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Ring-chain tautomerism in the products of the reaction between 5-substituted furfurylamines and anhydrides of α,β-unsaturated carboxylic acids

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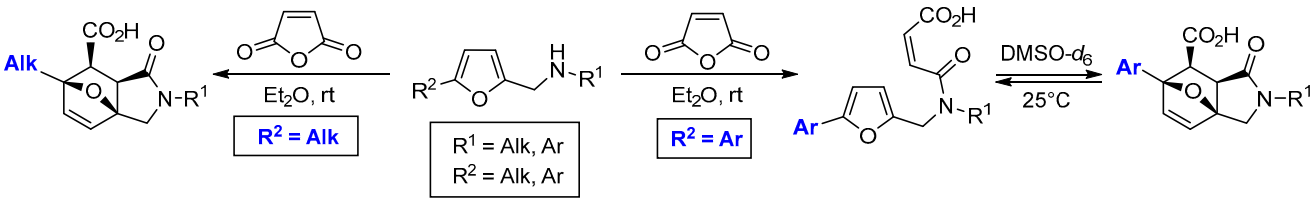


The reactions of 5-substituted furfurylamines with anhydrides of α,β-unsaturated carboxylic acids (acryloyl chloride and maleic anhydride) were studied. The first step of the reaction mechanism involved acylation of furfurylamine nitrogen atom, followed by a stereospecific, spontaneous intramolecular Diels–Alder reaction at the furan ring of the *N*-furfurylamide intermediates. When the starting materials were 5-alkyl-substituted furfurylamines, the expected 1-oxo-2,3,7,7a-hexahydro-1*H*-3a,6-epoxyisoindoles or the corresponding 7-carboxylic acids were obtained in up to 98% yields. The acylation of 5-aryl-substituted furfurylamines with maleic anhydride led to *N*-furfurylmaleic amides, which formed a dynamic equilibrium in solutions with adducts formed by intramolecular [4+2] cycloaddition, 3a,6-epoxyisoindole-7-carboxylic acids, as proved by NMR spectroscopy. X-ray structural analysis results show that these mixtures crystallized in the form of the cyclic tautomer.

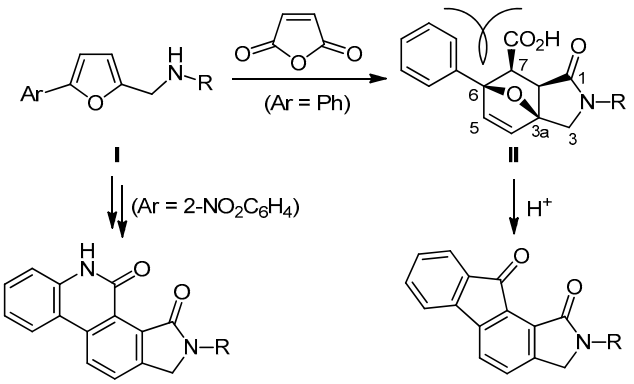
Keywords: furan, isoindole, [4+2] cycloaddition, dynamic stereochemistry, intramolecular Diels–Alder reaction, ring-chain tautomerism.

The tandem acylation/intramolecular [4+2] cycloaddition reaction between anhydrides of α,β-unsaturated carboxylic acids and furfurylamines, known as IMDAF (the IntraMolecular Diels–Alder Reaction of Furan), was thoroughly studied,[1] and recently reviewed.[2] This reaction has become a classic method for the construction of 3a,6-epoxyisoindoles, isoindoles, and their analogs fused with other heterocycles.[3] The patterns of cycloaddition were studied mainly with furfurylamines lacking substituents in the furan ring or in fewer cases with furfurylamines substituted in the furan ring,[3a,4] but 5-arylfurfurylamines have practically never been used in this reaction.[5]

Thus, the main purpose of this work was to study the sequence of acylation/intramolecular cycloaddition reactions between anhydrides of α,β-unsaturated carboxylic acids and 5-arylfurfurylamines **I** (Scheme 1). The most commonly available anhydrides, maleic anhydride and acryloyl chloride were used as model compounds. The aryl substituent at position 6 of 3a,6-epoxyisoindolo-7-carboxylic acids **II** was planned for use in a subsequent modification of the heterocyclic skeleton.

The nearly complete lack of reports about the possibility of obtaining isoindoles of type **II** bearing aryl substituents at position 6 by using IMDAF reactions may,

Scheme 1



in our opinion, be linked to the loss of conjugation between the aryl substituent and the furan ring in the transition state of intramolecular Diels–Alder reaction, thus increasing its energy and creating obstacles to the intramolecular [4+2] cycloaddition.

Initially we performed synthesis of the 5-aryl- and 5-alkylfurfurylamines **1a**–**k** with aryl substituents and substituents of various steric bulk at the nitrogen atom (Scheme 2) and then studied their interaction with maleic anhydride and acryloyl chloride. The 5-phenylfurfuryl-amines **1a**–**g**, 5-ethyl- and 5-propylfurfurylamines (**1h**,**i**) were obtained by the standard procedure from 5-phenyl- or 5-alkylfurancarbaldehydes and the appropriate primary amines without isolation of the azomethine intermediates. The 5-aryl-substituted furans **1j**,**k** were synthesized from the respective 5-bromo derivatives *via* a Suzuki–Miyaura reaction[6] (Scheme 2, Table 1).

The reaction sequence of one-pot acylation and [4+2] cycloaddition of 5-alkyl- and 5-aryl-substituted furfuryl-amines **1b**,**c**,**e**,**f**,**h**,**i** was performed in refluxing benzene by using acryloyl chloride in the presence of triethylamine (Scheme 3). As a result, 3a,6-epoxyisoindolones **2a**–**f** were isolated in moderate yields (Table 2). The lowest yield of the target adduct **2f** (28%) was obtained from acylation of the sterically hindered *tert*-butyl[(5-phenylfuran-2-yl) methyl]amine (**1f**).

The analogous reaction of 5-aryl-*N*-phenylfurfuryl-amines **1a**,**j**,**k** (R^1 = Ar, R^2 = Ph) ended with the formation of *N*-furfurylacrylamides **3a**–**c** (Scheme 3). The attempts to achieve thermal cyclization of amide **3a** ($R^1 = R^2$ = Ph) did not result in isolation of the target 3a,6-epoxyisoindolone **2**. Thus, increasing the reaction temperature to 140°C (refluxing in *o*-xylene, 8 h) or using microwave irradiation (benzene, 200°C, 9 bar, 30 min) led to partial resinification of the reaction mixtures, from which only the starting amide **3a** could be chromatographically isolated in a low yield. It should be noted that the presence of cyclic form in trace amounts along with the starting material **3a** and intractable products was revealed by ^{1}H NMR analysis of the reaction mixture obtained after refluxing in *o*-xylene. A system of coupled 7-CH_2 and 7a-CH protons characteristic for 3a,6-epoxyisoindole system was observed in the upfield region at δ 2.16 ppm (1H, dd, J = 9.0, 11.8 Hz), 2.45 ppm (1H, dd, J = 3.3, 11.8 Hz), and 2.89 ppm (1H, dd, J = 3.3, J = 9.0 Hz) ppm.

Scheme 2

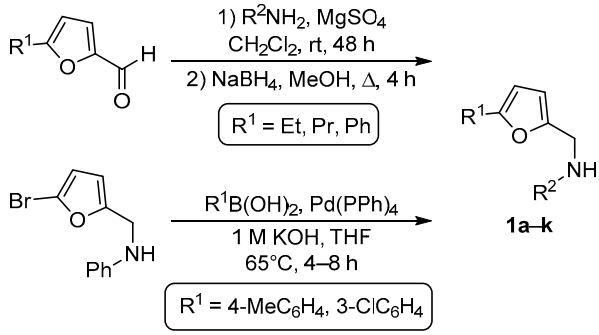


Table 1. Substituents and yields of furfurylamines **1a**–**k**

Com-pound	R^1	R^2	Yield, %
1a	Ph	Ph	80
1b	Ph	Bn	67
1c	Ph	*i*-Pr	42
1d	Ph	Cyclopentyl	58
1e	Ph	$(CH_2)_2OMe$	53
1f	Ph	*t*-Bu	58
1g	Ph	Et	35
1h	Et	*i*-Pr	55
1i	*n*-Pr	Ph	51
1j	4-MeC_6H_4	Ph	50
1k	3-ClC_6H_4	Ph	77

Scheme 3

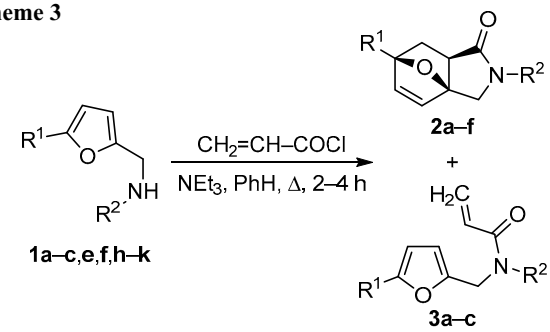


Table 2. Substituents and yields of acylation products **2a**–**f** and **3a**–**c**

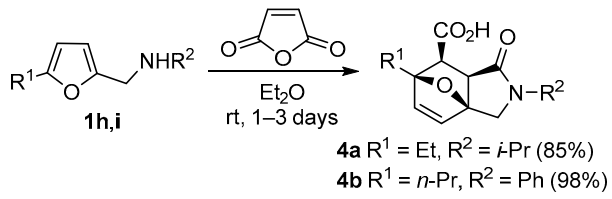
Starting material	R^1	R^2	Product	Yield, %
1h	Et	*i*-Pr	**2a**	45
1i	*n*-Pr	Ph	**2b**	45
1e	Ph	$(CH_2)_2OMe$	**2c**	32
1b	Ph	Bn	**2d**	43
1c	Ph	*i*-Pr	**2e**	47
1f	Ph	*t*-Bu	**2f**	28
1a	Ph	Ph	**3a**	57
1j	4-MeC_6H_4	Ph	**3b**	84
1k	3-ClC_6H_4	Ph	**3c**	67

The decreased reactivity of *N*-arylamides **3a**–**c** compared to their *N*-alkyl-substituted analogs towards intramolecular [4+2] cycloaddition remains unexplained and requires further study. On one hand, it has been previously shown[4a,7] that the reaction between phenylfurfurylamines **1** and acryloyl chloride, metacryloyl chloride, or maleic anhydride proceeds without complications, leading to 3a,6-epoxyisoindolones **2**. In this work we demonstrate that *N*-(5-propylfurfuryl)aniline (**1i**) can be transformed to the isoindole **2b** (Table 2). On the other hand, (5-phenylfurfuryl)alkylamines **1b**,**c**,**e**,**f** also cyclize under relatively mild conditions in the presence of acryloyl chloride (Scheme 3, Table 2), and only the amines **1a**,**j**,**k** bearing aryl substituents both at the nitrogen atom and position 5 of the furan ring give the acyclic amides **3a**–**c**, which practically can not undergo further intramolecular [4+2] cycloaddition.

The thermodynamic parameters of [4+2] cycloaddition reaction calculated by us for the model amides **3a** ($R^1 = R^2 = Ph$) and **3d** ($R^1 = Ph$; $R^2 = Bn$) at the B3LYP/6-311+G(d,p) level of theory did not show substantial differences between these compounds. Equilibrium can be observed for both reactions, and it can be shifted by solvation effects and/or packing in the crystal structure (Scheme 4, Table 3).

The reaction of 5-alkylfurfurylamines **1h**,**i** with maleic anhydride as a more reactive dienophile occurred at room temperature, providing high yields of the expected 3a,6-epoxyisoindole-7-carboxylic acids **4a**,**b** (Scheme 5).

Scheme 5



The reaction of 5-phenylfurfurylamines **1a**–**e**,**g** with maleic anhydride also proceeded easily, and the reaction products crystallized from ether. The precipitates formed at room temperature were identified from ^{1}H NMR data as mixtures of maleic amides **5a**–**f** and epoxyisoindolonecarboxylic acids **6a**–**f** (Scheme 6). The attempts to separate these mixtures by fractional crystallization or column chromatography were not successful. The fraction of cyclic adduct **6** also could not be increased by heating these mixtures in benzene or *o*-xylene. The analysis of ^{1}H NMR spectra showed that the ratio of isomers **5** and **6** remained practically the same after all manipulations. Thus, we concluded that a tautomeric equilibrium **5** ⇄ **6** existed in the solutions of these amides.

Detailed analysis of NMR spectra obtained for the tautomeric mixtures revealed the presence of three sets of all proton and carbon signals in the molecules **5a**–**f** and **6a**–**f**. The reason for this was the existence of the open-chain tautomer **5** in solution phase as a mixture of conformers **5A** and **5B** differing by rotation around the amide bond.

Scheme 4

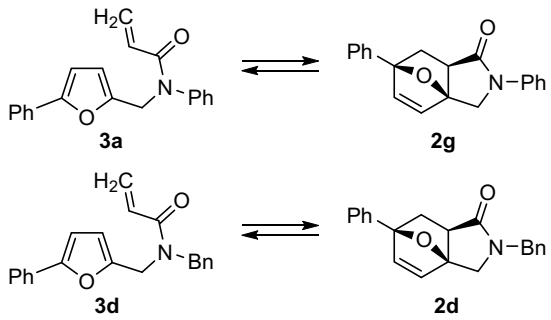


Table 3. The thermodynamic parameters of [4+2] cycloaddition reaction of amides **3a** and **3d** at the B3LYP/6-311+G(d,p) level of theory

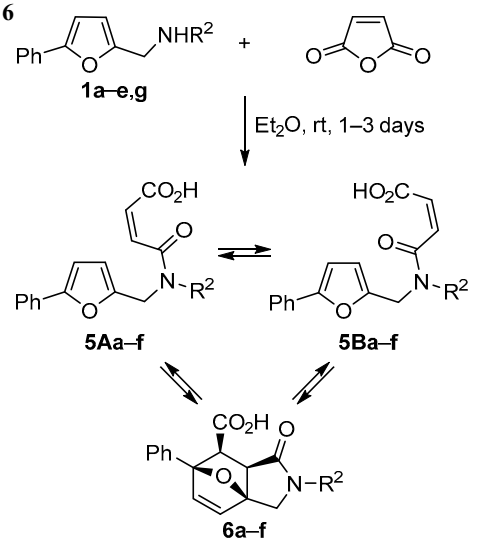
Parameters**	Structures		
	3a	TS (i525 cm^{-1})	**2g**
E_{tot}, a.u.	–977.47095	–977.42477	–977.46518
H^0, a.u.	–977.45028	–977.40596	–977.44697
G^0, a.u.	–977.52408	–977.47212	–977.51210
ΔE_{tot}, kcal/mol		**3.61**	
ΔE_{tot}, kcal/mol		**2.07**	
ΔE_{tot}, kcal/mol		**7.5**	
ΔE_{tot}, kcal/mol		29.00	
ΔE_{tot}, kcal/mol		27.81	
ΔE_{tot}, kcal/mol		32.60	
	3d	TS (i536 cm^{-1})	**2d**
E_{tot}, a.u.	–1016.77142	–1016.72308	–1016.76202
H^0, a.u..	–1016.74962	–1016.70284	–1016.74233
G^0, a.u.	–1016.82616	–1016.77406	–1016.81235
ΔE_{tot}, kcal/mol		**5.90**	
ΔH^0, kcal/mol		**4.58**	
ΔG^0, kcal/mol		**8.66**	
$\Delta E^{\neq}$, kcal/mol		30.33	
$\Delta H^{\neq}$, kcal/mol		29.35	
$\Delta G^{\neq}$, kcal/mol		32.69	

* Geometry optimization and calculations of thermodynamic parameters for isolated molecules was performed with the Gaussian 09 D.01 program package. The results of normal coordinate analysis were used to verify whether the optimized structures correspond to local minima (no imaginary frequencies) or transition states (one imaginary frequency) on the potential energy surface.

** The values of total energy E_{tot}, enthalpy H^0, and Gibbs energy G^0 of compounds **2d**,**g**, **3a**,**d** and the corresponding TS, the total energy ΔE_{tot}, enthalpy ΔH^0, Gibbs energy ΔG^0, activation full energy $\Delta E^{\neq}$, activation enthalpy $\Delta H^{\neq}$, and Gibbs energy of activation $\Delta G^{\neq}$ for reactions according to Scheme 4.

The composition of tautomeric mixtures **5** ⇄ **6** was determined by the integral intensity ratio of ^{1}H NMR signals due to the protons at the double bond of maleic amide moiety (for tautomers **5**) or in the oxabicycloheptene fragments (for tautomers **6**) (Table 4). The presence of atropoisomers **5A** and **5B** and their spatial structure were studied in detail by NOESY NMR experiments by using the isomers **5c** ⇄ **6c** as a reference mixture. The amide bond rotamers **5A**, **5B** were determined by the most characteristic signals of the CH_2 group at the furan ring and the H-2 protons of the maleic amide moiety (Fig. 1, Table 5). The key parameter used for the assignment of atropoisomers to series **A** or **B** was the difference between the chemical shifts of analogous protons, instead of the

Scheme 6



absolute chemical shift value, which varied widely depending on the nature of substituent at the nitrogen atom. For example, the CH_2 proton signals of the furfuryl group in rotamers **5B** were always observed at lower field than the respective signals for rotamers **5A**. This difference was 0.06–0.10 ppm for the amides **5a**,**b**,**e**,**f** and 0.01–0.04 ppm for compounds **5c**,**d**. In the latter two cases the chemical shift differences were small, therefore the rotamers were additionally characterized by the CH protons of isopropyl and cyclopentyl groups.

The data from Table 4 suggests that the position of ring-chain tautomerism in compounds **5** ⇄ **6** substantially depends on the steric bulk of substituent at the nitrogen atom. For example, the sufficiently bulky and sterically similar phenyl (in **5a** ⇄ **6a**), isopropyl (**5c** ⇄ **6c**), and cyclopentyl substituents (**5d** ⇄ **6d**) shifted the equilibrium towards the formation of cyclic form **6**. The fraction of cycloadducts **6a**,**c**,**d** in DMSO solutions was in range of 53–63%. On the other hand, the open-chain form dominated in tautomeric mixtures of compounds **5e** ⇄ **6e** and **5f** ⇄ **6f** containing small *n*-alkyl substituents at the nitrogen atom, while the content of cyclic forms **6e**,**f** was as low as 32–33%. This observation was in a good agreement with the well-known Thorpe–Ingold effect (the enthropy of transition state in intramolecular reactions decreases with a larger number and steric bulk of substituents in the chain).[8]

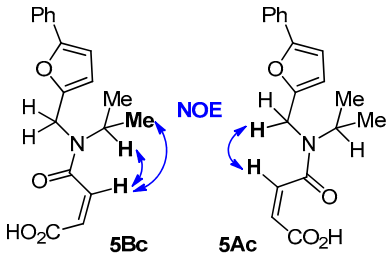


Figure 1. The most significant NOE cross peaks in 2D NOESY NMR spectra of the amide rotamers **5Ac** and **5Bc**.

Table 4. The characteristic chemical shifts in ^{1}H NMR spectra (DMSO-d_6) of rotamers **5A**/**5B** (ppm)

Products	R^2	Ratio**5A/5B/6***	Yield, %
5Aa/5Ba/6a	Ph	4/43/53	52
5Ab/5Bb/6b	Bn	22/37/41	38
5Ac/5Bc/6c	*i*-Pr	10/32/58	47
5Ad/5Bd/6d	Cyclopentyl	13/24/63	46
5Ae/5Be/6e	$(CH_2)_2OMe$	30/37/33	42
5Af/5Bf/6f	Et	32/36/32	71

* The ratio of tautomers in mixtures was determined from ^{1}H NMR spectra in DMSO-d_6 at 23–27°C.

The second conclusion that follows from the data of Table 4 concerns the population of conformers **5A** and **5B**, which also depends on the substituent R^2 at the nitrogen atom. The dominant conformer in solution phase in all cases was **5B**, the spatial structure of which did not favor intramolecular Diels–Alder reaction. The content of rotamer **5A** was especially low in the equilibrium mixture of *N*-phenyl-substituted compounds **5a** ⇄ **6a** (R^2 = Ph, **5Aa**/**5Ba**= 4/43).

The existence of dynamic equilibrium between the tautomers **5** ⇄ **6** was also confirmed by NMR experiments performed at different temperatures. The fraction of cyclic form **6** in tautomeric mixtures gradually decreased upon raising the temperature, which was demonstrated by detailed ^{1}H NMR spectral study of isomers **5c**/**6c** in DMSO-d_6 solutions over the temperature range from 30°C to 110°C (Table 6). The tautomeric equilibrium dynamics for compounds **5Ac**, **5Bc**, and **6c** depending on the temperature are shown in Figure 2.

According to Figure 3 and the data of Table 6, the ratio of open-chain forms **5Ac**/**5Bc** shifted towards higher content of rotamer **5Ac** upon increasing the temperature. When the temperature exceeded 80°C, the rotation of substituents around the amide bond became too fast on NMR timescale, therefore the signals of both rotamers **5Ac** and **5Bc** merged into one, while significant broadening of all ^{1}H NMR signals was observed.

It was proved by additional experiments that the tautomers **5** ⇄ **6** existed exclusively in cyclic form in the

Table 5. The characteristic chemical shifts in ^{1}H NMR spectra (DMSO-d_6) of rotamers **5A**/**5B**, ppm

Rotamers	CH_2Fur	Δδ, ppm	NCHAlk
5Aa/5Ba	4.90/4.98	+0.08	–
5Ab/5Bb	4.48/4.54	+0.06	–
5Ac/5Bc	4.47/4.51	+0.04	4.56/4.17
5Ad/5Bd	4.49/4.50	+0.01	4.52/4.15
5Ae/5Be	4.58/4.67	+0.09	–
5Af/5Bf	4.47/4.57	+0.10	–

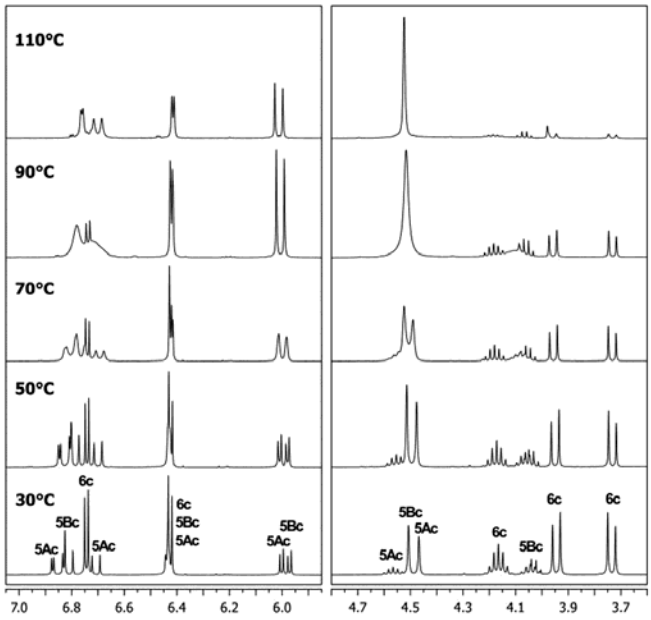


Figure 2. Fragments of ^{1}H NMR spectra for tautomeric mixtures of compounds **5Ac**, **5Bc**, **6c** at different temperatures (solutions in DMSO-d_6).

crystalline state. For example, recrystallization of compounds **5c** ⇄ **6c** from a mixture of solvents EtOAc/EtOH completely shifted the tautomeric equilibrium towards the cyclic form – the mixture crystallized as isoindolonecarboxylic acid **6c**, the molecular structure of which was established by X-ray structural analysis (Fig. 3).

Compound **6c** crystallized in triclinic space group $P\bar{1}$ with the unit cell containing two crystallographically independent molecules of similar geometry. All the five-membered rings in the molecule (pyrrolidone, 2,5-dihydrofuran, and tetrahydrofuran) assumed the regular envelope conformation. The N(2) nitrogen atom had a slightly pyramidalized configuration (the sum of valence angles for the two crystallographically independent molecules was equal to 358.5(4) and 358.9(4)°). The dihedral angle between the planes of substituent and 3a,6-epoxy bridge was 12.50(15) and 16.55(16)°, respectively.

Crystals of compound **6c** were racemic and consisted of enantiomeric pairs of molecules with the relative configuration of *rac*-3A*RS*,6*SR*,7*RS*,7A*SR* at the indicated centers. Molecules of compound **6c** formed a crystal structure featuring centrosymmetric dimers linked by two intermolecular O–H···O hydrogen bonds (Table 7). The crystal packing of dimers was stacked along the direction *a*.

We should note that incomplete intramolecular [4+2] cycloaddition has been reported previously[9] more than once, and the Diels–Alder reaction in alkenylfurfurylamines has been found to be reversible[4b,10] during analogous transformations. However, to the best of our knowledge, there has been no definite proof of interconversion between both tautomeric forms in either solution or solid phase.

Table 6. Tautomeric mixture compositions for products **5Ac**, **5Bc**, **6c** at different temperatures

Temperatura, °C	Ratio **5Ac/5Bc/6c***
30	15/20/65
50	28/27/45
70	35/34/31
90	82/18**
110	88/12**

* The tautomeric ratio in mixtures was measured by ^{1}H NMR spectra of DMSO-d_6 solutions.
** The signals of rotamers **5Ac** and **5Bc** were averaged due to the accelerated rotation of substituents relative to amide bond at higher temperatures.

In conclusion, the interaction of acryloyl chloride and maleic anhydride with 5-arylfurfurylamines was described for the first time. The reaction does not stop at the acylation stage and followed by spontaneous intramolecular Diels–Alder reaction leading to the formation of a 1-oxo-2,3,7,7a-hexahydro-1*H*-3a,6-epoxyisoindole system. The results of dynamic NMR experiments showed that ring-chain tautomerism of the products of the reaction of 5-arylfurfurylamines with maleic anhydride takes place in solution. According to X-ray structural analysis results, these products in crystals exist exclusively as the cyclic 3a,6-epoxyisoindole form.

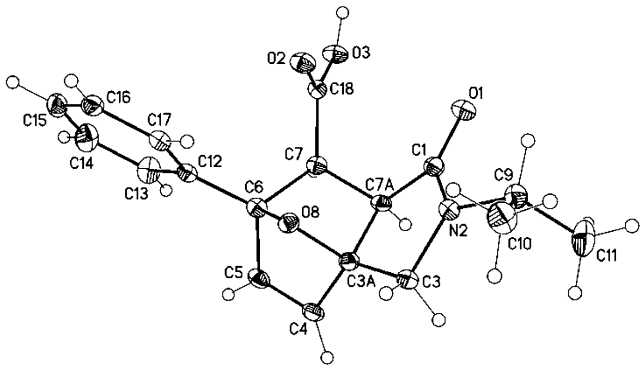


Figure 3. The molecular structure of compound **6c** (one of the two crystallographically independent molecules is shown). The atoms are represented by thermal vibration ellipsoids of 50% probability.

Table 7. The hydrogen bond parameters in compound **6c**

D–H···A*	Symmetry operation**	*d*(D–H), Å	*d*(H···A), Å	*d*(D···A), Å	Angle (D–H···A), deg
O(3)–H(3)···O(1)	(–*x*+1, –*y*+1, –*z*)	0.88(2)	1.83(2)	2.6932(2)	170.6(2)
O(3B)–H(3B)···O(1B)	(–*x*+1, –*y*+2, –*z*+2)	0.89(2)	1.73(2)	2.6177(2)	174.7(2)

* D – proton donor; A – proton acceptor.
** For the generation of equivalent atoms.

Experimental

IR spectra were recorded on an Infralum FT-801 FT-IR spectrometer in KBr pellets. ^{1}H NMR spectra were acquired on Bruker AMX-400 (400 MHz) or JEOL JNM-ECA600 (600 MHz) instruments, the internal standard for ^{1}H NMR spectra was TMS. ^{13}C NMR spectra were acquired on Bruker Avance 600 (150 MHz) or Bruker AMX-400 (100 MHz) instruments, the central signals of $CDCl_3$ triplet (77.4 ppm) or DMSO-d_6 multiplet (40.0 ppm) were used as internal standards. Mixing time for NOESY NMR experiment was 800 ms. Mass spectra were recorded on a Thermo Trace DSQ mass spectrometer (EI ionization at 70 eV, source temperature 200°C, direct introduction of sample) or a Thermo DSQ II – Focus GC GC-MS system (EI ionization at 70 eV, source temperature 200°C, carrier gas – helium, Rtx-5MS column). Chromato-mass spectra were recorded on a system including a liquid chromatograph Agilent 1100 Series, a mass spectrometer Agilent Technologies LC/MSDVL (electrospray ionization (ESI)), a detector Sedex 75 ELSD. Elemental analysis was performed on a EuroVectorEA 3000 CHNS-analyzer. Melting points of the synthesized compounds were determined on SMP 10 and SMP 30 instruments and were not corrected. TLC analysis was performed on Sorbfil PTSH-AF-A-UF-254 plates, visualization with iodine vapor or $KMnO_4$ solution. The ratio of products in isomeric mixtures was determined by ^{1}H NMR spectra as the integral ratio for the signals of analogous protons. Reagents were purchased from Acros Organics and Alfa Aesar and were used without additional purification, while solvents were distilled before use.

Synthesis of [(5-aryl- or 5-alkylfuran-2-yl)methyl]-amines 1a–i (General method). Anhydrous $MgSO_4$ powder (18 g, 0.15 mol) and the appropriate amine (0.05 mol) were added to a solution of 5-substituted furfurol (8.6 g, 0.05 mol) in CH_2Cl_2 (100 ml). The reaction mixture was stirred for 48 h at room temperature (control by TLC), the drying agent was removed by filtration, and the solvent was distilled off at reduced pressure. The residue was dissolved in methanol (50 ml), cooled in ice bath, and treated with sodium borohydride (1.90 g, 0.05 mol). The reaction mixture was refluxed for 4 h (control by TLC), poured into water (250 ml), and extracted with CH_2Cl_2 (3×70 ml). The organic extract was dried over anhydrous Na_2SO_4, the drying agent was removed by filtration, the solvent was distilled off at reduced pressure, and the residue was dissolved in acetone (5 ml). The obtained solution was treated with oxalic acid (4.5 g, 0.05 mol) in acetone (10 ml), the obtained oxalate was filtered off, washed with ether, decomposed with ammonia, and the product was extracted with ether (3×70 ml). The ethereal extract was dried over anhydrous Na_2SO_4, the drying agent was removed by filtration, and the solvent was distilled off at reduced pressure.

***N*-[(5-Phenylfuran-2-yl)methyl]aniline (1a)**. Yield 9.96 g (80%), viscous yellow oil. IR spectrum, ν, cm^{-1}: 3400 (N–H). ^{1}H NMR spectrum (600 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 4.35 (2H, s, NCH_2); 6.28 (1H, d, *J* = 3.4) and 6.56 (1H, d, *J* = 3.4, H-3,4 Fur); 6.69 (2H, d, *J* = 7.6, H-2,6 Ph); 6.74 (1H, tt, *J* = 7.6, *J* = 2.1, H-4 Ph); 7.19 (2H, t, *J* = 7.6, H-3,5 Ph); 7.23 (1H, t, *J* = 8.3, H-4 Ph); 7.35 (2H, dd, *J* = 8.3, *J* = 7.6, H-3,5 Ph); 7.63 (2H, d, *J* = 7.6, H-2,6 Ph). ^{13}C NMR spectrum (150 MHz, $CDCl_3$), δ, ppm: 41.8 (NCH_2); 105.9, 109.3 (C-3,4 Fur); 113.3, 118.2, 123.7, 127.4, 128.8, 129.4, 130.9, 147.7 (C Ph); 152.5, 153.5 (C-2,5 Fur). Mass spectrum (EI, 70 eV), *m*/*z* (I_{rel}, %): 249 [M]$^+$ (9), 157 (100), 128 (20), 115 (3), 77 (14), 65 (5), 51 (7), 39 (4). Found, %: C 81.78; H 6.12; N 5.74. $C_{17}H_{15}NO$. Calculated, %: C 81.90; H 6.06; N 5.62.

1-Phenyl-*N*-[(5-phenylfuran-2-yl)methyl]methan-amine (1b). Yield 8.81 g (67%), viscous yellow oil. IR spectrum, ν, cm^{-1}: 3318 (N–H). ^{1}H NMR spectrum (600 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 3.80 (4H, s, CH_2NHCH_2); 6.22 (1H, d, *J* = 3.4) and 6.54 (1H, d, *J* = 3.4, H-3,4 Fur); 7.18–7.33 (8H, m, H Ar); 7.61 (2H, d, *J* = 7.6, H-2,6 Ph). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ, ppm: 45.6 (NCH_2); 52.8 (NCH_2); 105.8, 109.5 (C-3,4 Fur); 123.8, 127.3 (2C), 128.5, 128.6, 128.8, 131.1, 139.9 (C Ar); 153.4, 153.6 (C-2,5 Fur). Mass spectrum (EI, 70 eV), *m*/*z* (I_{rel}, %): 263 [M]$^+$ (2), 172 (6), 157 (28), 128 (26), 115 (21), 104 (16), 91 (100), 77 (25), 65 (14), 51 (14), 39 (5). Found, %: C 82.18; H 6.57; N 5.22. $C_{18}H_{17}NO$. Calculated, %: C 82.10; H 6.51; N 5.32.

***N*-[(5-Phenylfuran-2-yl)methyl]propan-2-amine (1c)**. Yield 4.52 g (42%), viscous yellow oil. IR spectrum, ν, cm^{-1}: 2964 (N–H). ^{1}H NMR spectrum (600 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.13 (6H, d, *J* = 6.2, CH_3); 2.91 (1H, heptet, *J* = 6.2, NCH); 3.87 (2H, s, NCH_2); 6.28 (1H, d, *J* = 2.7) and 6.57 (1H, d, *J* = 2.7, H-3,4 Fur); 7.23 (1H, t, *J* = 7.8, H-4 Ph); 7.36 (2H, t, *J* = 7.8, H-3,5 Ph); 7.65 (2H, d, *J* = 7.8, H-2,6 Ph). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ, ppm: 22.8 ($2CH_3$); 44.0 (CH); 47.6 (CH_2); 105.7, 109.0 (C-3,4 Fur); 123.7, 127.2, 128.7, 131.1 (C Ph); 153.2, 154.0 (C-2,5 Fur). Mass spectrum (EI, 70 eV), *m*/*z* (I_{rel}, %): 215 [M]$^+$ (10), 172 (4), 157 (100), 128 (17), 110 (11), 100 (4), 77 (10), 71 (26), 51 (7), 43 (10). Found, %: C 78.15; H 7.91; N 6.59. $C_{14}H_{17}NO$. Calculated, %: C 78.10; H 7.96; N 6.51.

***N*-[(5-Phenylfuran-2-yl)methyl]cyclopentanamine (1d)**. Yield 7.01 g (58%), viscous yellow oil. IR spectrum, ν, cm^{-1}: 2952 (N–H). ^{1}H NMR spectrum (600 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.31–1.84 (8H, m, CH_2); 3.11 (1H, q, *J* = 6.9, NCH); 3.79 (2H, s, NCH_2); 6.21 (1H, d, *J* = 2.8) and 6.53 (1H, d, *J* = 2.8, H-3,4 Fur); 7.19 (1H, t, *J* = 7.6, H-4 Ph); 7.32 (2H, dd, *J* = 8.3, *J* = 7.6, H-3,5 Ph); 7.61 (2H, d, *J* = 8.3, H-2,6 Ph). ^{13}C NMR spectrum (150 MHz, $CDCl_3$), δ, ppm: 24.2, 33.2 ($4CH_2$); 45.2 (NCH); 58.8 (NCH_2); 105.7, 108.9 (C-3,4 Fur); 123.7, 127.1, 128.7, 131.1 (C Ph); 153.1, 154.2 (C-2,5 Fur). Mass spectrum (EI, 70 eV), *m*/*z* (I_{rel}, %): 241 [M]$^+$ (14), 172 (3), 157 (100), 136 (8), 128 (23), 115 (6), 97 (13), 77 (10), 51 (6), 41 (9). Found, %: C 79.52; H 8.04; N 5.69. $C_{16}H_{19}NO$. Calculated, %: C 79.63; H 7.94; N 5.80.

(2-Methoxyethyl)[(5-phenylfuran-2-yl)methyl]amine (1e). Yield 6.09 g (53%), viscous yellow oil. IR spectrum, ν, cm^{-1}: 3329 (N–H). ^{1}H NMR spectrum (600 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.88 (1H, br. s, NH); 2.85 (2H, t,

J = 5.3, NCH_2); 3.34 (3H, s, CH_3); 3.51 (2H, t, J = 5.3, OCH_2); 3.86 (2H, s, NCH_2); 6.26 (1H, d, J = 3.4) and 6.56 (1H, d, J = 3.4, H-3,4 Fur); 7.23 (1H, t, J = 7.6, H-4 Ph); 7.35 (2H, t, J = 7.6, H-3,5 Ph); 7.65 (2H, d, J = 7.6, H-2,6 Ph). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ, ppm: 46.4 (NCH_2); 48.5 (NCH_2); 58.7 (OCH_3); 72.0 (OCH_2); 105.7, 109.4 (C-3,4 Fur); 123.6, 127.1, 128.7, 131.1 (C Ph); 153.1, 153.8 (C-2,5 Fur). Mass spectrum (EI, 70 eV), *m*/*z* (I_{rel}, %): 231 $[M]^+$ (6), 172 (14), 157 (100), 128 (24), 115 (6), 105 (5), 77 (9), 51 (6), 45 (17). Found, %: C 72.61; H 7.35; N 6.16. $C_{14}H_{17}NO_2$. Calculated, %: C 72.70; H 7.41; N 6.06.

***t*-Butyl[(5-phenylfuran-2-yl)methyl]amine (1f)**. Yield 6.62 g (58%), viscous yellow oil. IR spectrum, ν, cm^{-1}: 3302 (N–H). ^{1}H NMR spectrum (600 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.18 (9H, s, $C(CH_3)_3$); 3.81 (2H, s, NCH_2); 6.26 (1H, d, J = 3.4) and 6.56 (1H, d, J = 3.4, H-3,4 Fur); 7.22 (1H, t, J = 7.6, H-4 Ph); 7.35 (2H, t, J = 7.6, H-3,5 Ph); 7.64 (2H, dd, J = 7.6, J = 1.4, H-2,6 Ph). ^{13}C NMR spectrum (150 MHz, $CDCl_3$), δ, ppm: 29.0 (2C), 29.1 ($3CH_3$); 40.3 (NC); 50.8 (NCH_2); 105.9, 108.4 (C-3,4 Fur); 123.6, 127.1, 128.6, 131.1 (C Ph); 153.1, 154.5 (C-2,5 Fur). Mass spectrum (EI, 70 eV), *m*/*z* (I_{rel}, %): 229 $[M]^+$ (14), 214 (6), 157 (100), 128 (13), 115 (4), 77 (6), 51 (3), 41 (4). Found, %: C 78.44; H 8.31; N 6.23. $C_{15}H_{19}NO$. Calculated, %: C 78.56; H 8.35; N 6.11.

***N*-[(5-Phenylfuran-2-yl)methyl]ethanamine (1g)**. Yield 3.53 g (35%), viscous yellow oil. IR spectrum, ν, cm^{-1}: 3317 (N–H). ^{1}H NMR spectrum (600 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.11 (3H, t, J = 6.9, CH_3); 2.68 (2H, q, J = 6.9, NCH_2); 3.80 (2H, s, NCH_2); 6.23 (1H, d, J = 3.4) and 6.55 (1H, d, J = 3.4, H-3,4 Fur); 7.20 (1H, t, J = 7.6, H-4 Ph); 7.33 (2H, dd, J = 8.3, J = 7.6, H-3,5 Ph); 7.63 (2H, dd, J = 8.3, J = 1.4, H-2,6 Ph). ^{13}C NMR spectrum (150 MHz, $CDCl_3$), δ, ppm: 15.2 (CH_3); 43.4 (NCH_2); 46.2 (NCH_2); 105.7, 109.1 (C-3,4 Fur); 123.7, 127.2, 128.7, 131.0 (C Ph); 153.3, 153.8 (C-2,5 Fur). Mass spectrum (EI, 70 eV), *m*/*z* (I_{rel}, %): 201 $[M]^+$ (37), 184 (21), 157 (100), 128 (27), 105 (14), 96 (32), 77 (20), 57 (19), 51 (14), 39 (6). Found, %: C 77.67; H 7.59; N 6.87. $C_{13}H_{15}NO$. Calculated, %: C 77.58; H 7.51; N 6.96.

***N*-[(5-Ethylfuran-2-yl)methyl]propan-2-amine (1h)**. Yield 4.61 g (55%), yellow oil. IR spectrum, ν, cm^{-1}: 3312 (N–H). ^{1}H NMR spectrum (600 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.08 (6H, d, J = 6.2, $2CH_3$); 1.21 (3H, t, J = 7.6, CH_3); 2.61 (2H, q, J = 7.6, CH_2); 2.83 (1H, heptet, J = 6.2, NCH); 3.73 (2H, s, NCH_2); 5.88 (1H, d, J = 3.4) and 6.04 (1H, d, J = 3.4, H-3,4 Fur). ^{13}C NMR spectrum (150 MHz, $CDCl_3$), δ, ppm: 12.2 (CH_3); 21.4 (CH_2); 22.8 ($2CH_3$); 44.1 (NCH); 47.7 (NCH_2); 104.3, 107.1, 152.3, 157.1 (C Fur). Mass spectrum (EI, 70 eV), *m*/*z* (I_{rel}, %): 167 $[M]^+$ (17), 152 (6), 109 (100), 96 (13), 71 (6), 43 (24). Found, %: C 71.72; H 10.21; N 8.52. $C_{10}H_{17}NO$. Calculated, %: C 71.81; H 10.25; N 8.37.

***N*-((5-Propylfuran-2-yl)methyl)aniline (1i)**. Yield 5.44 g (51%), viscous yellow oil. IR spectrum, ν, cm^{-1}: 3413 (N–H). ^{1}H NMR spectrum (600 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 0.97 (3H, t, J = 7.5, CH_3); 1.67 (2H, sextet, J = 7.5, CH_2); 2.58 (2H, t, J = 7.5, CH_2); 3.97 (1H, br. s, NH); 4.26 (2H, s, NCH_2); 5.91 (1H, d, J = 2.9) and 6.13 (1H, d, J = 2.9, H-3,4 Fur); 6.68 (2H, dd, J = 8.4, J = 1.1, H-2,6 Ph); 6.75 (1H, t, J = 7.3, H-4 Ph); 7.19 (2H, dd, J = 8.4, J = 7.3, H-3,5 Ph). ^{13}C NMR spectrum (150 MHz, $CDCl_3$), δ, ppm: 13.9 (CH_3); 21.4 (CH_2); 30.2 (CH_2); 41.7 (NCH_2); 105.5, 107.7 (C Fur); 113.3, 118.0, 129.3, 147.9 (C Ph); 150.7, 156.1 (C-2,5 Fur). Mass spectrum (EI, 70 eV), *m*/*z* (I_{rel}, %): 215 $[M]^+$ (15), 123 (100), 94 (7), 81 (11), 77 (10), 65 (6), 57 (7), 51 (6), 39 (5). Found, %: C 78.00; H 8.11; N 6.39. $C_{14}H_{17}NO$. Calculated, %: C 78.10; H 7.96; N 6.51.

Preparation of *N*-[(5-arylfuran-2-yl)methyl]anilines 1j,k (General method). The appropriate arylboronic acid (12.8 mmol) and $Pd(PPh)_4$ (0.37 g, 0.32 mmol) were added to a solution of *N*-(5-bromofurfuryl)aniline[13] (1.6 g, 6.4 mmol) in a 1:1 mixture of THF (20 ml) and 1 M KOH aqueuos solution. The reaction mixture was stirred under argon atmosphere for 4–8 h at 65°C (control by TLC, eluent hexane– AcOEt, 4:1), poured into water (100 ml), extracted with EtOAc (3×30 ml). The organic fractions were combined and dried over anhydrous $MgSO_4$. The solvent was removed by distillation and the product was purified by chromatography on a 1.8×28 cm silica gel column, eluent heptane).

***N*-[(5-(4-Methylphenyl)furan-2-yl]methyl)aniline (1j)**. Yield 0.85 g (50%), light-yellow powder. IR spectrum, ν, cm^{-1}: 3420 (N–H). ^{1}H NMR spectrum (600 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 2.36 (3H, s, CH_3); 4.37 (2H, s, NCH_2); 6.29 (1H, d, J = 3.3) and 6.51 (1H, d, J = 3.3, H-3,4 Fur); 6.71 (2H, d, J = 7.4, H-2,6 Ph); 6.75 (1H, t, J = 7.4, H-4 Ph); 7.17–7.22 (4H, m, HAr); 7.54 (2H, d, J = 8.2, H-2,6 Ar). ^{13}C NMR spectrum (150 MHz, $CDCl_3$), δ, ppm: 21.2 (CH_3); 41.6 (NCH_2); 104.9, 109.1 (C-3,4 Fur); 113.1 118.0, 123.6, 128.1, 129.2, 129.3, 137.1, 147.6 (C Ar); 151.9, 153.6 (C-2,5 Fur). Mass spectrum (EI, 70 eV), *m*/*z* (I_{rel}, %): 263 $[M]^+$ (4), 171 (100), 141 (5), 128 (23), 115 (5), 91 (4), 77 (4), 65 (4). Found, %: C 81.98; H 6.47; N 5.54. $C_{18}H_{17}NO$. Calculated, %: C 82.10; H 6.51; N 5.32.

***N*-{[5-(3-Chlorophenyl)furan-2-yl]methyl}aniline (1k)**. Yield 1.40 g (77%), viscous yellow oil. IR spectrum, ν, cm^{-1}: 3408 (N–H). ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 4.40 (2H, s, NCH_2); 6.33 (1H, d, J = 3.4) and 6.62 (1H, d, J = 3.4, H-3,4 Fur); 6.74 (2H, d, J = 7.5, H-2,6 Ph); 6.82 (1H, t, J = 7.5, H-4 Ph); 7.24–7.33 (4H, m, HAr); 7.53 (1H, dt, J = 8.1, J = 1.9, H-4 Ar); 7.67 (1H, t, J = 1.9, H-2 Ar). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ, ppm: 41.6 (NCH_2); 106.9, 109.3 (C-3,4 Fur); 113.3, 118.2, 121.7, 123.6, 127.2, 129.3, 130.0, 132.5, 134.7, 147.5 (C Ar); 151.9, 153.2 (C-2,5 Fur). Mass spectrum (EI, 70 eV), *m*/*z* (I_{rel}, %): 283 $[M]^+$ (10), 191 (100), 128 (42), 111 (11), 92 (9), 77 (29), 65 (27), 51 (25), 39 (17). Found, %: C 72.16; H 5.09; N 4.78. $C_{17}H_{14}ClNO$. Calculated, %: C 71.96; H 4.97; N 4.94.

Preparation of 3a,6-epoxyisoindol-1-ones 2a–f and *N*-[(5-arylfuran-2-yl)methyl]-*N*-phenylacrylamides 3a–c (General method). A solution of the appropriate furfurylamine **1a**–**c**,**e**,**f**,**h**–**k** (5 mmol), acryloyl chloride (0.45 ml, 5.5 mmol), and triethylamine (1.39 ml, 10 mmol) in benzene (50 ml) was refluxed for 2–4 h (control by TLC), cooled, and poured into water (100 ml). The organic layer

was separated, while the aqueous layer was extracted with EtOAc (3×30 ml). The organic fractions were combined and dried over anhydrous $MgSO_4$. The extract was evaporated and the residue was recrystallized from a suitable solvent (products **2b**–**f**, **3a**,**b**) or purified by chromatography (products **2a** and **3c**, 1.8×28 cm silica gel column, elution with a gradient from hexane to 10:1 hexane–EtOAc), giving the respective epoxyisoindolones **2a**–**f** or *N*-furfuryl-*N*-phenylacrylamides **3a**–**c**.

(3a*RS*,6*RS*,7a*SR*)-6-Ethyl-2-isopropyl-2,3,7,7a-tetrahydro-1*H*-3a,6-epoxyisoindol-1-one (2a). Yield 0.50 g (45%), orange oil. IR spectrum, ν, cm^{-1}: 1680 (NCO). ^1H NMR spectrum (600 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.05 (3H, t, *J* = 7.6, CH_3); 1.14 (3H, d, *J* = 6.9, CH_3); 1.18 (3H, d, *J* = 6.9, CH_3); 1.61 (1H, dd, *J* = 11.7, *J* = 8.9) and 1.91 (1H, dd, *J* = 11.7, *J* = 4.1, 7-CH_2); 1.95 (2H, q, *J* = 7.6, CH_2); 2.52 (1H, dd, *J* = 8.9, *J* = 4.1, 7a-CH); 3.65 (1H, d, *J* = 11.0) and 3.79 (1H, d, *J* = 11.0, 3-CH_2); 4.41 (1H, heptet, *J* = 6.9, NCH); 6.29 (1H, d, *J* = 5.5) and 6.42 (1H, d, *J* = 5.5, 4,5-CH). ^{13}C NMR spectrum (150 MHz, $CDCl_3$), δ, ppm: 9.3 (CH_3); 19.6, 20.1 ($2CH_3$); 25.8 (CH_2); 32.1 (C-7); 42.5, 44.4, 51.0 (C-3,7a, NCH); 88.5 (C-6); 91.3 (C-3a); 134.0, 139.0 (C-4,5); 173.5 (C-1). Mass spectrum (EI, 70 eV), *m*/*z* (I_{rel}, %): 221 $[M]^+$ (30), 178 (25), 164 (11), 124 (100), 109 (45), 94 (10), 77 (11), 55 (55), 43 (32). Found, %: C 70.54; H 8.60; N 6.42. $C_{13}H_{19}NO_2$. Calculated, %: C 70.56; H 8.65; N 6.33.

(3a*RS*,6*RS*,7a*SR*)-2-Phenyl-6-propyl-2,3,7,7a-tetrahydro-1*H*-3a,6-epoxyisoindol-1-one (2b). Yield 0.60 g (45%), light-yellow powder, mp 92–93°C (pentane). IR spectrum, ν, cm^{-1}: 1699 (NCO). ^1H NMR spectrum (600 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 0.98 (3H, t, *J* = 7.4, CH_3); 1.45–1.56 (2H, m, CH_2); 1.72 (1H, dd, *J* = 11.6, *J* = 8.3) and 2.06 (1H, dd, *J* = 11.6, *J* = 3.3, 7-CH_2); 1.91–1.94 (2H, m, CH_2); 2.72 (1H, dd, *J* = 8.3, *J* = 3.3, 7a-CH); 4.13 (1H, d, *J* = 11.6) and 4.39 (1H, d, *J* = 11.6, 3-CH_2); 6.33 (1H, d, *J* = 5.8) and 6.47 (1H, d, *J* = 5.8, 4,5-CH); 7.14 (1H, t, *J* = 7.4, H-4 Ph); 7.38 (2H, t, *J* = 7.4, H-3,5 Ph); 7.63 (2H, d, *J* = 7.4, H-2,6 Ph). ^{13}C NMR spectrum (150 MHz, $CDCl_3$), δ, ppm: 14.7 (CH_3); 18.6 (CH_2); 33.6, 35.2 (CH_2, C-7); 51.2, 51.6 (C-3,7a); 87.6, 91.1 (C-3a,6); 120.2, 124.7, 128.9, 133.6, 139.6, 139.7 (C Ph, C-4,5); 173.8 (C-1). Mass spectrum (EI, 70 eV), *m*/*z* (I_{rel}, %): 269 $[M]^+$ (6), 123 (100), 94 (4), 81 (6), 77 (5), 55 (7). Found, %: C 75.93; H 6.99; N 5.31. $C_{17}H_{19}NO_2$. Calculated, %: C 75.81; H 7.11; N 5.20.

(3a*RS*,6*RS*,7a*SR*)-2-(2-Methoxyethyl)-6-phenyl-2,3,7,7a-tetrahydro-1*H*-3a,6-epoxyisoindol-1-one (2c). Yield 0.46 g (32%), colorless needles, mp 79–80°C (petroleum ether–ether). IR spectrum, ν, cm^{-1}: 1678 (NCO). ^1H NMR spectrum (600 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 2.03 (1H, dd, *J* = 11.7, *J* = 8.9) and 2.31 (1H, dd, *J* = 11.7, *J* = 3.4, 7-CH_2); 2.67 (1H, dd, *J* = 8.9, *J* = 3.4, 7a-CH); 3.36 (3H, s, CH_3); 3.27–3.31 (1H, m), 3.51–3.57 (2H, m), and 3.77–3.82 (1H, m, OCH_2, NCH_2); 3.85 (1H, d, *J* = 12.4) and 4.17 (1H, d, *J* = 12.4, 3-CH_2); 6.48 (1H, d, *J* = 5.5) and 6.55 (1H, d, *J* = 5.5, 4,5-CH); 7.33 (1H, t, *J* = 7.6, H-4 Ph); 7.39 (2H, t, *J* = 7.6, H-3,5 Ph); 7.47 (2H, d, *J* = 7.6, H-2,6 Ph). ^{13}C NMR spectrum (150 MHz, $CDCl_3$), δ, ppm: 34.0 (C-7); 43.0, 50.6, 51.4, 58.8, 71.2 (C-3,7a, OCH_2, NCH_2, CH_3); 90.9, 89.6 (C-3a,6); 125.9, 128.2, 128.6, 133.9, 138.5, 140.0 (C Ph, C-4,5); 174.0 (C-1). Mass spectrum (EI, 70 eV), *m*/*z* (I_{rel}, %): 285 $[M]^+$ (20), 230 (57), 210 (29), 172 (23), 157 (100), 128 (37), 105 (13), 77 (17), 55 (44), 45 (16). Found, %: C 71.44; H 6.82; N 4.83. $C_{17}H_{19}NO_3$. Calculated, %: C 71.56; H 6.71; N 4.91.

(3a*RS*,6*RS*,7a*SR*)-2-Benzyl-6-phenyl-2,3,7,7a-tetrahydro-1*H*-3a,6-epoxyisoindol-1-one (2d). Yield 0.68 g (43%), colorless needles, mp 130–130.5°C (hexane–EtOAc). IR spectrum, ν, cm^{-1}: 1676 (NCO). ^1H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 2.06 (1H, dd, *J* = 11.8, *J* = 9.0) and 2.37 (1H, dd, *J* = 11.8, *J* = 3.7, 7-CH_2); 2.71 (1H, dd, *J* = 9.0, *J* = 3.7, 7a-CH); 3.66 (1H, d, *J* = 11.6) and 3.86 (1H, d, *J* = 11.6, 3-CH_2); 4.39 (1H, d, *J* = 15.0) and 4.71 (1H, d, *J* = 15.0, NCH_2); 6.48 (2H, s, 4,5-CH); 7.25–7.47 (10H, m, H Ar). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ, ppm: 34.3 (C-7); 46.8, 49.3 (NCH_2, C-3); 50.7 (C-7a), 89.2 (C-6), 90.9 (C-3a); 125.8, 127.7, 128.1, 128.2, 128.6, 128.8, 133.7, 136.3, 138.5, 140.1 (C Ph, C-4,5); 173.9 (C-1). Mass spectrum (EI, 70 eV), *m*/*z* (I_{rel}, %): 317 $[M]^+$ (9), 226 (41), 172 (100), 157 (16), 128 (20), 91 (25), 77 (11), 55 (44). Found, %: C 79.61; H 6.11; N 4.37. $C_{21}H_{19}NO_2$. Calculated, %: C 79.47; H 6.03; N 4.41.

(3a*RS*,6*RS*,7a*SR*)-2-Isopropyl-6-phenyl-2,3,7,7a-tetrahydro-1*H*-3a,6-epoxyisoindol-1-one (2e). Yield 0.63 g (47%), colorless prisms, mp 112–113°C (hexane–EtOAc). IR spectrum, ν, cm^{-1}: 1671 (NCO). ^1H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.13 (3H, d, *J* = 6.9, CH_3); 1.17 (3H, d, *J* = 6.9, CH_3); 1.99 (1H, dd, *J* = 11.8, *J* = 8.7) and 2.28 (1H, dd, *J* = 11.8, *J* = 3.7, 7-CH_2); 2.63 (1H, dd, *J* = 8.7, *J* = 3.7, 7a-CH); 3.73 (1H, d, *J* = 11.6) and 3.85 (1H, d, *J* = 11.6, 3-CH_2); 4.41 (1H, heptet, *J* = 6.9, NCH); 6.46 (1H, d, *J* = 5.5) and 6.51 (1H, d, *J* = 5.5, 4,5-CH); 7.28–7.45 (5H, m, H Ph). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ, ppm: 19.5, 20.0 ($2CH_3$); 34.0 (C-7); 42.5 (C-7a); 44.4 (C-3); 51.2 (NCH); 89.1 (C-6); 90.7 (C-3a); 125.9, 128.1, 128.5, 133.8, 138.5, 140.0 (C Ph, C-4,5); 173.0 (C-1). Mass spectrum (EI, 70 eV), *m*/*z* (I_{rel}, %): 269 $[M]^+$ (26), 226 (19), 172 (100), 157 (37), 128 (22), 115 (9), 77 (13), 55 (46). Found, %: C 75.66; H 7.24; N 5.41. $C_{17}H_{19}NO_2$. Calculated, %: C 75.81; H 7.11; N 5.20.

(3a*RS*,6*RS*,7a*SR*)-2-*tert*-Butyl-6-phenyl-2,3,7,7a-tetrahydro-1*H*-3a,6-epoxyisoindol-1-one (2f). Yield 0.40 g (28%), colorless needles, mp 120–122°C (petroleum ether–ether). IR spectrum, ν, cm^{-1}: 1671 (NCO). ^1H NMR spectrum (600 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.43 (9H, s, $C(CH_3)_3$); 1.96 (1H, dd, *J* = 11.7, *J* = 8.9) and 2.31 (1H, dd, *J* = 11.7, *J* = 3.4, 7-CH_2); 2.62 (1H, dd, *J* = 8.9, *J* = 3.4, 7a-CH); 3.90 (1H, d, *J* = 11.7) and 4.00 (1H, d, *J* = 11.7, 3-CH_2); 6.46 (1H, d, *J* = 5.5) and 6.50 (1H, d, *J* = 5.5, 4,5-CH); 7.33 (1H, t, *J* = 7.6, H-4 Ph); 7.39 (2H, t, *J* = 7.6, H-3,5 Ph); 7.47 (2H, d, *J* = 7.6, H-2,6 Ph). ^{13}C NMR spectrum (150 MHz, $CDCl_3$), δ, ppm: 27.8 ($3CH_3$); 34.2 (C-7); 48.2, 51.7, 54.3 ($\underline{C}(CH_3)_3$, C-3,7a); 88.4 (C-6); 90.8 (C-3a); 126.1, 128.2, 128.6, 134.1, 138.6, 140.0 (C Ph, C-4,5); 174.2 (C-1). Mass spectrum (EI, 70 eV), *m*/*z* (I_{rel}, %): 283 $[M]^+$ (7), 226 (56), 172 (100), 157 (96), 141 (14),

128 (39), 115 (29), 105 (14), 77 (29), 55 (63), 41 (37). Found, %: C 76.38; H 7.35; N 5.08. $C_{18}H_{21}NO_2$. Calculated, %: C 76.29; H 7.47; N 4.94.

***N*-Phenyl-*N*-((5-phenylfuran-2-yl)methyl)acrylamide (3a)**. Yield 0.86 g (57%), colorless needles, mp 110–111°C (petroleum ether–ether). IR spectrum, ν, cm^{-1}: 1656 (NCO). ^{1}H NMR spectrum (600 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 5.00 (2H, s, NCH_2); 5.54 (1H, dd, *J* = 10.3, *J* = 2.1, C$\underline{H}_2$=CH *cis*); 6.03 (1H, dd, *J* = 16.5, *J*= 10.3, CH_2=C$\underline{H}$); 6.29 (1H, d, *J* = 3.4) and 6.54 (1H, d, *J* = 3.4, H-3,4 Fur); 6.42 (1H, dd, *J* = 16.5, *J* = 2.1, C$\underline{H}_2$=CH *trans*); 7.14 (2H, dd, *J* = 7.6, *J* = 1.4, H-2,6 Ph); 7.23 (1H, t, *J* = 7.6, H-4 Ph), 7.33–7.39 (5H, m, H Ph); 7.56 (2H, dd, *J* = 8.3, *J* = 1.4, H-2,6 Ph). ^{13}C NMR spectrum (150 MHz, $CDCl_3$), δ, ppm: 45.0 (NCH_2); 105.9, 111.2 (C-3,4 Fur); 123.7, 127.3, 128.1 (2C), 128.5, 128.6, 128.7, 129.6, 130.8, 141.8 (C Ar, $\underline{C}$H=$\underline{C}H_2$); 150.3, 153.5 (C-2,5 Fur); 165.5 (C=O). Mass spectrum (EI, 70 eV), *m*/*z* (I_{rel}, %): 303 $[M]^+$ (6),157 (100), 128 (31), 115 (9), 105 (7), 77 (27), 55 (39), 51 (12). Found, %: C 79.25; H 5.61; N 4.69. $C_{20}H_{17}NO_2$. Calculated, %: C 79.19; H 5.65; N 4.62.

***N*-((5-(4-Methylphenyl)furan-2-yl)methyl)-*N*-phenylacrylamide (3b)**. Yield 1.33 g (84%), pinkish prisms, mp 147–148°C (pentane–EtOAc). IR spectrum, ν, cm^{-1}: 1688, 1655 (NCO). ^{1}H NMR spectrum (600 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 2.34 (3H, s, CH_3); 5.01 (2H, s, NCH_2); 5.55 (1H, br. dd, *J* = 10.7, *J* = 1.7, C$\underline{H}_2$=CH *cis*); 6.03 (1H, br. dd, *J* = 17.3, *J* = 10.7, CH_2=C$\underline{H}$); 6.28 (1H, d, *J* = 3.3) and 6.48 (1H, d, *J* = 3.3, H-3,4 Fur); 6.43 (1H, dd, *J* = 17.3, *J* = 1.7, C$\underline{H}_2$=CH *trans*); 7.14–7.17 (4H, m, H Ar); 7.33–7.40 (3H, m, H Ar); 7.46 (2H, d, *J* = 8.3, H Ar). ^{13}C NMR spectrum (150 MHz, $CDCl_3$), δ, ppm: 21.2 (CH_3); 45.9 (NCH_2); 105.0, 111.1 (C-3,4 Fur); 123.6, 128.0, 128.1, 128.4, 128.5, 129.3, 129.4, 137.1, 141.7, 145.7 (C Ar, $\underline{C}$H=$\underline{C}H_2$); 149.7, 153.6 (C-2,5 Fur); 164.0 (C=O). Mass spectrum (EI, 70 eV), *m*/*z* (I_{rel}, %): 317 $[M]^+$ (3), 171 (100), 141 (5), 128 (26), 115 (5), 91 (6), 77 (5), 55 (6). Found, %: C 79.31; H 5.92; N 4.56. $C_{21}H_{19}NO_2$. Calculated, %: C 79.47; H 6.03; N 4.41.

***N*-((5-(3-Chlorophenyl)furan-2-yl)methyl)-*N*-phenylacrylamide (3c)**. Yield 1.13 g (67%), pale-yellow needles, mp 90–91°C (pentane–EtOAc). IR spectrum, ν, cm^{-1}: 1654 (NCO). ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 5.00 (2H, s, NCH_2); 5.53 (1H, dd, *J*= 10.6, *J* = 1.9, C$\underline{H}_2$=CH *cis*); 6.03 (1H, dd, *J* = 16.8, *J* = 10.6, CH_2=C$\underline{H}$); 6.29 (1H, d, *J* = 3.1) and 6.54 (1H, d, *J* = 3.1, H-3,4 Fur); 6.42 (1H, br. dd, *J* = 16.8, *J* = 1.9, C$\underline{H}_2$=CH *trans*); 7.12–7.42 (8H, m, H Ar); 7.49 (1H, t, *J* = 1.9, H-2 Ar). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ, ppm: 45.9 (NCH_2); 106.9, 111.2 (C-3,4 Fur); 121.7, 123.6, 127.1, 128.1 (2C), 128.4, 128.5, 129.6, 129.9, 132.4, 134.7, 141.7 (C Ar, $\underline{C}$H=$\underline{C}H_2$); 151.0, 151.9 (C-2,5 Fur); 165.4 (C=O). Mass spectrum (EI, 70 eV), *m*/*z* (I_{rel}, %): 337 $[M]^+$ (7), 191 (100), 139 (7), 128 (43), 111 (9), 91 (6), 77 (25), 55 (91), 51 (20), 39 (7). Found, %: C 70.98; H 4.90; N 4.01. $C_{20}H_{16}ClNO_2$. Calculated, %: C 71.11; H 4.77; N 4.15.

Preparation of 3a,6-epoxyisoindole-7-carboxylic acid 4a,b, 6a–f and [(5-phenylfuran-2-yl)methyl]amino-4-oxobut-2-enoic acids 5a–f (General method). Maleic anhydride (0.49 g, 5 mmol) was added to a solution of the appropriate amine **1a**–**e**,**g**–**i** (5 mmol) in ether (40 ml) at 20° C and the reaction mixture was maintained for 1–3 days until the completion of reaction (control by TLC). The precipitate was filtered off and washed with ether (2×15 ml). The carboxylic acids **4a**,**b** and acids **6a**–**f** as colorless crystals were obtained. Acids **6a**–**f** are in ring-chain tautomerism with the respective *N*-furfuryl-*N*-phenylmaleic amides **5a**–**f**.

(3a*RS*,6*SR*,7*RS*,7a*SR*)-6-Ethyl-2-isopropyl-1-oxo-2,3,7,7a-tetrahydro-1*H*-3a,6-epoxyisoindole-7-carboxylic acid (4a). Yield 1.13 g (85%), colorless powder, mp 178.0–178.5°C (EtOAc–EtOH). IR spectrum, ν, cm^{-1}: 1740 (CO_2), 1669 (NCO). ^{1}H NMR spectrum (600 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 0.95 (3H, t, *J* = 7.6, CH_3); 1.05 (3H, d, *J* = 6.9, CH_3); 1.09 (3H, d, *J* = 6.9, CH_3); 1.82–1.94 (2H, m, CH_2); 2.48 (1H, d, *J* = 8.9) and 2.75 (1H, d, *J* = 8.9, 7,7a-CH); 3.57 (1H, d, *J* = 11.7) and 3.82 (1H, d, *J* = 11.7, 3-CH_2); 4.13 (1H, heptet, *J* = 6.9, NCH); 6.36 (1H, d, *J* = 5.5) and 6.63 (1H, d, *J* = 5.5, 4,5-CH); 12.06 (1H, br. s, CO_2H). ^{13}C NMR spectrum (100 MHz, DMSO-d_6), δ, ppm: 9.3 (CH_3); 19.3, 19.6 ($2CH_3$); 22.2 (CH_2); 41.8 (NCH); 43.2 (C-3); 46.8, 54.1 (C-7,7a); 87.5, 92.6 (C-3a,6); 137.2, 137.5 (C-4,5); 169.7, 171.7 (C-1, CO_2). Mass spectrum (ESI), *m*/*z*: 266 $[M+H]^+$ (100), 288 $[M+Na]^+$ (24), 304 $[M+K]^+$ (12). Found, %: C 63.43; H 7.27; N 5.15. $C_{14}H_{19}NO_4$. Calculated, %: C 63.38; H 7.22; N 5.28.

(3a*RS*,6*SR*,7*RS*,7a*SR*)-1-Oxo-2-phenyl-6-propyl-2,3,7,7a-tetrahydro-1*H*-3a,6-epoxyisoindole-7-carboxylic acid (4b). Yield 1.33 g (98%), colorless powder, mp 146–147°C (EtOAc–EtOH). IR spectrum, ν, cm^{-1}: 1743 (CO_2), 1666 (NCO). ^{1}H NMR spectrum (600 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 0.88 (3H, t, *J* = 7.4, CH_3); 1.35–1.44 (2H, m, CH_2); 1.76–1.90 (2H, m, CH_2); 2.59 (1H, d, *J* = 8.3) and 3.04 (1H, d, *J* = 8.3, 7,7a -CH); 4.01 (1H, d, *J* = 11.6) and 4.47 (1H, d, *J* = 11.6, 3-CH_2); 6.37 (1H, d, *J* = 5.8) and 6.65 (1H, d, *J* = 5.8, 4,5-CH); 7.10 (1H, t, *J* = 7.4, H-4 Ph); 7.34 (2H, t, *J* = 7.4, H-3,5 Ph); 7.62 (2H, d, *J* = 7.4, H-2,6 Ph); 12.23 (1H, br. s, CO_2H). ^{13}C NMR spectrum (150 MHz, DMSO-d_6), δ, ppm: 15.0 (CH_3); 18.7 (CH_2); 32.0 (CH_2); 48.5, 50.2, 55.2 (C-3,7,7a); 87.2, 92.8 (C-3a,6); 120.0, 124.5, 129.2, 137.3, 138.7, 140.1 (C Ph, C-4,5); 171.3, 172.3 (CO_2, C-1). Mass spectrum (ESI), *m*/*z*: 314 $[M+H]^+$ (100), 336 $[M+Na]^+$ (46), 352 $[M+K]^+$ (16). Found, %: C 69.06; H 5.98; N 4.59. $C_{18}H_{19}NO_4$. Calculated, %: C 68.99; H 6.11; N 4.47.

(2*Z*)-4-Oxo-4-{phenyl[(5-phenylfuran-2-yl)methyl]-amino}but-2-enoic acid (5a) and (3a*RS*,6*SR*,7*RS*,7a*SR*)-1-oxo-2,6-diphenyl-2,3,7,7a-tetrahydro-1*H*-3a,6-epoxyisoindole-7-carboxylic acid (6a). Yield 0.91 g (52%), colorless powder, mp 134.5–135.5°C (EtOAc–EtOH). The ratio of tautomers **5Aa/5Ba/6a** = 4/43/53. IR spectrum, ν, cm^{-1}: 1676 (NCO), 1745 (CO_2).

Compound 5Aa. The majority of ^{1}H NMR signals due to the minor rotamer **5Aa** overlapped with the proton signals of other tautomeric forms. Signal assignment was not performed.

Compound 5Ba. ^{1}H NMR spectrum (600 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 4.98 (2H, s, NCH_2); 5.78 (1H, d, *J* = 11.7, CH); 6.38 (1H, d, *J* = 3.4) and 6.81 (1H, d, *J* = 3.4, H-3,4 Fur); 6.41 (1H, d, *J* = 11.7, CH); 7.26–7.43 (8H, m, H Ph), 7.70 (2H, d, *J* = 7.6, H-2,6 Ph); 12.72 (1H, br. s, CO_2H).

Compound 6a. ^{1}H NMR spectrum (600 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 3.13 (1H, d, *J* = 8.9) and 3.28 (1H, d, *J* = 8.9, 7,7a-CH); 4.23 (1H, d, *J* = 11.7) and 4.64 (1H, d, *J* = 11.7, 3-CH_2); 6.53 (1H, d, *J* = 5.5) and 6.82 (1H, d, *J* = 5.5, 4,5-CH); 7.16 (1H, t, *J* = 7.6, H-4 Ph); 7.26–7.43 (7H, m, HPh); 7.69 (2H, dd, *J* = 8.1, *J* = 1.3, H-2,6 Ph); 11.89 (1H, br. s, CO_2H).

Mixture of compounds 5Ba and 6a. ^{13}C NMR spectrum (100 MHz, DMSO-d_6), δ, ppm: 44.4 (NCH_2); 49.5 (C-3); 49.7, 54.7 (C-7,7a); 87.0, 92.7 (C-3a,6); 106.3, 110.6 (C-3,4 Fur); 119.3, 123.2, 123.9, 125.2, 127.2 (2C), 127.8, 127.9, 128.6, 128.7, 129.0, 130.1 136.3, 136.4, 136.6, 139.5, 140.2, 140.9 (C Ph, 2CH, C-4,5); 150.0, 152.4 (C-2,5 Fur); 165.5, 166.1, 170.5, 170.6 (NCO, CO_2). Mass spectrum (EI, 70 eV), *m*/*z* (I_{rel}, %): 347 $[M]^+$ (10), 249 (49), 157 (100), 127 (28), 115 (20), 104 (13), 77 (41), 51 (33), 43 (22). Found, %: C 72.50; H 4.98; N 4.07. $C_{21}H_{17}NO_4$. Calculated, %: C 72.61; H 4.93; N 4.03.

(2*Z*)-4-{Benzyl[(5-phenylfuran-2-yl)methyl]amino}-4-oxobut-2-enoic acid (5b) and (3a*RS*,6*SR*,7*RS*,7a*SR*)-2-benzyl-1-oxo-6-phenyl-2,3,7,7a-tetrahydro-1*H*-3a,6-epoxyisoindole-7-carboxylic acid (6b). Yield 0.69 g (38%), colorless powder, mp 101.5–102°C (EtOAc–EtOH). The ratio of tautomers **5Ab/5Bb/6b** = 22/37/41. IR spectrum, ν, cm^{-1}: 1663 (NCO), 1745 (CO_2).

Rotamers 5Ab and 5Bb. ^{1}H NMR spectrum (600 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 4.43, 4.49, 4.52, 4.58 (2H, s, NCH_2); 6.05 (1H, d, *J* = 11.7, CH); 6.15 (1H, d, *J* = 12.4, CH); 6.44 (1H, d, *J* = 3.4) and 6.84, 6.87 (1H, d, *J* = 3.4, H-3,4 Fur); 6.82 (1H, d, *J* = 11.7, CH); 6.94 (1H, d, *J* = 12.4, CH); 7.23–7.42 (8H, m, H Ph); 7.62–7.66 (2H, m, H-2,6 Ph); 12.83 (1H, br. s, CO_2H).

Compound 6b. ^{1}H NMR spectrum (600 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 3.03 (1H, d, *J* = 8.9) and 3.08 (1H, d, *J* = 8.9, 7,7a-CH); 3.66 (1H, d, *J* = 11.7) and 3.96 (1H, d, *J* = 11.7, 3-CH_2); 4.43 (1H, d, *J* = 15.1) and 4.53 (1H, d, *J* = 15.1, NCH_2); 6.45 (1H, d, *J* = 5.5) and 6.74 (1H, d, *J* = 5.5, 4,5-CH); 7.23–7.42 (10H, m, H Ph); 11.78 (1H, br. s, CO_2H).

Mixture of rotamers 5Ab and 5Bb and compound 6b. ^{13}C NMR spectrum (100 MHz, DMSO-d_6), δ, ppm: 40.4, 43.9, 45.4, 46.8, 48.0, 48.9, 50.9, 53.5 (C-3,7,7a, NCH_2); 88.1, 92.5 (C-3a,6); 106.3, 106.4, 110.5, 111.1 (C-3,4 Fur); 123.2, 123.3, 125.0, 125.3, 126.9, 127.1, 127.2, 127.4 (2C), 127.5, 127.7, 127.8, 128.2, 128.4, 128.5, 128.7, 128.8, 130.0, 130.2, 136.4, 136.6, 136.7 (2C), 136.9, 137.0, 137.1, 139.9 (C Ph, C-4,5, 2CH); 149.6, 150.0, 152.4, 153.0 (C-2,5 Fur); 166.0 (2C), 166.8, 166.9, 170.6, 170.7 (CO_2, NCO). Mass spectrum (EI, 70 eV), *m*/*z* (I_{rel}, %): 361 $[M]^+$ (6), 270 (23), 263 (100), 246 (19), 186 (20), 172 (49), 158 (66), 128 (24), 119 (64), 106 (27), 91 (66), 79 (27), 65 (17), 55 (20), 51 (22), 44 (23). Found, %: C 73.24; H 5.36; N 3.70. $C_{22}H_{19}NO_4$. Calculated, %: C 73.12; H 5.30; N 3.88.

(2*Z*)-4-(Isopropyl((5-phenylfuran-2-yl)methyl)amino)-4-oxobut-2-enoic acid (5c) and (3a*RS*,6*SR*,7*RS*,7a*SR*)-2-isopropyl-1-oxo-6-phenyl-2,3,7,7a-tetrahydro-1*H*-3a,6-epoxyisoindole-7-carboxylic acid (6c). Yield 0.74 g (47%), colorless powder, mp 139–140°C (EtOAc–EtOH). Ratio of tautomers **5Ac/5Bc/6c** = 10/32/58 (tautomer ratio was measured using ^{1}H NMR spectra in DMSO-d_6 at 22°C). IR spectrum, ν, cm^{-1}: 1664 (NCO), 1745 (CO_2).

Compound 5Ac. ^{1}H NMR spectrum (400 MHz, 30°C, DMSO-d_6), δ, ppm (*J*, Hz): 1.15 (6H, d, *J* = 6.9, 2CH_3); 4.48 (2H, s, NCH_2); 4.57 (1H, heptet, *J* = 6.9, NCH); 6.00 (1H, d, *J* = 11.7, CH=C<u>H</u>CO_2H); 6.43 (1H, d, *J* = 2.8, H-3 Fur); 6.71 (1H, d, *J* = 11.7, CH=C<u>H</u>CO_2H); 6.87 (1H, d, *J* = 2.8, H-4 Fur); 7.25–7.43 (3H, m, H-3,4,5 Ph); 7.66 (2H, br. d, *J* = 7.6, H-2,6 Ph); 12.02 (1H, br. s, CO_2H). ^{13}C NMR spectrum (100 MHz, DMSO-d_6), δ, ppm: 20.5 (2CH_3); 36.3 (NCH_2); 49.4 (NCH); 106.5 (C-4 Fur); 110.1 (C-3 Fur); 123.0 (2C, C-3,5 Ph); 127.3 (C-4 Ph); 128.8 (3C, C-2,5 Ph, CH=<u>C</u>HCO_2H); 130.1 (C-1 Ph); 137.6 (<u>C</u>H=CHCO_2H); 151.6 (C-2 Fur); 152.4 (C-5 Fur); 165.9 (NCO), 166.8 (CO_2H).

Compound 5Bc. ^{1}H NMR spectrum (400 MHz, 30°C, DMSO-d_6), δ, ppm (*J*, Hz): 1.17 (6H, d, *J* = 6.9, 2CH_3); 4.04 (1H, heptet, *J* = 6.9, NCH); 4.51 (2H, s, NCH_2); 5.97 (1H, d, *J* = 12.4, CH=C<u>H</u>CO_2H); 6.44 (1H, d, *J* = 2.8, H-3 Fur); 6.80 (1H, d, *J* = 12.4, C<u>H</u>=CHCO_2H); 6.83 (1H, d, *J* = 2.8, H-4 Fur); 7.25–7.43 (3H, m, H-3,4,5 Ph); 7.66 (2H, br. d, *J* = 7.6, H-2,6 Ph); 12.02 (1H, br. s, CO_2H). ^{13}C NMR spectrum (100 MHz, DMSO-d_6), δ, ppm: 19.3 (2CH_3); 40.4 (NCH_2); 44.9 (NCH); 106.5 (C-4 Fur); 109.4 (C-3 Fur); 123.1 (2C, C-2,6 Ph); 123.6 (CH=<u>C</u>HCO_2H); 127.0 (C-4 Ph); 128.7 (2C, C-3,5 Ph); 130.4 (C-1 Ph); 138.4 (<u>C</u>H=CHCO_2H); 151.3 (C-5 Fur); 152.1 (C-2 Fur); 166.0 (NCO); 166.4 (CO_2H).

Compound 6c. ^{1}H NMR spectrum (400 MHz, 30°C, DMSO-d_6), δ, ppm (*J*, Hz): 1.11 (3H, d, *J* = 6.9, CH_3); 1.13 (3H, d, *J* = 6.9, CH_3); 2.94 (1H, d, *J* = 8.9, H-7a); 2.97 (1H, d, *J* = 8.9, H-7); 3.74 (1H, d, *J* = 11.7) and 3.95 (1H, d, *J* = 11.7, 3-CH_2); 4.17 (1H, heptet, *J* = 6.9, NCH); 6.43 (1H, d, *J* = 5.2, H-5); 6.73 (1H, d, *J* = 5.2, H-4); 7.25–7.43 (5H, m, H Ph); 12.02 (1H, br. s, CO_2H). ^{13}C NMR spectrum (100 MHz, DMSO-d_6), δ, ppm: 19.2 (CH_3); 19.5 (CH_3); 41.9 (NCH); 43.2 (C-3); 48.7 (C-7); 54.1 (C-7a); 87.9 (C-6); 92.4 (C-3a); 125.2 (2C, C-2,6 Ph); 127.0 (C-4 Ph); 127.7 (2C, C-3,5 Ph); 136.7 (C-4); 137.3 (C-1 Ph); 140 (C-5); 169.5 (NCO); 170.6 (CO_2H). Mass spectrum (EI, 70 eV), *m*/*z* (I_{rel}, %): 313 $[M]^+$ (58), 295 (19), 268 (45), 252 (27), 215 (56), 210 (13), 198 (38), 172 (40), 157 (100), 127 (29), 115 (27), 99 (26), 77 (19), 71 (11), 55 (19), 51 (12), 43 (20). Found, %: C 69.09; H 6.18; N 4.32. $C_{18}H_{19}NO_4$. Calculated, %: C 68.99; H 6.11; N 4.47.

(2*Z*)-4-Oxo-4-{[(5-phenylfuran-2-yl)methyl](cyclopentyl)-amino}but-2-enoic acid (5d) and (3a*RS*,6*SR*,7*RS*,7a*SR*)-2-cyclopentyl-1-oxo-6-phenyl-2,3,7,7a-tetrahydro-1*H*-3a,6-epoxyisoindole-7-carboxylic acid (6d). Yield 0.78 g (46%), colorless powder, mp 154°C (EtOAc–EtOH). Ratio of tautomers **5Ad/5Bd/6d** = 13/24/63. IR spectrum, ν, cm^{-1}: 1742 (CO_2), 1664 (NCO).

Rotamers 5Ad and 5Bd. ^{1}H NMR spectrum (600 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 1.46–1.76 (8H, m, 4CH_2); 4.14, 4.52 (1H, quin, *J* = 8.2, NCH); 4.49, 4.49 (2H, s, NCH_2); 5.98, 5.99 (1H, d, *J* = 12.0, CH); 6.42, 6.43 (1H, d, *J* = 3.4) and 6.84, 6.89 (1H, d, *J* = 3.4, H-3,4 Fur); 6.71, 6.82 (1H, d, *J* = 12.0, CH); 7.25–7.43 (3H, m, HPh); 7.64–7.66 (2H, m, HPh); 12.70 (1H, br. s, CO_2H).

Compound 6d. ^{1}H NMR spectrum (600 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 1.46–1.76 (8H, m, 4CH_2); 2.95 (1H, d,

J = 8.9) and 2.97 (1H, d, *J* = 8.9, 7,7a-CH); 3.75 (1H, d, *J* = 11.7) and 4.00 (1H, d, *J* = 11.7, 3-CH_2); 4.32 (1H, quin, *J* = 7.6, NCH); 6.43 (1H, d, *J* = 5.5) and 6.74 (1H, d, *J* = 5.5, 4,5-CH); 7.25–7.43 (5H, m, H Ph); 11.67 (1H, br. s, CO_2H).

Mixture of rotamers 5Ad, 5Bd and compound 6d. ^{13}C NMR spectrum (100 MHz, DMSO-d_6), δ, ppm: 14.0, 20.7, 23.2, 23.5, 23.9, 28.1, 28.3, 28.6, 29.1, 37.6, 42.2, 44.4, 48.8, 52.0, 54.1, 55.5, 59.2, 59.7 (4CH_2, C-3,7,7a, NCH, NCH_2); 87.9, 92.4 (C-3a,6); 106.5, 106.6, 109.3, 109.9 (C-3,4 Fur); 123.0, 123.2, 123.7, 124.3, 125.3, 127.1, 127.4, 127.8, 128.8, 130.1, 130.5, 136.7, 137.3, 138.3, 140.0 (C Ph, C-4,5, 2CH); 151.4, 151.5, 152.0, 152.5 (C-2,5 Fur); 165.9, 166.0, 166.8, 167.1, 170.0, 170.7 (CO_2, NCO). Mass spectrum (EI, 70 eV), *m*/*z* (I_{rel}, %): 339 $[M]^+$ (10), 241 (24), 172 (23), 157 (100), 136 (11), 128 (24), 105 (14), 97 (21), 76 (21), 54 (36), 43 (41). Found, %: C 70.56; H 6.28; N 4.18. $C_{20}H_{21}NO_4$. Calculated, %: C 70.78; H 6.24; N 4.13.

(2*Z*)-4-{(2-methoxyethyl)[(5-phenylfuran-2-yl)methyl]-amino}-4-oxobut-2-enoic acid (5e) and (3a*RS*,6*SR*,7*RS*,7a*SR*)-2-(2-methoxyethyl)-1-oxo-6-phenyl-2,3,7,7a-tetrahydro-1*H*-3a,6-epoxyisoindole-7-carboxylic acid (6e). Yield 0.69 g (42%), colorless powder, mp 86–87°C (EtOAc–EtOH). Ratio of tautomers **5Ae/5Be/6e** = 30/37/33. IR spectrum, ν, cm^{-1}: 1744 (CO_2), 1669 (NCO).

Rotamers 5Ae and 5Be. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 3.21, 3.29 (3H, s, CH_3); 3.44–3.64 (4H, m, CH_2CH_2); 4.57, 4.66 (2H, s, NCH_2); 6.02, 6.08 (1H, d, *J* = 11.9, CH); 6.49, 6.50 (1H, d, *J* = 3.2) and 6.88, 6.90 (1H, d, *J* = 3.2, H-3,4 Fur); 6.74, 6.85 (1H, d, *J* = 11.9, CH); 7.26–7.43 (3H, m, H Ph); 7.67–7.69 (2H, m, H Ph); 12.56 (1H, br. s, CO_2H).

Compound 6e. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 2.96 (1H, d, *J* = 9.2) and 2.99 (1H, d, *J* = 9.2, 7,7a-CH); 3.24 (3H, s, CH_3); 3.44–3.64 (4H, m, CH_2CH_2); 3.80 (1H, d, *J* = 11.9) and 4.13 (1H, d, *J* = 11.9, 3-CH_2); 6.44 (1H, d, *J* = 5.5) and 6.76 (1H, d, *J* = 5.5, 4,5-CH); 7.26–7.43 (3H, m, H Ph); 7.67–7.69 (2H, m, H Ph); 12.56 (1H, br. s, CO_2H).

Rotamers 5Ae, 5Be and compound 6e. ^{13}C NMR spectrum (100 MHz, DMSO-d_6), δ, ppm: 41.1, 41.8, 43.6, 45.5, 47.1, 48.8, 49.2, 53.4, 57.9, 58.1, 58.2, 69.4, 69.6, 69.8 (CH_3, OCH_2, C-3,7,7a, 2NCH_2); 88.2, 92.5 (C-3a,6); 106.4, 106.5, 110.2, 110.7 (C-3,4 Fur); 123.2, 123.3, 124.5, 125.2, 125.3, 127.1, 127.3, 127.5, 127.8, 128.8, 128.9, 130.1, 130.3, 136.7 (2C), 137.2, 137.3, 140.0 (C Ph, C-4,5, 2CH); 150.2, 150.7, 152.4, 153.0 (C-2,5 Fur); 166.0 (2C), 166.7, 166.9, 170.4, 170.7 (CO_2, NCO). Mass spectrum (ESI), *m*/*z*: 330 $[M+H]^+$ (100), 352 $[M+Na]^+$ (26), 368 $[M+K]^+$ (12). Found, %: C 65.52; H 5.76; N 4.40. $C_{18}H_{19}NO_5$. Calculated, %: C 65.64; H 5.81; N 4.25.

(2*Z*)-4-Oxo-4-{[(5-phenylfuran-2-yl)methyl](ethyl)-amino}but-2-enoic acid (5f) and (3a*RS*,6*SR*,7*RS*,7a*SR*)-2-ethyl-1-oxo-6-phenyl-2,3,7,7a-tetrahydro-1*H*-3a,6-epoxy-isoindole-7-carboxylic acid (6f). Yield 1.06 g (71%), colorless powder, mp 103.5–104.5°C (EtOAc–EtOH). Ratio of tautomers **5Af/5Bf/6f** = 32/36/32. IR spectrum, ν, cm^{-1}: 1747 (CO_2), 1664 (NCO).

Rotamers 5Af and 5Bf. ^{1}H NMR spectrum (600 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 1.07 (3H, t, *J* = 7.0, CH_3); 3.14, 3.40 (2H, q, *J* = 7.0, NCH_2); 4.51, 4.61 (2H, s, NCH_2); 6.01, 6.06 (1H, d, *J* = 12.1, CH); 6.50 (1H, d, *J* = 3.3) and 6.88, 6.90 (1H, d, *J* = 3.3, H-3,4 Fur); 6.81, 6.83 (1H, d, *J* = 12.1, CH); 7.26–7.43 (3H, m, H Ph), 7.66–7.69 (2H, m, H Ph); 12.76 (1H, br. s, CO_2H).

Compound 6f. ^{1}H NMR spectrum (600 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 1.03 (3H, t, *J* = 7.0, CH_3); 2.94 (1H, d, *J* = 9.2) and 2.97 (1H, d, *J* = 9.2, 7,7a-CH); 3.33 (2H, q, *J* = 7.0, CH_2); 3.73 (1H, d, *J* = 11.7) and 4.08 (1H, d, *J* = 11.7, 3-CH_2); 6.44 (1H, d, *J* = 5.5) and 6.75 (1H, d, *J* = 5.5, 4,5-CH); 7.26–7.43 (3H, m, H Ph), 7.66–7.69 (2H, m, H Ph); 11.72 (1H, br. s, CO_2H).

Mixture of rotamers 5Af, 5Bf and compound 6f. ^{13}C NMR spectrum (100 MHz, DMSO-d_6), δ, ppm: 11.9, 12.3, 13.4, 36.6, 40.0, 42.3, 44.1, 47.5, 48.7, 53.7 (CH_3, C-3,7,7a, 2NCH_2); 88.0, 92.5 (C-3a,6); 106.4, 106.5, 110.3, 110.7 (C-3,4 Fur); 123.2, 123.3, 124.5, 124.9, 125.2, 127.1, 127.3, 127.4, 127.8, 128.8 (2C), 130.1, 130.3, 136.7, 137.0, 137.2 (2C), 140.0 (C Ph, C-4,5, 2CH); 150.3, 150.7 (C-2,5 Fur); 165.9, 166.1, 169.9, 170.7 (CO_2, NCO). Mass spectrum (ESI), *m*/*z*: 300 $[M+H]^+$ (100), 322 $[M+Na]^+$ (18), 338 $[M+K]^+$ (9). Found, %: C 68.14; H 5.61; N 4.82. $C_{17}H_{17}NO_4$. Calculated, %: C 68.21; H 5.72; N 4.68.

X-ray structural study of compound 6c. The unit cell parameters and intensities of reflections for monocrystal of compound **6c** were measured on a Bruker SMART APEX II CCD automated three-circle diffractometer (MoKα radiation, graphite monochromator, φ- and ω-scanning). The absorption of X-ray radiation was accounted for by semiempirical method using the SADABS software.[11] The structures were determined by direct method and refined according to full matrix method of least squares by F^2 in anisotropic approximation for non-hydrogen atoms. The hydrogen atoms of OH group in compound **6c** were revealed objectively from differential Fourier syntheses and refined isotropically with fixed shift parameters (U_{iso}(H) = 1.2U_{eq}(N) and U_{iso}(H) = 1.5U_{eq}(O)). The rest of the hydrogen atom positions were calculated geometrically and included in the refinement with fixed positional parameters (the "rider" model) and isotropic shift parameters (U_{iso}(H) = 1.5U_{eq}(C) for CH_3 groups and U_{iso}(H) = 1.2U_{eq}(C) for the rest of the groups). All calculations were performed by using the SHELXTL software suite.[12] The tables of atomic coordinates, bond lengths, valence and torsion angles, and anisotropic temperature parameters for compound **6c** were deposited at the Cambridge Crystallographic Data Center as deposit CCDC 1023933. The data are available by request from CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk or www.ccdc.cam.ac.uk).

The Supplementary information file, containing the complete X-ray structural analysis data for compound **6c** and NMR spectra copies for tautomeric mixture of compounds **5Ac**, **5Bc**, **6c**, is available online at http://link.springer.com/journal/10593.

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