-ylmethylene)-substituted indolin-2-ones (see also: ref. (3)).



were tested to find suitable conditions for isolation of both isomers. Reverse phase chromatography using a gradient of water–acetonitrile and trifluoroacetic acid as additives and a variety of stationary phases, including C8–C18 and phenyl series, allowed the separation of the stereoisomers. For hydantoin derivatives, the major component of the *E*–*Z* mixture eluted earlier than the minor one. In contrast, for the TZD mixture the major component eluted in second place, which suggested a change of stereoselectivity relative to the hydantoin series.

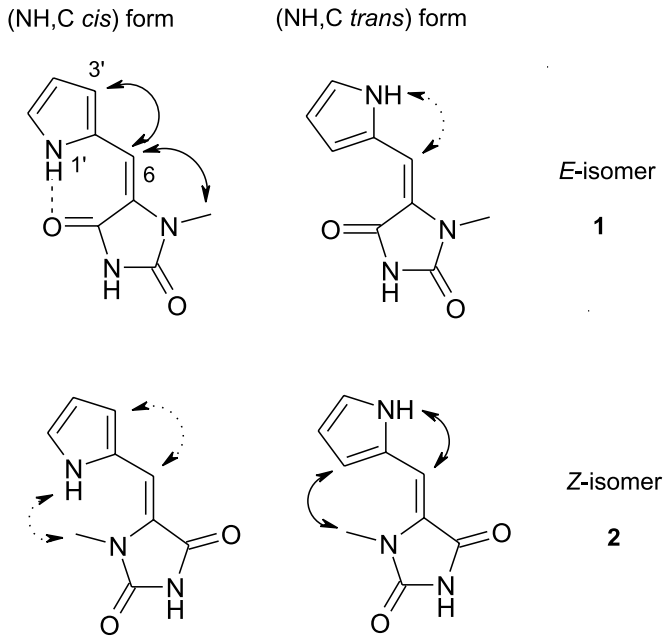
As the reaction was carried out under thermodynamic control conditions, we envisioned that internal hydrogen bond formation between the C4 carbonyl group and the NH1′ of the pyrrole ring should favour the formation of the corresponding *E* isomer. In fact, the predominance of this configuration had been reported (100% of population based on NOE data) for related 3-(1*H*-pyrrol-2-ylmethylene)-indolin-2-ones (Fig. 2). The authors postulated an intramolecular hydrogen, located between the C-2 carbonyl oxygen atom of the indolin-2-one ring and the proton on the N1′ of pyrrole, to explain this selectivity. They did not, however, provide any experimental evidence to support its existence. In our experiments, analytical studies detected the presence of both stereoisomers and showed different isomer ratios for each case. Integration of the ^{1}H NMR spectra of the mixtures confirmed the change in stereoselectivity inferred from HPLC data. While the reaction progressed with high selectivity for the N-methyl (**1**, **2**) and the N-phenyl (**3**, **4**) hydantoins (93:7 and 86:14 *E*:*Z* mixture ratios, respectively), no significant selectivity was found for the NH hydantoins (**5**, **6**) (44:56, *E*:*Z*). Unexpectedly, the opposite selectivity was found for the TZDs (**7**, **8**), and the *Z*-isomer was the major product of the reaction (11:89, *E*:*Z*). The configurational assignment is described in detail in the following section.

Hydrogen bond formation alone, therefore, can not explain the observed stereoselectivity, and other factors have to be considered. Our data indicates that steric hindrance is more important than intramolecular hydrogen bonding in determining the stereoselectivity of the reaction. Steric interferences between the pyrrole ring and the N-substituent are present for the *Z*-isomers **2** and **4**, which favour the formation of the *E*-isomers **1** and **3** with high selectivity. However, the absence of steric hindrance for the *Z*-isomer **6** increases the proportion of this isomer. Moreover, the isomeric ratio obtained for TZD further supports the minor role of hydrogen bonding. For this latter compound, the *Z*-isomer **8** does not exhibit steric interferences and is the major product of the reaction.

Stereochemistry assignment

The first step was the assignment of all the proton and carbon resonances on the basis of ^{1}H, ^{13}C, correlation spectroscopy (COSY), heteronuclear single-quantum correlation (HSQC), and heteronuclear multiple-bond correlation (HMBC) experiments recorded in DMSO. The NH proton of the pyrrole ring was distinguished from the NH proton of the hydantoin moiety through its coupling to the pyrrole protons, as observed in a COSY experiment. The configuration at the double bond was determined through one-dimensional NOE spectroscopy (1D-NOESY) experiments. Inversion of the methyl protons in **1** produced a nuclear Overhauser effect (NOE) to the olefinic proton H6, whereas no NOEs to the pyrrole protons were detected, indicating that the methyl group and the olefinic proton are on the same side of the

Fig. 3. Summary of the relevant NOEs observed for each conformer of hydantoins **1** and **2**. Solid and dotted arrows represent strong and weak NOEs respectively. The detected hydrogen bond is also shown.



molecule (Fig. 3). On the other hand, NOEs between the methyl protons and the pyrrole protons were observed for **2**. These results reveal that **1** is the *E*-isomer and **2** is the *Z*-isomer. Analogously, NOEs between H6 and the *ortho* protons of the N-phenyl ring, and between H6 and NH1, were observed for **3** and **5**, respectively, corresponding to the *E*-isomer. By contrast, NOEs between the pyrrole protons and the *ortho* protons of the N-phenyl ring, and between the pyrrole protons and the NH proton, were detected for **4** and **6**, respectively, which is consistent with the Z-isomers.

We have found a correlation between the *Z*–*E* configuration of the compounds and the chemical shifts of H6 and H1′ (Table 1). In this regard, the pyrrole H1′ appears at high frequency in the *E*-isomer relative to the *Z*-isomer, whereas the olefinic proton exhibits the opposite behaviour. This relationship may be attributed to the influence of the carbonyl group of the hydantoin ring. While the NH-pyrrole (H1′) is deshielded by the carbonyl in the *E*-isomer, the olefinic proton (H6) is deshielded in the *Z*-isomer, and the corresponding proton signals move to higher shifts.

Unfortunately, NOE analysis cannot be utilized for the elucidation of the stereochemistry of compounds **7** and **8**. Although Prabhakar et al. (2(*b*)) have proposed to use IR data for the configurational assignment of TZD analogues, we have been able to determine the stereochemistry by NMR data, using the relationship between configuration and chemical shift derived for compounds **1**–**6**. Thus, the comparison of H1′ and H6 chemical shifts of **7** and **8** (Table 1) suggest that the compounds correspond to the *E*- and the *Z*-isomer, respectively. This empirical assignment can be confirmed through three-bond ^{1}H-^{13}C coupling constants. It is well known that these couplings present a Karplus-type dependence on the dihedral bond that can be used for identification of configurational isomers (4). The magnitude of the

Table 1. H6 and H1′ chemical shifts and (H6/H3′):(H6/H1′) NOE intensity ratios determined for compounds **1**–**8**.

Compound	Configuration	$\delta_{H1'}$	δ_{H6}	NOE ratio (H6/H3′):(H6/H1′)
1	*E*	11.99	6.47	7:1
2	Z	11.23	6.52	1:8
3	*E*	12.01	6.07	4:1
4	*Z*	11.22	6.72	1:11
5	*E*	11.93	6.32	5:1
6	*Z*	11.18	6.41	1:3
7	*E*	12.16	7.25	—
8	*Z*	11.67	7.66	1:10

Note: — indicates data not measured.

coupling from the olefinic proton (H6) to the carbonyl carbon (C4) across the double bond should indicate the relative disposition, which is higher for the *trans* arrangement (*E*-isomer). The validity of this prediction was verified for hydantoins **1**–**6**, whose stereochemistry was elucidated through NOE analysis as outlined above. $^{3}J_{C,H}$ spin-spin coupling constants were measured from gated ^{1}H-decoupling ^{13}C NMR spectra. C4 appeared as a doublet for the N-methyl and N-phenyl derivatives (**1**–**4**), and as a triplet for the N-H derivatives (**5** and **6**) because the carbon was also coupled to NH1. This extra coupling was removed by acquiring a ^{13}C spectrum with selective NH1 decoupling, resulting in a doublet from which the coupling of interest could be measured. The $^{3}J_{H6,C4}$ value for compounds **1**, **3**, and **5** (*E*-isomers) is 10.2 Hz in all the cases, whereas compounds **2**, **4**, and **6** (*Z*-isomers) present a lower value (5.9 Hz), consistent with NOE-based assignments. This relevant H,C coupling constant was also determined for **8**. The experimental value for this compound is 5.9 Hz, which indicates the *Z*-configuration at the double bond, in agreement with the stereochemistry deduced from chemical shift data.

Conformational analysis

The conformation of these derivatives depends on rotation around the C2′—C6 bond, which determines the relative orientation of the pyrrole and the hydantoin or TZD rings. The compounds can adopt the (NH,C *cis*) form or the (NH,C *trans*) form, as shown in Fig. 3 for **1** and **2**. The conformational analysis of 2-substituted pyrroles has attracted special attention in the literature. In particular, 2-formyl pyrrole has been extensively studied through several methods (5). The less polar (NH,O *cis*) form, stabilized by a hydrogen bond, was determined to be the most stable conformer through dipolar moment measurements (5(*a*)), IR data (5(*b*)), and NMR spectroscopy (5(*c*)). Particularly, coupling constant analysis showed that the (NH,O *cis*) conformer was 95% populated in solution (5(*c*)). This conformational preference was rationalized through molecular orbital calculations (6). Analogously, the conformation of 2-substituted imine derivatives has also been studied through dipolar moment measurements and five-bond H,H couplings (7). These studies demonstrated the preponderance of the (NH,N *cis*) conformer in solution, which was also proposed to be stabilized by a hydrogen bond. In contrast, divergent conclusions have been reported for 2-vinyl pyrroles, and the major conformation in solution remains unclear (8). In our

case, we predict the (NH,C *cis*) form to be the major conformer in solution for the *E*-isomers, allowing the pyrrole-NH and the carbonyl oxygen to form an intramolecular hydrogen bond; however, a preferred conformation cannot be anticipated for the *Z*-isomers.

The major conformation in solution was determined for the hydantoins **1**–**6** through 1D-NOESY experiments in DMSO. The H6/H3′ and the H6/H1′ NOEs are exclusive for the (NH,C *cis*) and the (NH,C *trans*) forms, respectively (Fig. 3). For **1**, **3**, and **5** (*E*-isomers), the H6/H3′ NOE is much stronger than the H6/H1′ NOE, indicating that the (NH,C *cis*) form is the preferred conformer in solution. The (H6/H3′):(H6/H1′) NOE intensity ratios, which account for the relative conformer populations, suggest that the N-methyl hydantoin displays the highest population of the (NH,C *cis*) conformer (Table 1). Interestingly, for hydantoins **2** and **4** (*Z*-isomers), the NOE intensities are interchanged and the H6/H1′ NOE is now much stronger than the H6/H3′ NOE. This finding reflects the existence of a conformational change around the C2′—C6 bond, and the (NH,C *trans*) form becomes the major conformer in solution for both compounds. This conclusion is reinforced by the observation of strong NOEs between H3′ and the methyl protons for **2**, and between H3′ and the phenyl protons for **4**. It is interesting to note that, for **4**, the predominance of this conformer can also be deduced from chemical shift data. Some of the pyrrole protons in this compound present anomalous, low δ_H values due to the shielding produced by the phenyl ring. While H3′ presents the lowest chemical shift (4.51 ppm), H1′ has a typical value (11.22 ppm), which reveals the proximity of H3′ to the phenyl ring, showing the predominance of the (NH,C *trans*) form. For the *Z*-isomer **6**, the H6/H1′ NOE is also stronger than the H6/H3′ NOE (Table 1), which indicates that the (NH,C *trans*) form is the major conformer in solution, although its population decreases relative to **2** and **4**.

As the pyrrole-NH and the carbonyl oxygen are located on the same side in the preferred conformer of the *E*-isomers, an internal hydrogen bonding may exist for this configuration, as proposed by Sun et al. (3) for the indolin-2-one series (Fig. 2). The exchangeable protons involved in hydrogen bonds tend to appear at higher shifts owing to the effect of the oxygen atom (9). Indeed, the chemical shifts of the pyrrole-NH in compounds **1**, **3**, and **5** are higher than the values in compounds **2**, **4**, and **6** (Table 1), which suggests the presence of an intramolecular hydrogen bond. This prediction has been demonstrated experimentally by studying the change of $\delta_{H1'}$ with temperature, expressed by the chemical shift temperature coefficient (9). As temperature changes affect the mobility of solvent molecules, the chemical shifts of exchangeable protons that are involved in intermolecular hydrogen bonds with the solvent have larger chemical shift temperature-dependence than the intramolecularly hydrogen bonded protons, which have little interaction with the solvent. The temperature coefficient of H1′ was determined for hydantoins **1**–**6**. The experimental values measured for **1**, **3**, and **5** (–1.0, –1.1, and –1.1 ppb K^{-1}, respectively) are much smaller than those obtained for **2**, **4**, and **6** (−4.4, −6.9, and −4.1 ppb K^{-1}, respectively). The comparison between sets of values confirms the presence of an intramolecular hydrogen bond for the *E*-isomers.

Similar investigations were performed for TZDs in DMSO. The temperature coefficients of H1′ for the *E*-isomer (**7**) and for the *Z*-isomer (**8**) are –1.2 and –4.4 ppb, respectively. These values indicate the presence of a hydrogen bond in **7**, which implies that the (NH,C *cis*) form is the preferred conformer for the *E*-isomer. Moreover, 1D-NOESY experiments were carried out for compound **8** (Fig. 2*b*). H6 inversion produces a strong NOE to H1′ and a weak NOE to H3′ (intensity ratio 10:1), demonstrating the predominance of the (NH,C *trans*) for the *Z*-isomer. The results point out that the conformational preferences for TZDs are similar to those found for hydantoins, and swapping the nitrogen atom for a sulfur atom at the 1-position does not change the conformational behaviour of the molecules.

The predominance of the (NH,C *cis*) form over the (NH,C *trans*) form for the *E*-isomers can be interpreted in terms of an intramolecular hydrogen bond that stabilizes this conformation. Nevertheless, there is no clear explanation for the preference of the (NH,C *trans*) form for the *Z*-isomers. As the pyrrole-NH is more accessible to the solvent in this latter conformer, we suggest that this orientation may facilitate the formation of intermolecular hydrogen bonds with solvent molecules.

Experimental section

Starting materials (1-methyl hydantoin (**9**), hydantoin (**10**), and thiazolidine-2,4-dione (**11**)) and reagents were commercially available (Aldrich Co.). 1-Phenyl hydantoin (**12**) was prepared according to the procedure reported by Casagrande et al. (10) as follows: N-phenyl glycine (3.02 g, 20 mmol) was suspended in 90 mL of water and 0.1 mL of glacial acetic acid. The mixture was stirred and heated at 60°C for 30 min. A solution of potassium cyanate (1.62 g, 20 mmol) in 10 mL of water was slowly added and the solution heated for 1.5 h. Then, 2.5 mL of concentrated HCl (35%) was added dropwise and the reaction was heated at 90°C for 16 h. After cooling the solution at room temperature, a precipitate was formed. The solid was filtered off, rinsed with water, dried under high vacuum, and triturated thoroughly to yield 1.75 g of pure product (49% yield). ES-MS: 175.0 ($[M^+ - H]$).

General procedure for the synthesis of imidazolidine-2,4-diones (1–6) and thiazolidine-2,4-diones (7–8)

To a suspension of the starting material (**9**–**12**, 1 equiv) in THF (10 mL), pyrrole 2-carboxaldehyde (2 equiv) was added in one portion. A catalytic amount of piperidine (0.1 equiv) was added, and the mixture stirred and heated at reflux for 5–16 h. Then, the reaction was cooled down to room temperature and the solvent evaporated in vacuo. The residue was diluted with EtOAc and sequentially washed with 5% aqueous HCl, water, and brine. After drying over Na_2SO_4 and evaporating the solvents in vacuo, the crude product was prepurified by silica gel chromatography to remove the excess of starting aldehyde and to afford pure *E*–*Z* mixtures. These mixtures were then subjected to preparative HPLC, as detailed in the text.

1-Methyl-5-(1H-pyrrol-2-ylmethylene)-imidazolidine-2,4-dione:* E-*isomer (1) and* Z-*isomer (2)

Obtained as a 93:7 *E–Z* mixture, with 65% overall yield after purification of the crude product using hexane–acetone (6:1). **1**: ^{1}H NMR (DMSO): 11.99 (s, 1H, NH1′), 11.45 (s, 1H, NH3), 7.08 (m, 1H, H5′), 6.58 (m, 1H, H3′), 6.47 (s, 1H, H6), 6.20 (m, 1H, H4′), 3.07 (s, 3H, Me). ^{13}C NMR (DMSO): 164.6 (C4), 152.7 (C2), 126.6 (C2′), 123.9 (C5), 122.0 (C5′), 116.0 (C3′), 110.0 (C4′), 107.9 (C6), 25.7 (Me). **2**: ^{1}H NMR (DMSO): 11.23 (s, 1H, NH1′), 11.20 (s, 1H, NH3), 6.96 (m, 1H, H5′), 6.52 (s, 1H, H6), 6.46 (m, 1H, H3′), 6.17 (m, 1H, H4′), 3.20 (s, 3H, Me). ^{13}C NMR (DMSO): 164.5 (C4), 155.3 (C2), 125.5 (C5), 123.8 (C2′), 121.3 (C5′), 112.4 (C3′), 110.0 (C4′), 102.3 (C6), 29.3 (Me). **1**, **2**: ESI+-MS: 192.1 ($[M + H]^+$).

1-Phenyl-5-(1H-pyrrol-2-ylmethylene)-imidazolidine-2,4-dione:* E-*isomer (3) and* Z-*isomer (4)

Obtained as an 86:14 *E–Z* mixture, with 60% overall yield after purification of the crude product using hexane–EtOAc (2:1). **3**: ^{1}H NMR (DMSO): 12.01 (s, 1H, NH1′), 11.73 (s, 1H, NH3), 7.57 (t, 2H, *m*-protons phenyl), 7.49 (t, 1H, *p*-proton phenyl), 7.42 (d, 2H, *o*-protons phenyl), 7.09 (m, 1H, H5′), 6.54 (m, 1H, H3′), 6.16 (m, 1H, H4′), 6.07 (s, 1H, H6). ^{13}C NMR (DMSO): 164.3 (C4), 152.1 (C2), 133.0, 129.6, 128.6, 128.5, 126.0 (C2′), 124.8 (C5), 122.6 (C5′), 116.6 (C3′), 110.2 (C4′), 108.2 (C6). **4**: ^{1}H NMR (DMSO): 11.46 (s, 1H, NH3), 11.22 (s, 1H, NH1′), 7.36–7.43 (m, 3H, *m*- and *p*-protons phenyl), 7.29 (d, 2H, *o*-protons phenyl) 6.83 (m, 1H, H5′), 6.72 (s, 1H, H6), 5.77 (m, 1H, H4′), 4.51 (m, 1H, H3′). ^{13}C NMR (DMSO): 164.7 (C4), 154.2 (C2), 124.1 (C2′), 134.6, 128.8, 128.5, 127.4, 123.3 (C5′), 116.6 (C5), 113.4 (C3′), 110.2 (C4′), 103.4 (C6). **3**, **4**: ESI+-MS: 254.1 ($[M + H]^+$).

5-(1H-Pyrrol-2-ylmethylene)-imidazolidine-2,4-dione:* E-*isomer (5) and* Z-*isomer (6)

Obtained as a 44:56 *E–Z* mixture, with 55% overall yield after purification of the crude product using hexane–EtOAc (1:3). **5**: ^{1}H NMR (DMSO): 11.93 (s, 1H, NH1′), 11.24 (s, 1H, NH3), 10.12 (s, 1H, NH1), 7.05 (m, 1H, H5′), 6.52 (m, 1H, H3′), 6.32 (s, 1H, H6), 6.17 (m, 1H, H4′). ^{13}C NMR (DMSO): 165.3 (C4), 153.2 (C2), 126.7 (C2′), 122.8 (C5), 121.6 (C5′), 115.2 (C3′), 109.7 (C4′), 107.6 (C6). **6**: ^{1}H NMR (DMSO): 11.18 (s, 1H, NH1′), 10.98 (s, 1H, NH3), 10.04 (s, 1H, NH1), 6.98 (m, 1H, H5′), 6.80 (m, 1H, H3′), 6.41 (s, 1H, H6), 6.19 (m, 1H, H4′). ^{13}C NMR (DMSO): 165.4 (C4), 155.0 (C2), 125.5 (C2′), 122.1 (C5), 121.6 (C5′), 112.3 (C3′), 110.5 (C4′), 100.9 (C6). **5**, **6**: ESI+-MS: 178.0 ($[M + H]^+$).

5-(1H-Pyrrol-2-ylmethylene)-thiazolidine-2,4-dione:* E-*isomer (7) and* Z-*isomer (8)

Obtained as an 11:89 *E–Z* mixture, with 75% overall yield after purification of the crude product using hexane–EtOAc (5:1–1:1). **7**: ^{1}H NMR (DMSO): 12.25 (s, 1H, NH3), 12.16 (s, 1H, NH1′), 7.27 (m, 1H, H5′), 7.25 (s, 1H, H6), 6.73 (m, 1H, H3′), 6.29 (m, 1H, H4′). **8**: ^{1}H NMR (DMSO): 12.25 (s, 1H, NH3), 11.67 (s, 1H, NH1′), 7.66 (s, 1H, H6), 7.20 (m, 1H, H5′), 6.47 (m, 1H, H3′), 6.35 (m, 1H, H4′). ^{13}C NMR (DMSO): 167.8 (C2), 167.2 (C4), 126.9 (C2′), 124.3 (C5′), 122.2 (C6), 115.1 (C5), 113.5 (C3′), 111.9 (C4′). **7**, **8**: ESI+-MS: 195.0 ($[M + H]^+$).

Analytical HPLC

The chromatographic system consisted of an HP 1100 liquid chromatograph (Hewlett-Packard, Germany) coupled in series with an HP photodiode array detector (PAD), an evaporation light scattering detector (Polymer Labs, U.K), and an HP single quadrupole mass-selective detector (MSD) with an installed electrospray ionization (ESI) source. Process control and data handling were carried out using HP ChemStation software. The chromatographic studies were performed using Spherisorb C8/C18 and Spherisorb P (Waters, U.S.A.) reverse phase columns (250 × 4.6 mm I.D., 5 μm particle size) protected by a pre-column filter filled with the corresponding stationary phases. The mobile phase consisted of water–TFA (0.05%, solvent A) and acetonitrile–TFA (0.05%, solvent B). Elution was carried out using a linear gradient, starting from 30% solvent B to 100% solvent B over 15 min. This gradient was followed by a 5 min isocratic elution with 100% B before going back to the initial solvent mixture in 5 min. An interval of 10 min was allowed between subsequent runs. When the phenyl package was the selected stationary phase, the gradient elution went from 5 to 65% B over 15 min, while the rest of the chromatographic parameters were kept as described above. All runs were performed at room temperature at a flow rate of 1 mL min^{-1}. The eluent was monitored by PDA detector and the absorbance spectra (210–400 nm) were recorded continuously during the course of each run.

Preparative HPLC

Reverse-phase purification was carried out using a Waters Delta Prep^{TM} 4000 liquid chromatograph (Waters, U.S.A.) controlled through the Millenium 32 software package. Purifications were conducted with a 250 × 2 cm Spherisorb C18 column, using the same eluents as in analytical HPLC but at a flow rate of 10 mL min^{-1}. All isomers so obtained were examined for purity by analytical HPLC.

NMR experiments

NMR spectra of **1**–**8** were acquired on a Bruker Avance 500 spectrometer in DMSO at 30°C with an inverse probe. Proton spectra were also recorded at 70°C. Proton and carbon chemical shifts were referenced to the residual solvent signals at 2.50 and 39.5 ppm, respectively. Different types of carbon experiments were performed: standard ^{13}C NMR spectra with proton broadband decoupling, the gated ^{1}H-decoupling version that yields proton-coupled spectra, and ^{13}C spectra with ^{1}H single frequency decoupling. One-dimensional spectra were acquired using 32K data points, which were zero-filled to 64K data points previous to Fourier transformation. Absolute value COSY, phase-sensitive HSQC, and HMBC spectra were acquired using gradient-selection techniques (gs-COSY, gs-HSQC, and gs-HMBC). Acquisition data matrices were defined by 1K × 256 points in t_2 and t_1, respectively. The 2D data matrices were multiplied by appropriate window functions and zero-filled to 1K × 512 matrices prior to Fourier transformation. 1D-NOESY experiments were carried out with the selective 1D double-pulse field gradient spin echo module (11) using a mixing time of 400 ms.

2D-NOESY experiments were also performed with the same mixing time and with 2K × 256 matrices. Data were processed using the XWINNMR Bruker program on a Silicon Graphics computer.

Conclusions

This report describes the synthesis, stereochemical assignment, and conformational studies of a number of 5-(1*H*-pyrrol-2-ylmethylene)-substituted imidazolidine-2,4-diones and thiazolidine-2,4-diones that may exhibit inhibitory activity against a wide range of receptors. We have demonstrated that, regardless of the type of ring (hydantoin or TZD) or the N-substitution for the hydantoin derivatives, the (NH,C *cis*) form is the most stable conformer for the *E*-isomer and the (NH,C *trans*) form is the most stable conformer for the *Z*-isomer. The conformation around the C2′—C6 bond is therefore controlled by the configuration at the double bond.

We have shown that the *E*-isomer has the pyrrole-NH involved in an internal hydrogen bond with the carbonyl oxygen of the hydantoin or TZD rings, whereas such interaction is absent in the *Z*-isomer, leaving both groups available to establish intermolecular hydrogen bonds with the protein receptor. On the other hand, the pyrrole-NH in the *E*-isomer may form simultaneous hydrogen bonds with two donor atoms: the carbonyl oxygen of the ligand and a second electronegative atom of the receptor. These three-centre hydrogen bonds are common in the crystal structures of protein complexes (12). Thus, the knowledge of the conformational preferences and the spatial relationship between the hydrogen bond donors (NH) and the acceptors (C=O) for these compounds constitutes useful information for developing structure–activity relationships.

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