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Diastereoselective synthesis of benzofuran-3(2*H*)-one-hydantoin dyads

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ABSTRACT

A convenient diastereoselective rearrangement of the racemic (*R*/*S*)-spiro[chroman-2,4′-imidazolidine]-2′,4,5′-triones **3a**–**c** into (2′*R*,5*S*)- and (2′*S*,5*R*)-5-(3-oxo-2,3-dihydrobenzofuran-2-yl)imidazolidine-2,4-diones **4a**–**c** under alkali conditions is described. The obtained σ bridged benzofuran-3(2*H*)-one-hydantoin dyads **4a**–**c** are subsequently transformed into π conjugated benzofuran-3(2*H*)-one-hydantoin dyads **5a**–**c** by a diastereoselective dehydrogenation using I_2 (catalytic)/DMSO system to predominantly yield the (*Z*)-isomer. The novel single and double bonded benzofuran-3(2*H*)-one-hydantoin conjugate structures **4a**–**c** and **5a**–**c** were unambiguously elucidated by single-crystal X-ray diffraction and 2D NMR techniques allowing an in-depth stereochemical and mechanistic discussions.

1. Introduction

The structural diversity of natural and synthetic heterocycles has become a key topic in organic, bioorganic and medicinal chemistry. Recent investigations are focused at the synthesis of new conjugates of small bioactive molecules derived from well-known organic compounds, such as flavonoids, stilbenes, coumarins, alkaloids, terpenoids, peptides and glycosides.[1] Indeed, the structural combination of two or more of these medicinal relevant molecules in one organic framework usually leads to additive and/or new biological properties different from those of the parent material. Although, uncommonly encountered in nature, the titled dihydrobenzofuran-3-one and hydantoin are important oxygen and nitrogen containing heterocycles, which play outstanding biological roles.[2–6] The dihydrobenzofuran-3-one nucleus (Fig. 1) is represented by aurones, a natural flavonoid-type of compounds showing two possible (*E*)- and (*Z*)-isomers. Hydantoins are imidazolidine derived compounds sharing two carbonyl functions at positions C-2 and C-4 with substituents bonded via carbon C-5 and/or nitrogen N-1, N-3 atoms (Fig. 1).[3]

Recent interests have considered the biological significance of dihydrobenzofuran-3-one and hydantoin compounds to develop and update new synthetic routes.[2,7] Filloux et al.[7c] reported a multicatalytic, one-pot, enantioselective Michael/Stetter synthesis of dihydrobenzofuran-3-one by reaction of salicylaldehydes with electron deficient alkynes. A one-pot, three-component sequential reaction is updated for the synthesis of diversely 1,3,5- and 1,3,5,5-poly-substituted hydantoins from azides, iso(thio)cyanates and substituted α-haloacetic carboxylic acids.[8a] This methodology and others similar are appropriately designated for the synthesis of spiro hydantoins, being particularly useful synthetic precursors to perform other interesting chemical alterations and, for this purpose, we consider their use as starting material in the present study.[8]

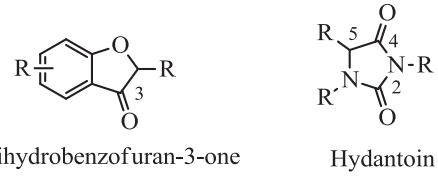

Fig. 1. Dihydrobenzofuran-3-one and hydantoin heterocyclic systems.

The development of natural mimic heterocyclic combinations, using greener synthetic methods, is an attractive goal in the medicinal chemistry area. In this framework, we point fingers to the covalently combined heterocycles and their stereoselective

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synthetic endpoint. Indeed, the available literature is carelessly taking into consideration the stereoselective organic access to σ single bonded or π conjugated heterocyclic dyads. The geometrical factor remains a critical issue to arguably justify certain structure–activity relationships. From this point of view, Singh et al.[9] have reported the synthesis and antitumour activity of various chromone-based conjugated combinations with indole, pyrazole and pyrimidine moieties. Nevertheless the (*E*/*Z*)-isomeric aspect was completely omitted regarding to the undertaken Knoevenagel condensation route, and its influence as an important geometrical parameter on the newly discovered antitumour activity. Indirubin derivatives,[10a] the active ingredients of Danggui Longhui Wan (a mixture of plants that is used in traditional Chinese medicine to treat chronic diseases), are π-conjugated hybrids of indolin-(2 and 3)-ones exhibiting potent cyclin-dependent kinases and cancer cell proliferation inhibitory effect. Many published studies are devoted to investigate the synthetic routes and the biological manifestations of natural indirubin derivatives and related compounds, but the structural relevance of the (*E*/*Z*) geometry remains unexplored to date (Fig. 2).[10]

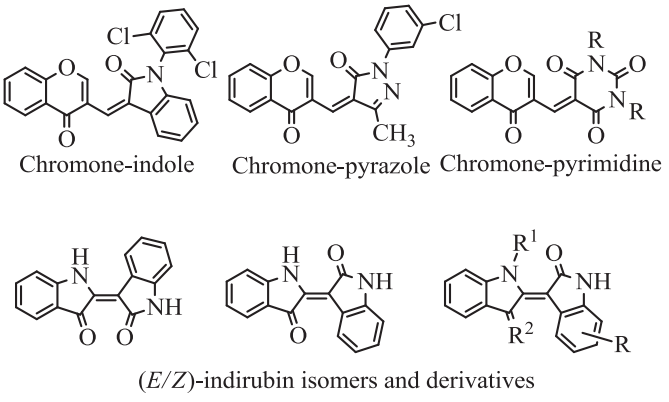
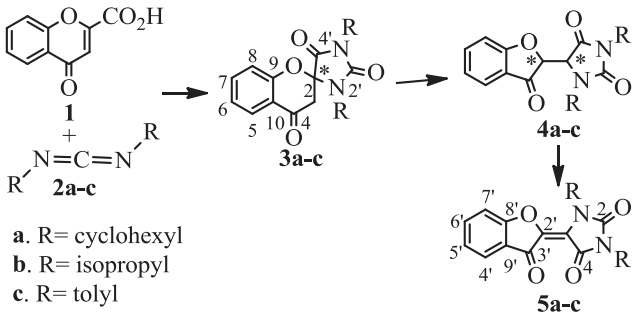


Fig. 2. Synthetic and natural conjugated heterocyclic dyads.

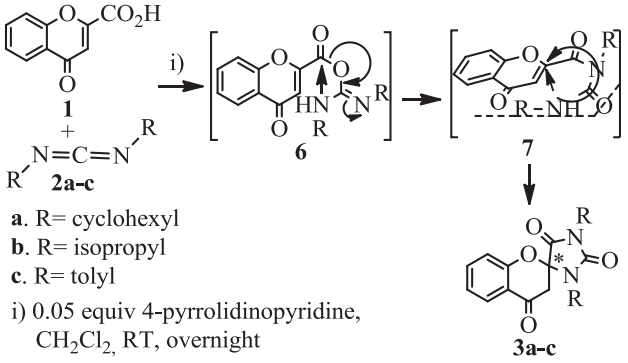
Due to the valuable biological outcome of such conjugated heterocyclic dyads, our attention is directed towards designing mimic skeletons. Herein we combine both the biologically active dihydobenzofuran-3-one and hydantoin in a single bonded **4a**–**c** or double bonded dyads **5a**–**c** bearing asymmetric or diastereomeric centres, respectively. The synthetic strategy is based on a three-step reaction sequence, starting from the readily accessible spiro bicyclic chromanone–hydantoin **3a**–**c** to be diastereoselectively transformed into the benzofuran-3(2*H*)-one-hydantoin dyads **4a**–**c** and **5a**–**c** (Scheme 1). The stereochemical course of the relevant transformations is investigated by means of high-resolution spectroscopic techniques allowing the discussion of their formation mechanism.



Scheme 1. Reaction sequence to synthesize benzofuran-3-one-hydantoin dyads.

2. Results and discussion

Spiro bicyclic chromanone–hydantoins **3a**–**c** have only been reported in the primary literature by Filliatre and Servens.[8b] They reported the synthesis of 1′,3′-dicyclohexylspiro[chroman-2,4′-imidazolidine]-2′,4,5′-trione **3a** by the action of chromone-2-carboxylic acid **1** on *N*,*N*-dicyclohexylcarbodiimide **2a** in a two-step procedure.[8b] In their method the isolation of 2-chromone-*N*-acylurea as intermediate is required at the first stage in order to carry out a subsequent intramolecular N-cyclization affording the desired spiro bicyclic chromanone–hydantoin **3a**. Alternatively, we have herein shorten the protocol into a one-step synthetic route of 1′,3′-disubstituted-spiro[chroman-2,4′-imidazolidine]-2′,4,5′-triones **3a**–**c** via the organo-catalytic coupling of the cheap chromone-2-carboxylic acid **1** with carbodiimides **2a**–**c** using a catalytic amount of 4-pyrrolidinopyridine (Scheme 2). Our improved procedure delivers high yields (66–88%) and readily isolated materials **3a**–**c** after recrystallization. The formation of compounds **3a**–**c** has been rationalized on the basis of density functional theory (DFT) studies,[8c] by a mechanism involving three steps: a nucleophilic addition of chromone-2-carboxylic acid **1** on the carbodiimide C=N double bond followed by an O→N acyl shift of the intermediate **6** to give the chromone-2-*N*-acylurea **7**, which is reported as an experimentally isolated product.[8b] The last step consists in an intramolecular cyclization via aza-Michael addition at position C-2 of the chromone, which has led to the creation of a spiro asymmetric carbon joining both of the chromanone and hydantoin rings at positions C-2/C-4′ **3a**–**c**. A racemic (*R*/*S*) mixture is resulted from the equiprobable C-2 nucleophilic attack of the nitrogen atom on both sides of the sp^2 plan in the 2-chromone-*N*-acylurea intermediate **7** (Scheme 2). The crystal structures of the representative compounds **3a** and **3c** confirm their presence as racemic mixtures (Fig. 3). Both (*R*)- and (*S*)-absolute configurations (1:1 ratio) at the C-2 asymmetric spiro carbon can be recognized from the centrosymmetric monoclinic crystal space groups $P2_1/c$ and $C2/c$ in which compounds **3a** and **3c** crystallize, respectively.



Scheme 2. Synthesis of spiro[chroman-2,4′-imidazolidine]-2′,4,5′-triones **3a**–**c** and the proposed mechanism for their formation as a racemic mixture.

Our synthetic approach concerns the ring transformation of the spiro bicyclic chromanone–hydantoin scaffolds **3a**–**c** into the benzofuran-3(2*H*)-one-hydantoin **4a**–**c**. This rather rare rearrangement is performed by treatment of **3a**–**c** with sodium ethoxide. The transformation permits the creation of a second asymmetric centre in the resulting C2′–C5 σ bridged benzofuran-3(2*H*)-one-hydantoins **4a**–**c**, which are obtained in acceptable yields (47–63%) after column chromatography purification and recrystallization (Scheme 3). The O1→C2 to O1→C3 rearrangement was initially monitored by ^{1}H NMR analysis. The ^{1}H NMR spectra of benzofuran-3(2*H*)-one-hydantoins **4a**–**c** present two signals as doublets at 4.55–5.34 and 4.89–4.93 ppm, with a small vicinal coupling constant (^3J=1.9–2.0 Hz), attributed to the proton

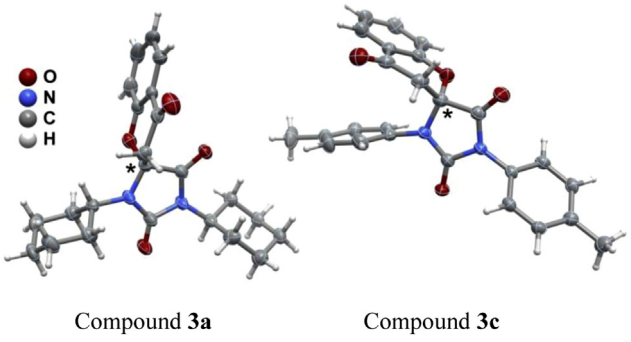
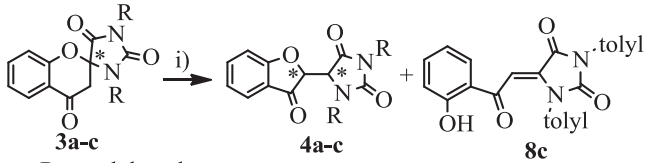


Fig. 3. Molecular structures of compounds $C_{23}H_{28}N_2O_4$ (**3a**) and $C_{25}H_{20}N_2O_4$ (**3c**). While for **3a** the asymmetric unit coincides with a whole molecule, for **3c** the asymmetric unit comprises two crystallographic independent molecules (only one is represented for clarity). Asymmetric carbons are depicted by an asterisk (*). Non-hydrogen atoms are represented as thermal ellipsoids drawn at the 50% probability level, while hydrogen atoms are represented as small spheres with arbitrary radii.

resonances of H-5 and H-2′ of the C2′–C5 σ single bond, respectively. The aforementioned ^{1}H NMR patterns of compounds **4a**–**c** are the sole difference in comparison with the ^{1}H NMR spectra of the starting material **3a**–**c**, which display a clear AB spin system [assigned at 2.89–3.14 ppm and 3.22–3.30 ppm (^2J=16.7–16.9 Hz)] due to the geminal diastereotopic protons of the chromanone C-3 methylene group. ^{1}H NMR data are otherwise useless to discuss the ambiguous stereochemical aspect of the eventual chromanone→dihydrobenzofuran-3-one rearrangement.



Scheme 3. Synthesis of 1,3-disubstituted-5-(3-oxo-2,3-dihydrobenzofuran-2-yl)imidazolidine-2,4-diones **4a**–**c**.

The reaction of the racemic **3a**–**c** compounds must logically generate the rearranged products **4a**–**c** as 1:1 mixture of two diastereomers, thus two pairs of enantiomers are expected. In fact, a unique racemic pair of enantiomer (2′*R*,5*S* and 2′*S*,5*R*) is determined by single-crystal X-ray diffraction studies of compounds **4a** and **4c** (Fig. 4). Convincible crystallographic data reveal that the centrosymmetric space groups, triclinic Pī in **4a** and monoclinic $P2_1/n$ in **4c**, impose both of (*R*)- and (*S*)-absolute configurations at the asymmetric carbons C-2′ and C-5 in a 1:1 ratio. Aside, the crystallization conditions of the candidate compounds **4a** and **4c** in ethanol at 6 °C, yielded crystals exhibiting a preferential enrichment of the gauche conformer relatively to the central σ single bond C2′–C5 with dihedral angle (CH_2'–CH_5) of 64° calculated from the crystallographic parameters (Fig. 5).

The HSQC experiment of the σ bridged benzofuran-3(2*H*)-one-hydantoin **4a**–**c** indicated that both H-2′ and H-5 are carried by two different carbons C-2′ at 80.6–82.3 ppm and C-5 at 59.9–62.1 ppm, respectively. The neighbouring carbon resonances of H-2′ and H-5 are assigned from the main HMBC correlations (Fig. 6): (i) H-5 correlates with three carbonyl groups C-2 (153.6–156.2 ppm) and C-4 (166.2–168.1 ppm) from the hydantoin moiety and C-3′ (196.8–196.9 ppm) from the benzofuran-3(2*H*)-one moiety; and (ii) H-2′ correlates with carbonyls C-4 and C-3′ together with *C*-8′ (172.5–176.6 ppm) and C-5. Further HMBC features enable to

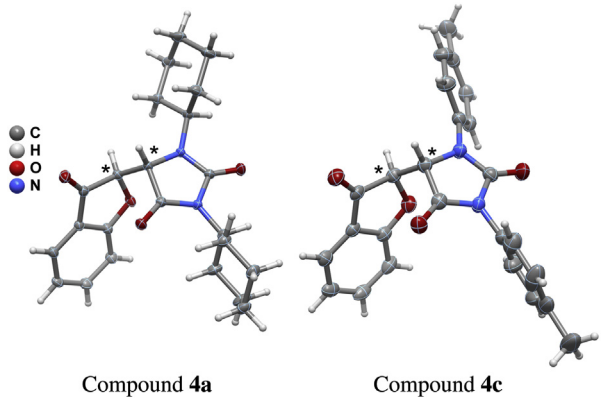


Fig. 4. Molecular structures of compounds $C_{23}H_{28}N_2O_4$ (**4a**) and $C_{25}H_{20}N_2O_4$ (**4c**). While for **4a** the asymmetric unit is composed of a whole molecule co-crystallizing with an ethanol molecule (not shown), for **4c** the asymmetric unit comprises instead four crystallographic independent molecules (for clarity, only one is represented). Asymmetric carbons are depicted by an asterisk (*). Non-hydrogen atoms are represented as thermal ellipsoids drawn at the 50% probability level, while hydrogen atoms are represented as small spheres with arbitrary radii.

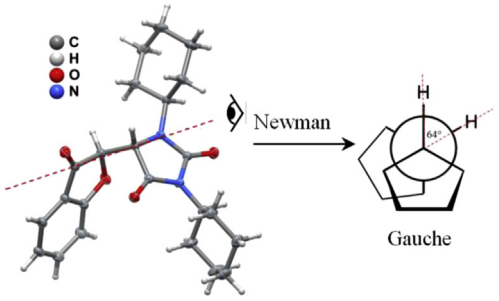


Fig. 5. Asymmetric unit of compound **4a** showing the (2′*R*,5*S*)-enantiomer and the corresponding Newman gauche projection.

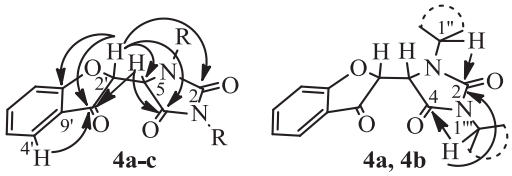


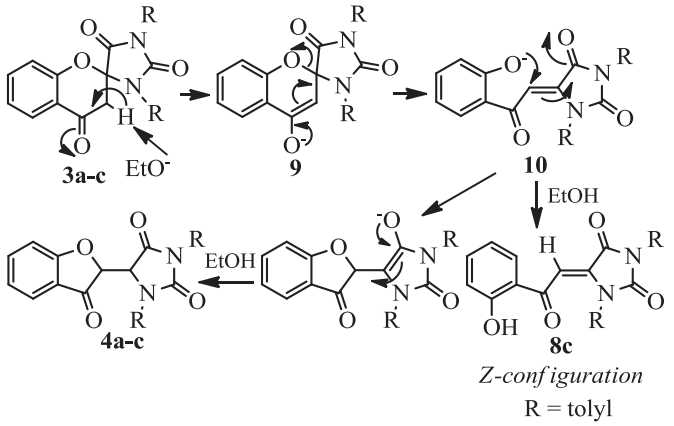
Fig. 6. Main connectivities observed in the HMBC spectra of compounds **4a**–**c**.

differentiate between the carbonyl groups. For instance in all compounds **4a**–**c** the carbonyl C-3′ is coupled to H-4′ (7.69–7.74 ppm) proving its position in the benzofuran-3(2*H*)-one ring. In the case of compounds **4a** and **4b**, H-1‴ (3.81 and 4.22 ppm) correlates to both carbonyls of the hydantoin ring C-2 and C-4, while H-1″ shows only a weak HMBC correlation with carbonyl C-2, therefore allowing the assignment of the 1-*N*- and 3-*N*-cyclohexyl/isopropyl hydantoin substituents.

Appreciable information is gained from the NOESY spectrum of **4a**. Strong NOE effects between H-2′ (4.90 ppm) and H-5 (4.56 ppm) are present, consistently proving the relative C2′–C5 gauche conformation in solution and as previously described for the crystals (Figs. 4 and 5). The σ bridged benzofuran-3(2*H*)-one-hydantoin molecules **4a**–**c** adopt the desirable gauche conformer in order to increase their chemical stability by adjusting between both electronegative atoms repulsion forces and heterocyclic tensions at the same time.

From a chemical stability perspective, the spiro bicyclic precursors **3a**–**c** have a high tension that may favour an expected

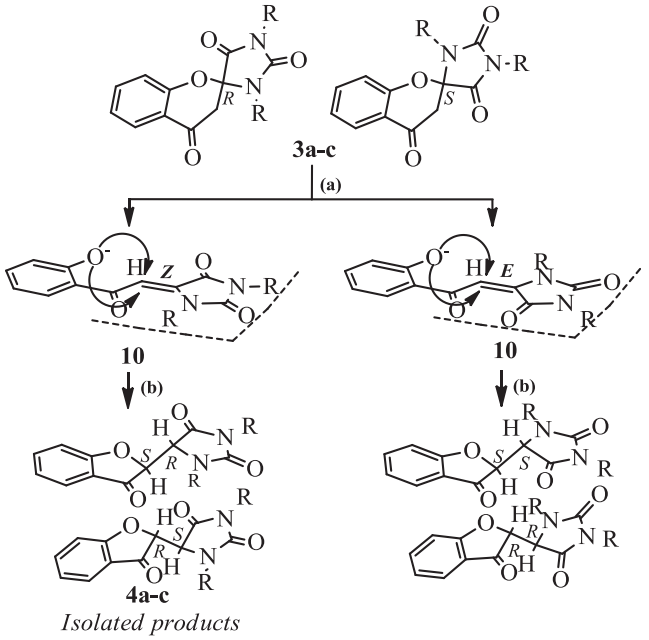
rearrangement or opening the heterocycles. The formation of the rearranged products **4a**–**c** can be envisaged by an initial deprotonation of the active methylene group in **3a**–**c** by the strong base sodium ethoxide, followed by a chromanone ring-opening of **9** and a five-membered ring closure of **10** to finally afford the benzofuran-3(2*H*)-one-hydantoin **4a**–**c** (Scheme 4). The reaction using derivative **3c** (with the tolyl substituent) was the unique case where a small amount (5%) of the opened conjugated-form (*Z*)-1,3-ditolyl-5-[2-(2-hydroxyphenyl)-2-oxoethylidene]imidazolidine-2,4-dione **8c** was isolated and established by NMR analysis and analytical data. These results unequivocally confirm the chromanone ring-opening of the spiro bicyclic compounds **3a**–**c** to give the intermediate **10** (Scheme 4). In such a spiro bicyclic structure, the heterolytic cleavage is found more susceptible to occur over the highly polarized O–C σ bond of the chromanone than the N–C one of the hydantoin nucleus making this latter more chemically stable.



Scheme 4. Proposed mechanism for diastereoselective rearrangement of **3a**–**c** onto **4a**–**c**.

The rationale behind the diastereoselective rearrangement of the spiro bicyclic chromanone–hydantoin **3a**–**c** into the benzofuran-3(2*H*)-one-hydantoin **4a**–**c** is mainly deduced from the isolated conjugated-form **8c**. Unless considered as an intermediate of reaction, the opened conjugated-form **10** presents the systematic 1:1 (*E*/*Z*)-isomeric mixture arising from a racemic mixture of the starting spiro bicyclic compounds **4a**–**c** [step (a), Scheme 5]. Statistically, the involvement of both *E*- and (*Z*)-configurations of **10** in the reaction mechanism may, respectively, provide two pairs of enantiomers (2′*R*,5*R* and 2′*S*,5*S*) and (2′*R*,5*S* and 2′*S*,5*R*) in a 1:1 ratio [step (b), Scheme 5]. Since the experimentally isolated compounds **4a**–**c** are structured as a unique pair of the mentioned enantiomers (2′*R*,5*S* and 2′*S*,5*R*), the opening of the racemic *R*/*S* spiro bicyclic compounds **3a**–**c** is compulsory driven to the most stable (*Z*)-isomer of the intermediate **10**, assuming a greater planarity and suitability for the ring-closure, while the (*E*)-isomer is probably found destabilized by the internal electronic repulsion between carbonyl groups C-2′ and C-4. Based on these mechanistic explanations, we have been convinced by further empirical studies: the NOESY spectrum analysis of the isolated compound **8c** (as represented by the intermediate **10**) show undoubtedly the (*Z*)-configuration because no significant NOE effects are observed between the vinylic proton and tolyl protons so to evidence the *E*-configuration.

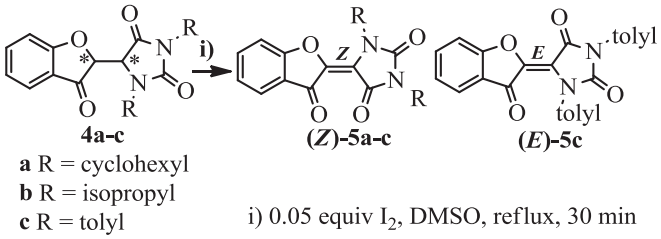
In short, the origin of the diastereoselective rearrangement of the spiro bicyclic chromanone–hydantoin **3a**–**c** into the benzofuran-3(2*H*)-one-hydantoin **4a**–**c** is based on the chromanone ring-opening of **3a**–**c** (Scheme 5), which provides the conjugated intermediate **10** in its most stable (*Z*)-form. The oxygen nucleophilic attack usually occurs on both sides of the C1′—C5 sp^2 plane of **10**



Scheme 5. Stereochemical features of the diastereoselective rearrangement of **3a**–**c** into **4a**–**c**.

leading to a racemic character of the carbon C-2′ (*R*/*S* in a 1:1 ratio). However the adjacent C-5 asymmetric carbon is most likely taking the opposite configuration (*R* or *S*) of C-2′ as clearly seen in the O1′–C2′–C5–H5 arrangement of compounds' **4a**–**c** gauche conformation (Figs. 4 and 5).

The final step of our synthetic strategy consisted in the construction of a rigid π double bond between the benzofuran-3(2*H*)-one and the hydantoin rings. We have attempted the dehydrogenation of compounds **4a**–**c** using a catalytic amount of iodine in refluxing DMSO. The desired 1,3-disubstituted-5-(3-oxobenzofuran-2(3*H*)-ylidene)imidazolidine-2,4-diones **5a**–**c** have been selectively obtained as their (*Z*)-isomer (35–65%, Scheme 6). A remarkable case in the dehydrogenation consists of the parallel isolation of (*E*)-isomer (in low yield 21%) only when dealing with the tolyl derivative **4c**.



Scheme 6. Synthesis of 1,3-disubstituted 5-(3-oxobenzofuran-2(3*H*)-ylidene)imidazolidine-2,4-diones **5a**–**c**.

This final dehydrogenation step was firstly monitored by NMR analysis. The ^{1}H NMR spectra of the resulting compounds **5a**–**c** show the clear disappearance of both H-2′ and H-5 when compared to those of the starting materials **4a**–**c**. A double bond bridging both moieties of the benzofuran-3(2*H*)-one-hydantoin structure is formed as determined by the high-resolution mass spectra showing a loss of a hydrogen molecule in compounds **5a**–**c**. In such circumstances, 2D NMR experiments were less informative for the study of the stereochemical course of this transformation. The determination of (*E*)- or (*Z*)-configuration in the resulting olefins **5a**–**c** is unsolvable using particularly the NOESY technique because no characteristic protons exist around the C2′=C5 double bond.

This structural feature could only be unveiled by single-crystal X-ray diffraction studies. The crystallization of the conjugated dyads **5a**–**c** was not a trivial task. As a matter of fact, compound **5a** could not be isolated as single-crystals with quality enough for a full structural elucidation even after using a myriad of solvents and crystallization conditions. Compound **5c** was, however, successfully crystallized as long fine needles using toluene solution at 6 °C. Several attempts for finding both isomers were considered, but only crystals of the (*Z*)-enriched product (*Z*)-**5c** could be isolated (Fig. 7).

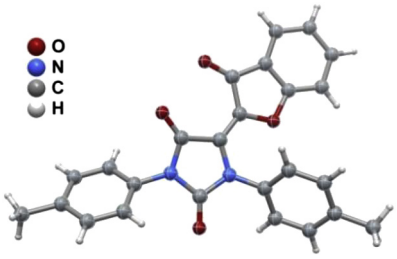
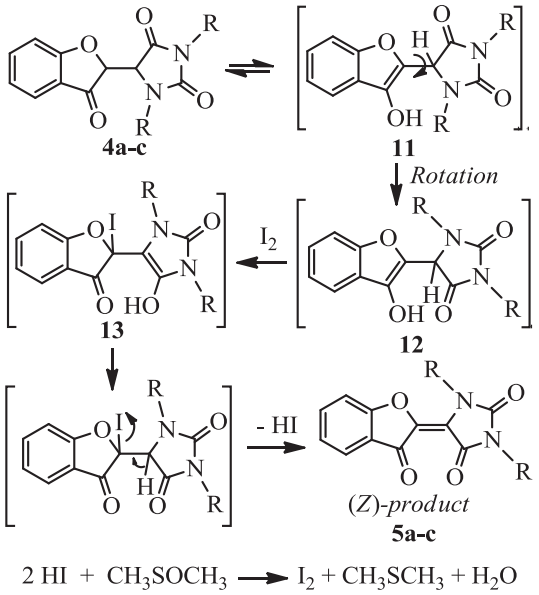


Fig. 7. Schematic representation of the asymmetric unit of compound $C_{25}H_{18}N_2O_4$ [(*Z*)-**5c**], which comprises a whole molecular unit in the (*Z*)-configuration around the double bond. Non-hydrogen atoms are represented as thermal ellipsoids drawn at the 50% probability level, while hydrogen atoms are represented as small spheres with arbitrary radii.

A piece of the utmost importance must be emphasized regarding the dehydrogenation process of the single bonded benzofuran-3(2*H*)-one-hydantoin **4a**–**c**. In the case of the tolyl derivative **4c**, the dehydrogenation process allows the formation of a minor amount of (*E*)-isomer of **5c**, which is isolated by preparative TLC along with (*Z*)-**5c**. We assume that this compound must feasibly be the (*E*)-isomer because of its similar features of both the ^{1}H NMR and the high-resolution mass spectra relative to those of the (*Z*)-isomer of **5c**. Several crystallization attempts of (*E*)-**5c** were carried out, but no valuable crystallographic data could be derived. Thus, the structure of (*E*)-**5c** was elucidated on the basis of extensive NMR data that clearly sort the great differences in terms of proton and carbon chemical shifts to those of (*Z*)-**5c**. Despite of their similar yellow physical appearance, the isomer (*Z*)-**5c** is a solid that could be visually distinguished from the (*E*)-**5c** one. Additionally, their melting points are largely different (see Experimental). As a result, we have accomplished the isolation of two separable diastereomers of compound **5c** (*E*/*Z*) obtained in a 1:3 ratio (calculated by NMR chemical shift integration and confirmed by HPLC analysis). Therefore, we disclose a diastereoselective dehydrogenation majorly yielding the (*Z*)-**5a**–**c** isomers.

The last σ→π conversion can be mechanistically outlined by the formation of the benzofuran-3(2*H*)-ones enolic form **11**, which should take the stabilized rotamer **12** due to an intramolecular hydrogen bond. It subsequently undergoes a sequence of α-iodination to give **13**, and E_2 elimination of hydroiodic acid to yield the final (*Z*)-**5a**–**c**. The formed hydroiodic acid follows its redox cycle by reacting with DMSO to regenerate the catalyst molecular iodine and producing the thioether, which smells during the course of the reaction (Scheme 7). In these particular conjugated heterocyclic hybrids, the (*Z*)-configuration is apparently the most stable due to the quasi-planarity of the scaffold (Fig. 7). This geometrical feature is not expected for the (*E*)-configured scaffold, which obviously inflicts a very close proximity, and a consequent considerable steric hindrance, between the benzofuran-3(2*H*)-one carbonyl group and the neighbouring substituent. Thus, rotation over the central C-2′–C5 bond minimizes the internal structural interactions ultimately promoting the appearance of the thermodynamic most stable (*Z*)-product.



Scheme 7. Proposed mechanism for the diastereoselective dehydrogenation of compounds **5a**–**c**.

3. Conclusion

The present study describes convenient synthetic approaches leading to a facile bridging of two biologically active heterocycles. Starting from the easily prepared spiro bicyclic chromanone–hydantoin skeleton, σ single bonded and π double bonded benzofuran-3-one-hydantoin dyads have been produced following diastereoselective organic pathways. In-depth spectroscopic studies, single-crystal X-ray diffraction and NMR techniques, have revealed various structural features regarding the stereochemical course of the sequential transformations. Important diastereoselective patterns, conformational and geometrical factors have been underlined due to their influence on future chemical and biological applications.

4. Experimental section

4.1. General

Melting points were measured on a Buchi melting point B-545 apparatus and are uncorrected. NMR spectra were recorded on a 300 Bruker Avance spectrometer operating at 300.13 for ^{1}H and 75.47 MHz for ^{13}C, with $CDCl_3$ as solvent if not stated otherwise. Chemical shifts (δ) are reported in parts per million and coupling constants (J) in Hertz. The internal standard was TMS. The signals are described as s (singlet), d (doublet), dd (doublet of doublet), ddd (double doublet of doublet), t (triplet), tt (triplet of triplets), q (quartet), sept (septet) and m (multiplet). Unequivocal ^{13}C assignments were made with the aid of 2D HSQC and HMBC (delays for one bond and long-range $J_{C/H}$ couplings were optimized for 145 and 7 Hz, respectively) experiments. Exact mass measurements were recorded using a TOF-Q analyser and elemental analysis on Truspec 630-200-200 equipment.

4.2. Synthesis of 1′,3′-disubstituted spiro[chroman-2,4′-imidazolidine]-2′,4,5′-triones 3a–c

Chromone-2-carboxylic acid **1** (2 g, 10.52 mmol) was added to a solution of the appropriate carbodiimides **2a**–**c** (10.52 mmol, 1 equiv) in dichloromethane (20 mL), followed by the addition of a catalytic amount of 4-PPy (0.52 mmol, 0.08 g, 0.05 equiv).

The resulting mixture was allowed to stir overnight at room temperature. After that period, the solvent was evaporated to dryness and the resulting resinous solid was directly recrystallized from ethanol to afford compounds **3a**–**c**.

4.2.1. (R/S)-1′,3′-Dicyclohexylspiro[chroman-2,4′-imidazolidine]-2′,4,5′-trione ***3a***. $C_{23}H_{28}N_2O_4$ (white solid, 3.32 g, yield 80%; mp=189–190 °C, lit. 188 °C[8b]). ^{1}H NMR (300.13 MHz, $CDCl_3$): δ=1.10–2.16 (m, 20H, –C*H*$_2$–cyclohexyl), 2.89 (d, *J*=16.7 Hz, 1H, H-3), 3.30 (d, *J*=16.7 Hz, 1H, H-3), 3.33 (tt, *J*=12.2, 3.8 Hz, 1H, H-1‴), 3.83 (tt, *J*=12.2, 3.8 Hz, 1H, H-1″), 6.96 (dd, *J*=8.3, 0.8 Hz, 1H, H-8), 7.05–7.11 (m, 1H, H-6), 7.50 (ddd, *J*=8.3, 7.2, 1.6 Hz, 1H, H-7), 7.88 (dd, *J*=7.8, 1.6 Hz, 1H, H-5). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ=24.9, 25.0, 25.68, 25.71, 26.15, 26.15, 29.29, 29.33, 30.8 and 31.0 (–*C*H$_2$–cyclohexyl), 41.3 (C-3), 51.6 (C-1″), 54.0 (C-1‴), 88.5 (C-2), 117.6 (C-8), 119.8 (C-10), 122.3 (C-6), 126.2 (C-5), 136.3 (C-7), 153.8 (C-2′), 158.4 (C-9), 168.7 (C-5′), 188.7 (C-4). HRMS (ESI$^+$), *m*/*z* calcd for $[C_{23}H_{28}N_2O_4+Na]^+$: 419.1947; found: 419.1939. Anal. Calcd for $C_{23}H_{28}N_2O_4$: C 69.67, H 7.12, N 7.07. Found: C 69.36, H 7.10, N 7.11%.

4.2.2. (R/S)-1′,3′-Diisopropylspiro[chroman-2,4′-imidazolidine]-2′,4,5′-trione ***3b***. $C_{17}H_{20}N_2O_4$ (white solid, 2.20 g, yield 66%, mp=157–158 °C). ^{1}H NMR (300.13 MHz, $CDCl_3$): δ=1.39 (d, *J*=6.9 Hz, 6H, H-2″), 1.46 (d, *J*=6.9 Hz, 3H, H-2‴), 1.51 (d, *J*=6.9 Hz, 3H, H-2‴), 2.93 (d, *J*=16.7 Hz, 1H, H-3), 3.27 (d, *J*=16.7 Hz, 1H, H-3), 3.77 (sept, *J*=6.9 Hz, 1H, H-1‴), 4.26 (sept, *J*=6.9 Hz, 1H, H-1″), 6.97 (dd *J*=8.3, 0.9 Hz, 1H, H-8), 7.04–7.12 (m, 1H, H-6), 7.51 (ddd, *J*=8.3, 7.3, 1.8 Hz, 1H, H-7), 7.88 (dd, *J*=7.8, 1.8 Hz, 1H, H-5). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ=19.57 and 19.63 (C-2″), 20.96 and 21.03 (C-2‴), 41.0 (C-3), 43.9 (C-1″), 45.9 (C-1‴), 88.6 (C-2), 117.5 (C-8), 119.7 (C-10), 122.3 (C-6), 126.3 (C-5), 136.4 (C-7), 153.6 (C-2′), 158.4 (C-9), 168.6 (C-5′), 188.5 (C-4). HRMS (ESI$^+$), *m*/*z* calcd for $[C_{17}H_{20}N_2O_4+Na]^+$: 339.1321; found: 339.1324. Anal. Calcd for $C_{17}H_{20}N_2O_4$: C 64.54, H 6.37, N 8.86. Found: C 64.49, H 6.38, N 8.91%.

4.2.3. (R/S)-1′,3′-Ditolylspiro[chroman-2,4′-imidazolidine]-2′,4,5′-trione ***3c***. $C_{25}H_{20}N_2O_4$ (pale yellow solid, 3.80 g, yield 88%, mp=182–183 °C). ^{1}H NMR (300.13 MHz, $CDCl_3$): δ=2.33 and 2.35 (2s, 6H, 4″-C*H*$_3$ and 4‴-C*H*$_3$), 3.14 (3d, *J*=16.9 Hz, 1H, H-3), 3.22 (d, *J*=16.9 Hz, 1H, H-3), 6.98–7.09 (m, 2H, H-6, H-8), 7.18 and 7.23 (2d, *J*=8.1 Hz, 4H, tolyl), 7.28 and 7.35 (2d, *J*=8.4 Hz, 4H, tolyl), 7.44–7.53 (m, 1H, H-7), 7.76 (dd, *J*=7.8, 1.7 Hz, 1H, H-5). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ=21.06 and 21.08 (4″-*C*H$_3$ and 4‴-*C*H$_3$), 41.1 (C-3), 89.2 (C-2), 117.4 (C-8), 119.8 (C-10), 122.4 (C-6), 125.5 and 128.4 (C-2″ and C-2‴), 126.2 (C-5), 127.9 and 129.5 (C-1″ and C-1‴), 129.6 and 130.1 (C-3″ and C-3‴), 136.3 (C-7), 138.4 and 139.1 (C-4″ and C-4‴), 153.1 (C-2′), 158.0 (C-9), 167.1 (C-5′), 187.8 (C-4). HRMS (ESI$^+$), *m*/*z* calcd for $[C_{25}H_{20}N_2O_4+Na]^+$: 435.1321; found: 435.1309. Anal. Calcd for $C_{25}H_{20}N_2O_4$: C 72.80, H 4.89, N 6.79. Found: C 72.75, H 5.05, N 6.89%.

4.3. Synthesis of 1,3-disubstituted 5-(3-oxo-2,3-dihydrobenzofuran-2-yl)imidazolidine-2,4-diones 4a–c

Sodium (10.52 mmol, 0.242 g) was added to ethanol (5 mL) and the resulting solution was added dropwise (for 15 min) to a solution of the appropriate 1′,3′-disubstituted spiro[chroman-2,4′-imidazolidine]-2′,4,5′-trione **3a**–**c** (10.52 mmol) in ethanol (20 mL), placed in an ice-water bath (0 °C). The reaction was left for 1 h to reach room temperature under constant stirring. After TLC monitoring, the ethanolic solution was poured in ice and water to be neutralized to pH 7 with diluted hydrochloric acid. A yellowish white precipitate appeared, which was then purified by silica gel column chromatography using a (1:1) of light petroleum/dichloromethane as eluent. The resulting pure compounds were recrystallized from ethanol to afford compounds **4a**–**c**. In the case of the reaction of compound **3c**, the opened conjugated compound **8c** was first eluted from the column chromatography, isolated and recrystallized from ethanol.

4.3.1. (2′R,5S)/(2′S,5R)-1,3-Dicyclohexyl-5-(3-oxo-2,3-dihydrobenzofuran-2-yl)imidazolidine-2,4-dione ***4a***. $C_{23}H_{28}N_2O_4$ (white solid, 2.38 g, yield 57%, mp=154–155 °C). ^{1}H NMR (300.13 MHz, $CDCl_3$): δ=1.23–2.03 (m, 20H, –C*H*$_2$-cyclohexyl), 3.67 (tt, *J*=12.0, 4.1 Hz, 1H, H-1″), 3.81 ppm (tt, *J*=12.2, 3.8 Hz, 1H, H-1‴), 4.56 (d, *J*=2.0 Hz, 1H, H-5), 4.90 (d, *J*=2.0 Hz, 1H, H-2′), 7.07 (d, *J*=8.5 Hz, 1H, H-7′), 7.11–7.17 (m, 1H, H-5′), 7.61 (ddd, *J*=8.5, 7.3, 1.5 Hz, 1H, H-6′), 7.69–7.74 (m, 1H, H-4′). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ=24.9, 25.4, 25.71, 25.74, 25.76, 25.82, 29.8, 29.2, 30.3 and 31.4 (-*C*H$_2$-cyclohexyl), 51.8 (C-1‴), 54.1 (C-1″), 60.1 (C-5), 82.3 (C-2′), 112.9 (C-7′), 121.7 (C-9′), 122.7 (C-5′), 124.3 (C-4′), 138.0 (C-6′), 156.2 (C-2), 168.1 (C-4), 172.5 (C-8′), 196.9 (C-3′). HRMS (ESI$^+$), *m*/*z* calcd for $[C_{23}H_{28}N_2O_4+Na]^+$: 419.1947; found: 419.1947.

4.3.2. (2′R,5S)/(2′S,5R)-1,3-Diisopropyl-5-(3-oxo-2,3-dihydrobenzofuran-2-yl)imidazolidine-2,4-dione ***4b***. $C_{17}H_{20}N_2O_4$ (white solid, 1.574 g, yield 47%, mp=122 °C). ^{1}H NMR (300.13 MHz, $CDCl_3$): δ=1.30, 1.32 and 1.35 (d, *J*=7.0 Hz, 12H, H-2″ and H-2‴), 4.10 ppm (sept, *J*=7.0 Hz, 1H, H-1″), 4.22 ppm (sept, *J*=7.0 Hz, 1H, H-1‴), 4.55 (d, *J*=2.0 Hz, 1H, H-5), 4.89 ppm (d, *J*=2.0 Hz, 1H, H-2′), 7.08 (dd, *J*=8.4, 0.7 Hz, 1H, H-7′), 7.11–7.18 (m, 1H, H-5′), 7.58–7.65 (m, 1H, H-6′), 7.70–7.74 (m, 1H, H-4′). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ=19.2, 19.5, 19.9 and 21.1 (C-2′ and C-2‴), 44.2 (C-1‴), 46.0 (C-1″), 59.9 (C-5), 82.2 (C-2′), 112.9 (C-7′), 121.7 (C-9′), 122.8 (C-5′), 124.4 (C-4′), 138.0 (C-6′), 156.0 (C-2), 168.0 (C-4), 172.5 (C-8′), 196.8 (C-3′). HRMS (ESI$^+$), *m*/*z* calcd for $[C_{17}H_{20}N_2O_4+Na]^+$: 339.1324; found: 339.1318. Anal. Calcd for $C_{17}H_{20}N_2O_4$: C 64.54, H 6.37, N 8.86. Found: C 64.49, H 6.38, N 8.91%.

4.3.3. (2′R,5S)/(2′S,5R)-1′,3′-Ditolyl-5-(3-oxo-2,3-dihydrobenzofuran-2-yl)imidazolidine-2,4-dione ***4c***. $C_{25}H_{20}N_2O_4$ (white solid, 2.74 g, yield 63%, mp=181–183 °C). ^{1}H NMR (300.13 MHz, $CDCl_3$): δ=2.34 and 2.36 (2s, 6H, 4″-C*H*$_3$, 4‴-C*H*$_3$), 4.93 (d, *J*=1.9 Hz, 1H, H-2′), 5.34 (d, *J*=1.9 Hz, 1H, H-5), 7.00 (d, *J*=8.5 Hz, 1H, H-7′), 7.06–7.13 (m, 1H, H-5′), 7.18–7.29 (2m, 6H, tolyl) and 7.36 (d, *J*=8.4 Hz, 2H, tolyl), 7.55 (ddd, *J*=8.5, 7.3, 1.5 Hz, 1H, H-6′), 7.69 (d, *J*=7.7 Hz, 1H, H-4′). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ=20.92 and 21.15 (4″-*C*H$_3$, 4‴-*C*H$_3$), 62.1 (C-5), 80.6 (C-2′), 113.0 (C-7′), 121.5 (C-9′), 122.7 (C-5′), 123.5 and 126.0 (C-2″ and C-2‴), 124.3 (C-4′), 128.5 and 131.8 (C-1″ and C-1‴), 129.7 and 129.9 (C-3″ and C-3‴), 136.6 and 138.5 (C-4″ and C-4‴), 138.1 (C-6′), 153.6 (C-2), 166.2 (C-4), 172.6 (C-8′), 196.8 (C-3′). HRMS (ESI$^+$), *m*/*z* calcd for $[C_{25}H_{20}N_2O_4+Na]^+$: 435.1321; found: 435.1329.

4.3.4. (Z)-1,3-Ditolyl-5-[2-(2-hydroxyphenyl)-2-oxoethylidene] imidazolidine-2,4-dione ***8c***. $C_{25}H_{20}N_2O_4$ (yellow solid, 0.22 g, yield 5%, mp=223–224 °C). ^{1}H NMR (300.13 MHz, $CDCl_3$): δ=2.31 and 2.41 (2s, 6H, 4′-C*H*$_3$ and 4″-C*H*$_3$), 6.86–6.93 (m, 2H, H-3‴, H-5‴), 6.93 (s, 1H, H-1‴), 7.01–7.07, 7.30–7.35 (2m, 4H, tolyl), 7.32 and 7.40 (2d, *J*=8.1 Hz, 4H, tolyl), 7.44–7.48 (m, 1H, H-4‴), 7.71 (dd, *J*=8.0, 1.6 Hz, 1H, H-6‴), 11.31 (s, 1H, 2‴-O*H*). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ=21.1 and 21.2 (4′-*C*H$_3$ and 4″-*C*H$_3$), 104.3 (C-1‴), 118.2 (C-3‴), 119.0 (C-5‴), 120.2 (C-1‴), 125.7 and 126.2 (C-2′ and C-2″), 128.2 (C-1′ or C-1″), 129.7 and 129.9 (C-3′ and C-3″), 131.0 (C-6‴, C-1″ or C-1′), 135.1 (C-5), 137.0 (C-4‴), 138.8 (C-4′ and C-4″),152.9 (C-2), 161.7 (C-4), 162.3 (C-2‴), 194.5 (C-2‴). HRMS (ESI$^+$), *m*/*z* calcd for $[C_{25}H_{20}N_2O_4+Na]^+$: 435.1321; found: 435.1329. Anal. Calcd for $C_{25}H_{20}N_2O_4$: C 72.80, H 4.89, N, 6.79. Found: C 72.71, H 4.89, N 6.84%.

4.4. Synthesis of 1,3-disubstituted 5-[3-oxobenzofuran-2(3*H*)-ylidene]imidazolidine-2,4-dione 5a–c

Iodine (0.068 g dissolved in 1 mL of DMSO) was added to a -solution of the appropriate 1,3-disubstituted 5-(3-oxo-2,3-

dihydrobenzofuran-2-yl)imidazolidine-2,4-dione **4a**–**c** (5.26 mmol) in DMSO (3 mL) and the reaction mixture was refluxed under nitrogen flow and shielded from intense light for 30 min. After TLC monitoring, the reaction solution was poured into ice (10 g) and water (20 mL). An intense yellow precipitate appeared, which was filtrated and washed with water. The obtained solid was taken in dichloromethane (150 mL) and washed with a saturated solution of sodium thiosulfate (2×150 mL). After solvent evaporation the residue dissolved in dichloromethane was purified by silica gel column chromatography using a (1:1) mixture of light petroleum and dichloromethane as eluent. The resulting pure compound was recrystallized from ethanol to give compounds (*Z*)-**5a**–**c**. In the case of **4c**, two isomers (*Z*)-**5c** and (*E*)-**5c** were jointly obtained in a 3:1 ratio (evaluated by NMR proton integration and confirmed by HPLC analysis: Gilson HPLC conditions: column: Silica gel, mobile phase: hexane/THF (80:20), flow rate: 1 mL/min, UV–visible detection: λ=254; analysis: (*E*)-**5c** retention time=10.4 min, (*Z*)-**5c** retention time=14.5 min). Subsequently, the two isomers were separated and isolated by preparative TLC using dichloromethane as eluent, being (*E*)-**5c** the first compound eluted and recrystallized from ethanol, while (*Z*)-**5c** was recrystallized from toluene. Please note: it is strongly recommended to work away from intense light since these compounds are photosensitive.

*4.4.1. (Z)-1,3-Dicyclohexyl-5-[3-oxobenzofuran-2(3H)-ylidene] imidazolidine-2,4-dione (Z)-**5a**.* $C_{23}H_{26}N_2O_4$ (yellow solid, 1.36 g, yield 65%, mp=203–204 °C). ^{1}H NMR (300.13 MHz, $CDCl_3$): δ=1.26–2.31 (m, 20H, –C*H*$_2$–cyclohexyl), 4.02 (tt, *J*=12.3, 3.5 Hz, 1H, H-1″), 4.63 (tt, *J*=12.0, 3.6 Hz, 1H, H-1‴), 7.22–7.29 (m, 2H, H-5′, H-7′), 7.61–7.68 (m, 1H, H-6′), 7.82–7.85 (m, 1H, H-4′). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ=25.0, 25.1, 25.82, 25.85, 26.0, 26.3, 29.24, 29.29, 30.5 and 30.6 (–CH_2–, cyclohexyl), 52.2 (C-1‴), 60.4 (C-1″), 113.2 (C-7′), 121.7 (C-2′), 123.5 (C-5′), 124 (C-9′), 124.3 (C-4′), 136.2 (C-5), 137.0 (C-6′), 153.3 (C-2), 161.6 (C-4), 165.9 (C-8′), 183.5 (C-3′). HRMS (ESI$^+$), *m*/*z* calcd for $[C_{23}H_{26}N_2O_4+Na]^+$: 417.1790; found: 417.1792.

*4.4.2. (Z)-1,3-Diisopropyl-5-[3-oxobenzofuran-2(3H)-ylidene] imidazolidine-2,4-dione (Z)-**5b**.* $C_{17}H_{18}N_2O_4$ (yellow solid, 0.58 g, yield 35%, mp=135–137 °C). ^{1}H NMR (300.13 MHz, $CDCl_3$): δ=1.45 and 1.58 (d, *J*=6.9 Hz, 12H, H-2″ and H-2‴), 4.44 ppm (sept, *J*=6.9 Hz, 1H, H-1‴), 4.22 ppm (sept, *J*=6.9 Hz, 1H, H-1″), 7.23–7.29 (m, 2H, H-7′, H-5′), 7.62–7.68 (m, 1H, H-6′), 7.82–7.86 (m, 1H, H-4′). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ=19.6 and 21.8 (C-2′ and C-2‴), 44.8 (C-1‴), 48.3 (C-1″), 112.3 (C-7′), 121.7 (C-5), 122.3 (C-9′), 124.0 (C-5′), 125.0 (C-4′), 135.0 (C-2′), 136.3 (C-6′), 153.7 (C-2), 159.6 (C-4), 163.5 (C-8′), 180.5 (C-3′). HRMS (ESI$^+$), *m*/*z* calcd for $[C_{17}H_{18}N_2O_4+Na]^+$: 337.1164; found: 337.1156.

*4.4.3. (Z)-1,3-Ditolyl-5-[3-oxobenzofuran-2(3H)-ylidene]imidazolidine-2,4-dione (Z)-**5c**.* $C_{25}H_{18}N_2O_4$ (yellow solid, 1.35 g, yield 62%, mp=232 °C). ^{1}H NMR (300.13 MHz, $CDCl_3$): δ=2.39 and 2.46 (2s, 6H, H-4″-C*H*$_3$ and 4‴-C*H*$_3$), 6.74 (dd, *J*=8.9, 0.6 Hz, 1H, H-7′), 7.13–7.20 (m, 1H, H-5′), 7.24–7.29 (2m, 6H, tolyl) and 7.40 (d, *J*=8.4 Hz, 2H, tolyl), 7.46–7.54 (m, 1H, H-6′), 7.74–7.77 (m, 1H, H-4′). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ=21.1 and 21.2 (4″-*C*H$_3$ and 4‴-*C*H$_3$), 112.4 (C-7′), 119.7 (C-5), 121.7 (C-9′), 123.9 (C-5′), 124.7 (C-4′), 125.9 and 127.6 (C-2″ and C-2‴), 128.3 and 131.4 (C-1″ and C-1‴), 129.3 and 129.7 (C-3″ and C-3‴), 136.40 (C-2′), 136.43 (C-6′), 138.5 and 138.9 (C-4″ and C-4‴),152.8 (C-2), 158.3 (C-4), 163.9 (C-8′), 180.5 (C-3′). HRMS (ESI$^+$), *m*/*z* calcd for $[C_{25}H_{18}N_2O_4+Na]^+$: 433.1164; found: 433.1171. Anal. Calcd for $C_{25}H_{18}N_2O_4$: C 73.16, H 4.42, N 6.83. Found: C 73.23, H 4.52, N 6.70%.

*4.4.4. (E)-1,3-Ditolyl-5-[3-oxobenzofuran-2(3H)-ylidene]imidazolidine -2,4-dione (E)-**3c**.* $C_{25}H_{18}N_2O_4$ (yellow solid, 0.46 g, yield 21%, mp=208–210 °C). ^{1}H NMR (300.13 MHz, $CDCl_3$): δ=2.42 and 2.45 (2s, 6H, 4″-C*H*$_3$ and 4‴-C*H*$_3$), 7.15–7.21 (m, 1H, H-5′), 7.28–7.35 and 7.37–7.42 (2m, 9H, H-7′ and tolyl), 7.58–7.68 (m, 2H, H-6′, H-4′). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ=21.2 and 21.3 (4″-*C*H$_3$ and 4‴-*C*H$_3$), 112.4 (C-7′), 118.8 (C-5), 121.8 (C-9′), 124.0 (C-5′), 124.8 (C-4′), 126.0 and 127.7 (C-2″ and C-2‴), 128.3 and 131.5 (C-1″ and C-1‴), 129.3 and 129.7 (C-3″ and C-3‴), 136.5 (C-6′), 137.0 (C-2′), 138.6 and 139.0 (C-4″ and C-4‴), 152.9 (C-2), 164.0 (C-8′), 180.6 (C-4), 191.3 (C-3′). HRMS (ESI$^+$), *m*/*z* calcd for $[C_{25}H_{18}N_2O_4+Na]^+$: 433.1164; found: 433.1171.

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Supplementary data

Supplementary data associated with this article [spectroscopic data for the all reported compounds; X-ray data (CIF files) and additional crystallographic details for compounds **3a**, **3c**, **4a**, **4c**, and (*Z*)-**5c**]. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.04.111.

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