Regio- and diastereoselective synthesis of *trans*-dihydrofuran-3-carboxamides by radical addition of 1,3-dicarbonyl compounds to acrylamides using manganese(III) acetate and determination of exact configuration by X-ray crystallography

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Abstract

In this study, we investigated the radical addition of 1,3-dicarbonyl compounds to acrylamide derivatives including phenyl, 2-thienyl and 5-methyl-2-furyl groups mediated by manganese(III) acetate. *trans*-3-Carboxamide-dihydrofurans were obtained in modarate to good yields, as well as regio- and diastereoselectievly. Structural analyses of these compounds were made by NMR techniques such as HMBC and NOSY spectra. Also, exact configuration and structures of these (**7b**, **7i** and **7j**) compounds were determined by X-ray crystallography.

Keywords: Manganese(III) acetate, radical addition, cyclization, dihydrofuran-carboxamide, X-ray analysis, diastereoselective

Introduction

Substituted dihydrofurans constantly occur as subunits for many medicinally important compounds and biologically active natural compounds, such as clerodin, aflatoxin B_1, rocoglamide, austocystin A and fercoprolone.[1-3] On the other hand, the carboxamide group is an important structural moiety in many biologically active compounds and in some drugs, such as acridine carboxamide (topoisomerase inhibitor), nicotineamide, pyrazineamide (a drug for tuberclosis), dacarbazine (antineoplastic), valpromide (a drug for epilepsy). It was reported that some dihydrofurans including carboxamide,[4] and carbonitrile[5] show antifungal and antibacterial activity. Thus, development of effective synthetic methods to prepare polysubstituted dihydrofurans has been focused on this area.

Manganese(III) acetate[6-10] and cerium(IV) ammonium nitrate (CAN)[11-14] are widely used for C-C bond formation and synthesis of polyfunctional organic compounds. It is well known that $Mn(OAc)_3$ or CAN mediated radical reaction of 1,3-dicarbonyl compounds with alkenes produce dihydrofuran derivatives. $Mn(OAc)_3$, CAN or Ag(I)/Celite mediated radical reactions of 1,3-dicarbonyl compounds with unsymmetrically alkenes such as (1-pyridin-2-yl)-enones,[9] unsaturated ketones,[15,16] cinnamates,[7,14] and unsaturated ether,[11, 17] have been reported. Our research group has focused on the radical reaction of 1,3-dicarbonyls and 3-oxopropanenitriles with unsaturated systems.[18-27] We first reported the reaction of (*E*)-2-styrylthiophene and (*E*)-2-methyl-5-styrylfuran with 3-oxopropanenitriles,[18, 20] fluorinated-1,3-dicarbonyls[21] and 1,3-diketones[22, 23] lead to formation of 2-thienyl and 2-furylsubstituted *trans*-dihydrofurans (**1** and **2**). Although there are two possible different cyclization routes with these reactions, we reported that, this cyclization occurs only at the C-1 carbon (adjacent to thienyl or furyl groups) regioselectively (Figure 1).[18, 20]

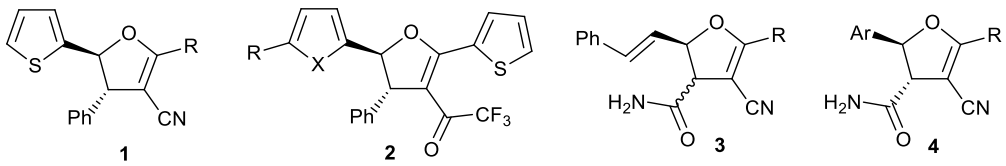


Figure 1

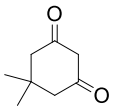
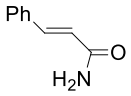
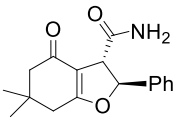
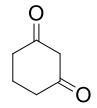
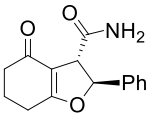
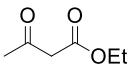
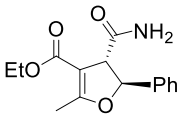
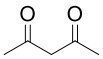
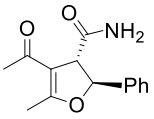
Previously, we obtained *cis*- and *trans*-diastereomer mixtures of dihydrofurans **(3)** from the reaction of (*E*,*E*)-5-phenyl-2,4-pentandienamide with 3-oxopropanenitrile. We clearly reported that coupling constants of the H2 and H3 vicinal protons of this compounds are J_{cis} 9.6-10.3 Hz and J_{trans} 6.8-7.5 Hz, respectively.[19, 27] Based on the coupling constants of the *trans*-diastereomers, we decided that 2,3-dihydrofuran-3-carboxamides (**4)** obtained from the reaction of 3-oxopropanenitriles with (2*E*)-3-(2-thienyl)acrylamide and (2*E*)-3-(5-methyl-2-furyl)acrylamide are in trans configuration (Fig 1).[19]

Depending on the substituents attached to dihydrofuran ring, coupling constant of the vicinal protons can show some inequality. Hence, if both *cis*- and *trans*-diastereomers do not form in the reaction of unsymmetrical alkenes, coupling constants of the vicinal protons or NOSY (or NOE-DIFF) spectra may not be inadequate to determine configuration of the dihydrofurans in all cases. The most exact proof of structure and configuration of the compounds can only be obtained from X-ray crystallography. Thus, in the present study, we reported the radical addition of acrylamide derivatives with various 1,3-dicarbonyl compounds using $Mn(OAc)_3$, lead to *trans*-3-carboxamide-substituted dihydrofurans as regio- and diastereoselectively. Absolute structure and configuration of these compounds were determined by X-ray analysis.

Results and Discussion

(2*E*)-3-Phenylacrylamide **5a**, (2*E*)-3-(2-thienyl)acrylamide **5b**, (2*E*)-3-(5-methyl-2-furyl)acrylamide **5c** and (2*E*)-3-(3-thienyl)acrylamide **5d** were prepared by the reaction of suitable acyl chloride and NH_3/NaOH as described in literature.[28, 19]

Table 1. The reaction of 1,3-dicarbonyls **(6a-d)** with (2*E*)-3-phenylacrylamide **5a**.

Entry	1,3-dicarbonyl	acrylamide	dihydrofuran	yield[A], (%)
1	 **6a**	 **5a**		**7a**, 68
2	 **6b**	**5a**		**7b**, 55
3	 **6c**	**5a**		**7c,** 50
4	 **6d**	**5a**		**7d**, 41

[A]Yield of isolated product based on the conjugated amides **5a.**

Treatments of (2*E*)-3-phenylacrylamide **5a** with dimedone **6a** and 1,3-cyclohexandione **6b** in the presence of $Mn(OAc)_3$ in HOAc in a **2**:**1**:**3** molar ratio (1,3-dicarbonyl : acrylamide : $Mn(OAc)_3$) at 70 °C gave 2-phenyl-3-carboxamide-dihydrobenzofurans **7a** in 68% and **7b** in 55% yields (Table 1). In the ^{1}H NMR spectra of these compounds, the H-2 and H-3 (C8-H and C7-H in the x-ray graphic for **7b**, respectively) protons of the dihydrobenzofurans **7a** and **7b** appeared as two doublets with a *vicinal* coupling constant of *J* 6.0 Hz. The H-2 protons (δ 6.14 and 6.27 ppm) resonate at low field due to inductive effect of neighbouring etheric oxygen atom. Since the HMBC spectra of **7a** shows that the H-2 proton correlates with the *ortho*-carbon of phenyl resonates at 125.3 ppm, phenyl group attached to the C-2 carbon in the dihydrobenzofuran ring. Also, we verified absolute configuration and the assignment of regio- and diastereoselectivity through X-ray analysis of **7b** (2*R*, 3*R*) in Figure 2.

Treatments of ethyl 3-oxobutanoate **6c** and 2,4-pentanedione **6d** with **5a** gave *trans*-2,3-dihydrofurans **7c** and **7d** in moderate yields, respectively. Compounds **7c** and **7d** show only two doublets for two protons at C2- and C3-position with the coupling constants of 5.2 and 4.8 Hz, which obviously indicated that these 2,3-dihydrofurans are in *trans*-configuration.

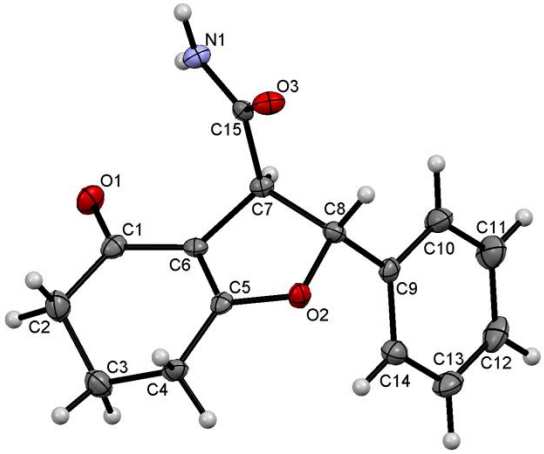


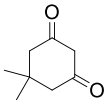
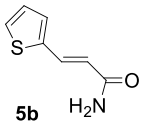
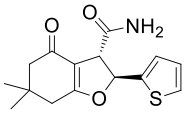
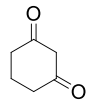
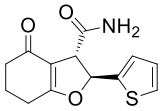
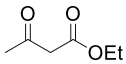
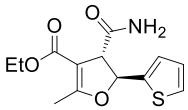
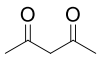
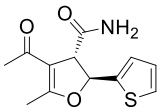
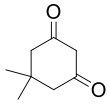
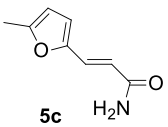
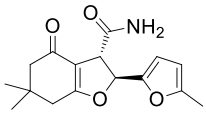
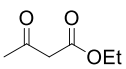
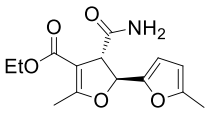
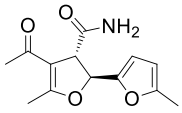
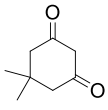
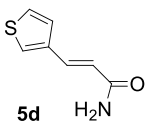
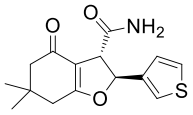
Figure 2. Molecular structure of the compound **7b**.

It has been reported that the *vicinal* coupling constants of two methine protons in *cis*-dihydrofuran are J_{cis} 8-11 Hz, while in *trans*-dihydrofurans *vicinal* coupling constants are J_{trans} 2.5-7.5 Hz.[18-27, 29, 30] Based on this information, the previously assigned *cis*-stereomer should likely be the *trans*-stereomer for the dihydrofurans obtained from the $Mn(OAc)_3$ mediated radical reactions of 1,3-dicarbonyl compounds with chalcones,[15] 2-styrylthiophene[10] and from the radical reactions of 1,3-dicarbonyls with cinnamates,[14] unsaturated ketones[16] promoted by CAN as these dihydrofurans had vicinal coupling constants of 5.8-7.2 Hz.

As seen in the Table 2, radical addition of dimedone **6a** to **5b** afforded *trans*-3-(2-thienyl)-2,3-dihydrobenzofuran-3-carboxamide **7e** which was characterized by ^{1}H NMR, ^{13}C NMR, NOSY and HMBC spectra. In the ^{1}H NMR spectrum of **7e**, *vicinal* coupling constants of H-2 and H-3 are J_{trans} 5.6 Hz. In the HMBC spectrum, H-3 proton resonated at 4.1 ppm correlates with the thiophene carbon resonated at 142.5 ppm. These results show that 2-thienyl attached to the C-2. Moreover, similar results were obtained by the radical reaction of 1,3-dicarbonyls **6b-d** with **5b** forming *trans*-3-(2-thienyl)-dihydrofuran-3-carboxamides **7f-h** with *vicinal* coupling constants of 5.2 - 4.2 Hz appearing in corresponding ^{1}H NMR spectra (Table 2, Entries 2-4). On the other hand, *trans*-3-(5-methyl-2-furyl)dihydrobenzofuran-3-carboxamide **7i** was obtained by the treatment of dimedone **6a** with (2*E*)-3-(5-methyl-2-furyl)acrylamide **5c** in 80% yield. Reaction of **6c** and **6d** with **5c** afforded *trans*-2,3-dihydrofuran-3-carboxamides **7j** (67%) and **7k** (70%) in good yields (Table 2, Entries 6 and 7). Also, the radical reaction of (2*E*)-3-(3-thienyl)acrylamide **5d** with **6a** gave corresponding compound **7l** in 36% yield. All dihydrofurans were obtained in moderate to good yields.

Related unsaturated amides used in radical reactions regained with column chromatography from each crude products in 15-25 % yields. To accurately understand if there are any possible compounds (especially *cis*- isomers) formed in this type of radical addition reactions , the crude products from experiments **7a** and **7e** were analysed with LC-MS (without purification). The results from these analyses showed that there are no isomers with same masses formed beside the *trans*- products.

Table 2. Radical reaction of 1,3-dicarbonyl compounds **7a-d** with **2c** and **2d**

entry	1,3-dicarbonyl	acrylamide	dihydrofuran	yield[A] (%)
1	 **6a**	 **5b**		**7e**, 55
2	 **6b**	**5b**		**7f**, 54
3	 **6c**	**5b**		**7g**, 46
4	 **6d**	**5b**		**7h**, 52
5	 **6a**	 **5c**		**7i**, 80
6	 **6c**	**5c**		**7j**, 67
7	 **6d**	**5c**		**7k**, 70
8	 **6a**	 **5d**		**7l**, 36

[A]: Yield of isolated product based on the conjugated amides **5b** and **5c.** Moreover, structural assignment of compounds **7i** (2*S*, 3*S*) and **7j** (2*R*, 3*R*) were further characterized by x-ray single

crystal analysis (Figs 3 and 4), as a result of this, we can conclude that these vicinal protons are definitely in *trans*-configuration.

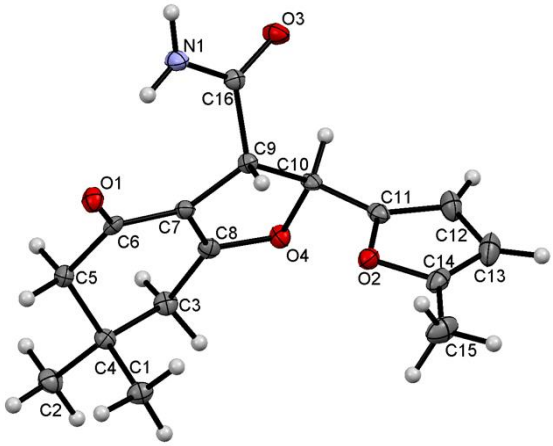


Figure 3. Molecular structure of the compound **7i**.

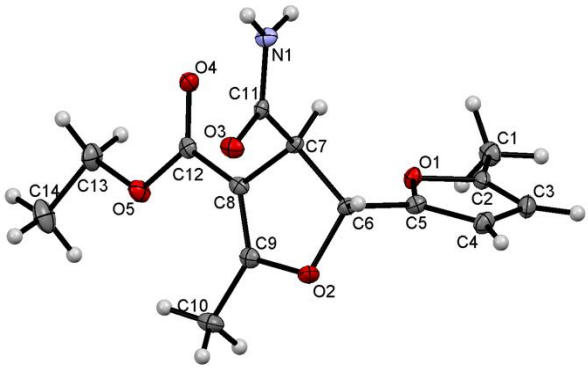
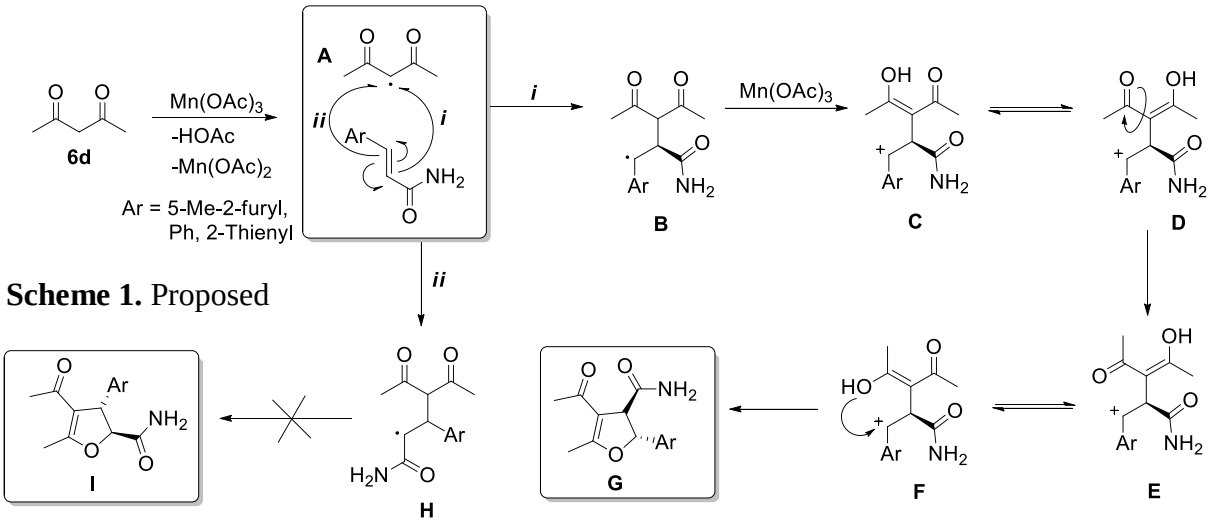


Figure 4. Molecular structure of the compound **7j**. Displacement ellipsoids are drawn at the 50 % probability level. H-atoms are shown as small spheres of arbitrary radii.

The proposed mechanism for the formation of dihydrofuran-carboxamides is illustrated in scheme 1. According to the mechanism, whilst Mn^{+3} reduces to Mn^{+2}, a carbon radical forms on the 1,3-dicarbonyl. The intermediate product **A** can be added to acrylamides with two ways. An adduct intermediate **B** forms with pathway-*i* then structure **B** is oxidized to carbocation **C** with $Mn(OAc)_3$ and then enolizes to intermediate **E**. Dihydrofuran **G** is formed by intramolecular cyclization of **F**. Dihydrofuran **I** which occurred by the cyclization of the other adduct intermediate **H** obtained by pathway-*ii*. However, dihydrofuran **I** was not isolated, only dihydrofurans **G** were obtained as sole products. The reason behind regioselective addition is that intermediate **B** is being more stable than intermediate **H**. Also, diastereoselectivity can be explained by intramolecular cyclization in structure **F** preferring *trans*-isomer which has less steric hindrance and more thermodynamically stable.



Scheme 1. Proposed mechanism for the formation of *trans*-dihydrofuran-carboxamides.

Conclusions

We obtained 3-carboxamide-dihydrofurans in good yields as diastereoselectively by the manganese(III) acetate mediated reaction of acrylamide derivatives and 1,3-dicarbonyl compounds. It is seen that coupling constants of vicinal protons of the dihydrofurans in this work are 1-1.5 Hz less than that of 3-cyano-carboxamides. These results show that the substituents attached on the C=C double bond in the dihydrofuran rings significantly effect on the coupling constants of vicinal protons. Our studies based on the X-ray analyses continue to determine substituent effects on the coupling constant of vicinal protons and definite configurations of some dihydofurans whose structure is open to debate.

Experimental Section

General. Melting points were determined on an electrothermal capillary melting point apparatus. IR spectra (ATR) were obtained with a Bruker Tensor-27 400-4000 cm^{-1} range with 2 cm^{-1} resolution. ^{1}H NMR, ^{13}C NMR, HMBC, NOSY, spectra were recorded on a Bruker Avance DPX-400 MHz and Varian Mercury-400 High performance Digital FT-NMR spectrophotometers. High Resolution Mass Time-of-Flight spectra (TOF) were measured on a Agilent 1200/6210 LC/MS spectrophotometer. Unit cell measurements and intensity data collection was performed on an Bruker APEX II QUAZAR three-circle diffractometer using monochromatized Mo Kα microfocus sealed-tube (λ = 0.71073 Å) using φ and ω technique at 120 K. Thin layer chromatography (TLC) was performed on Merck aluminum-packed silica gel

plates. Purification of the products was performed by column chromatography on silica gel (Merck silica gel 60, 40-63 mm) or preparative TLC on silica gel of Merck ($PF_{254-366nm}$).

General procedure for dihydrofuran-carboxamides (7). A solution of manganese(III) acetate dihydrate (3 mmol, 0.804 g) in 10 mL of glacial acetic acid was heated on oil bath under a nitrogen atmosphere at 80 °C until it dissolved. After $Mn(OAc)_3$ dissolved completely, the solution was cooled down to 60 °C. A solution of 1,3-dicarbonyl compound (2 mmol) and acrylamide (1 mmol) in 5 mL of acetic acid was added to this mixture and the temperature was raised to 70 °C. The reaction was complete when the dark brown color of the solution disappeared (monitoring by TLC). 30 mL water was added to the solution and extracted by $CHCl_3$ (3x20 mL). The combined organic extracts were neutralized with 10 mL of satd $NaHCO_3$ solution, and dried over anhydrous Na_2SO_4 and evaporated. The crude products were purified by column chromatography or preparative TLC (20x20 cm plates, 2 mm thickness) using n-hexane/EtOAc (1:1) as eluent.

***trans*-6,6-Dimethyl-4-oxo-2-phenyl-2,3,4,5,6,7-hexahydro-1-benzofuran-3-carboxamide (7a).** Colorless solid, yield 68%, 193 mg, mp 157-158 °C; IR (ν_{max}, cm^{-1}): 698, 761, 798, 1101, 1382, 1616 (C=C), 1683 (C=O), 2916, 2949, 3188, 3365; ^{1}H NMR (400 MHz, $CDCl_3$): δH 1.29 (6H, s, 2xMe), 2.43 (2H, s, H5), 2.71 (2H, s, H7), 3.97 (1H, d, *J*HH 6.0 Hz, H3), 6.14 (1H, d, *J*HH 6.0 Hz, H2), 7.34 (1H, s, NH), 7.65-7.59 (5H, m, phenyl CH), 7.68 (1H, s, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δC 28.6 (Me), 28.8 (Me), 34.5, 38.3, 41.2, 53.2, 87.9 (C2), 110.3 (C3a), 126.1, 128.1 (2xCH), 129.3, 129.6, 140.8, 173.2 (C7a), 179.5 (C=O), 197.3 (C=O); HRMS (ESI^+): *m/z* $(M+H)^+$ calcd for $C_{17}H_{20}NO_3$: 286.14376; found: 286.14142.

***trans*-4-Oxo-2-phenyl-2,3,4,5,6,7-hexahydro-1-benzofuran-3-carboxamide (7b).** Colorless solid, yield 55%, 141 mg, mp 126-128 °C; IR (ν_{max}, cm^{-1}): 702, 754, 935, 1174, 1388, 1614 (C=C), 1647 (C=O), 1681 (C=O), 2939, 3186, 3381; ^{1}H NMR (400 MHz, $CDCl_3$): δH (400 MHz, $CDCl_3$) 1.94 (2H, m, H6), 2.28 (2H, m, H5), 2.42 (2H, t, *J*HH 6.0 Hz, H7), 3.78 (1H, d, *J*HH 6.0 Hz, H3), 5.34 (1H, s, NH), 6.27 (1H, d, *J*HH 6.0 Hz, H2), 7.21-7.08 (5H, m, phenyl CH), 7.65 (1H, s, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δC 21.4, 24.3, 36.6, 52.9 (3C), 97.1 (C2), 111.1 (C3a), 125.4 (2xCH), 128.6, 128.8 (2xCH), 139.9, 172.1 (C7a), 179.4 (C=O), 196.7(C=O); HRMS (ESI^+): *m/z* $(M+Na)^+$ calcd for $C_{15}H_{15}NO_3Na$: 280.09441; found: 280.09520.

***trans*-Ethyl 4-carbamoyl-2-methyl-5-phenyl-4,5-dihydrofuran-3-carboxylate (7c).** Colorless solid, yield 50%, 137 mg, mp 126-128 °C; IR (ν_{max}, cm^{-1}): 694, 748, 1095, 1263, 1649 (C=C), 1654 (C=O), 1701 (C=O), 2920, 2987, 3199, 3375; ^{1}H NMR (400 MHz, $CDCl_3$): δH 1.31 (3H, t, *J*HH 7.2 Hz, -CH_2CH_3), 2.34 (3H, d, 5*J*HH 1.2 Hz, Me), 3.86 (1H, dq, ^{3}*J*HH 5.2, ^{5}*J*HH 1.2 Hz, H4), 4.22 (2H, q, *J*HH 7.2 Hz, -OCH_2CH_3), 5.70 (1H, s, NH), 6.18 (1H, d, *J*HH 5.2 Hz, H5), 6.91 (1H, s, NH), 7.31-7.26 (2H, m), 7.39-7.33 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δC 14.3 (Me), 15.0 (Me), 56.0 (C4), 60.4170.2 (C2), 84.7 (C5), 101.3 (C3), 125.2 (2xCH), 128.4, 128.8 (2xCH), 140.4, 166.5 (C=O), 175.5 (C=O); HRMS (ESI^+): *m/z* $(M+Na)^+$ calcd for $C_{15}H_{17}NO_4Na$: 298.10497; found: 298.10354.

***trans*-4-Acetyl-5-methyl-2-phenyl-2,3-dihydrofuran-3-carboxamide (7d).** Colorless solid, yield 41%, 100 mg, mp 125-128 °C; IR (ν_{max}, cm^{-1}): 692, 748, 941, 1261, 1581 (C=C), 1660 (C=O), 1676 (C=O), 2848, 2914, 3186, 3348; ^{1}H NMR (400 MHz, $CDCl_3$): δH 2.53 (3H, s, Me), 2.56 (3H, s, Me), 4.15 (1H, d, *J*HH 4.81 Hz, H3), 5.80 (1H, s, NH), 6.38 (1H, d, *J*HH 4.83 Hz, H2), 7.22 (1H, s, NH), 7.43 (2H, d, *J*HH 6.11 Hz, phenyl CH), 7.49 (3H, m, phenyl CH); ^{13}C NMR (100 MHz, $CDCl_3$): δC 16.2 (Me), 29.3 (Me), 55.8 (3C), 84.4 (2C), 114.0 (4C), 125.2 (2xCH), 128.5 (2xCH), 128.8, 140.1, 169.9 (5C), 173.2 (C=O), 194.4 (C=O); HRMS (ESI^+): *m/z* $(M+H)^+$ calcd for $C_{14}H_{16}NO_3$: 246.11246; found: 246.11111.

***trans*-6,6-Dimethyl-4-oxo-2-(thiophen-2-yl)-2,3,4,5,6,7-hexahydro-1-benzofuran-3-carboxamide (7e).** Colorless solid, yield 55%, 160 mg, mp 153-155 °C; IR (ν_{max}, cm^{-1}): 613, 640, 713, 800, 1060, 1101, 1379, 1612 (C=C), 1685 (C=O), 2924, 2952, 3184, 3315; ^{1}H NMR (400 MHz, $CDCl_3$): δH 1.14 (3H, s, Me), 1.15 (3H, s, Me), 2.34 (2H, s, H5), 2.40 (2H, d, *J*HH 2.0 Hz, H7), 4.11 (1H, d, *J*HH 5.60 Hz, H3), 5.39 (1H, s, NH), 6.68 (1H, d, *J*HH 5.60 Hz, H2), 6.99 (1H, dd, *J*HH 5.20, 3.60 Hz, thiophene CH), 7.11 (1H, d, *J*HH 3.2 Hz, thiophene CH), 7.30 (1H, d, *J*HH 4.8 Hz, thiophene CH), 7.75 (1H, s, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δC 28.7 (2xMe), 34.6, 38.3, 51.2, 52.9 (C3), 83.9 (C2), 109.8 (C3a), 126.3, 126.6, 127.3, 142.5, 171.7 (C7a), 177.9 (C=O), 196.3 (C=O); HRMS (ESI^+): *m/z* $(M+Na)^+$ calcd for $C_{15}H_{17}NO_3SNa$: 314.08213; found: 314.08170.

***trans*-4-Oxo-2-(thiophen-2-yl)-2,3,4,5,6,7-hexahydro-1-benzofuran-3-carboxamide (7f).** Colorless solid, yield 54%, 142 mg, mp 100-103 °C; IR (ν_{max}, cm^{-1}): 705, 756, 837, 904, 1377, 1400, 1608 (C=C), 1670 (C=O), 1697 (C=O), 2902, 2947, 3192, 3315; ^{1}H NMR (400 MHz, $CDCl_3$): δH 2.09 (2H, m, H6), 2.45 (2H, m, H5), 2.53 (2H, t, *J*HH 6.0 Hz, H7), 4.10 (1H, d, *J*HH 5.2 Hz, H3), 5.80 (1H, s, NH), 6.65 (1H, d, *J*HH 5.60 Hz, H2), 6.99 (1H, dd, *J*HH 4.8, 3.6 Hz, thiophene CH), 7.11 (1H, d, *J*HH 3.2 Hz, thiophene CH), 7.31 (1H, dd, *J*HH 4.8, 1.2 Hz, thiophene CH), 7.76 (1H, s, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δC 21.6, 24.5, 36.7, 53.0 (C3), 83.6 (C2), 111.4 (C3a), 126.3, 126.6, 127.3, 142.3, 171.9 (C7a), 178.7 (C=O), 196.9 (C=O); HRMS (ESI^+): *m/z* $(M+Na)^+$ calcd for $C_{13}H_{13}NO_3SNa$: 286.05083; found: 286.05155.

***trans*-Ethyl 4-carbamoyl-2-methyl-5-(thiophen-2-yl)-4,5-dihydrofuran-3-carboxylate (7g).** Colorless solid, yield 46%, 129 mg, mp 82-86 °C; IR (ν_{max}, cm^{-1}): 696, 765, 975, 1095, 1201, 1649 (C=C), 1658 (C=O), 1701 (C=O), 2920, 2981, 3197, 3379; ^{1}H NMR (400 MHz, $CDCl_3$): δH 1.36 (3H, t, *J*HH 7.12 Hz, Me), 2.30 (3H, d, *J*HH 1.20 Hz, Me), 4.04 (1H, dd, *J*HH 4.62, 1.24 Hz, H3), 4.27 (2H, q, *J*HH 7.13 Hz, -OCH_2-),5.35 (1H, s, NH), 6.46 (1H, d, *J*HH 4.65 Hz, H2), 7.00 (1H, dd, *J*HH 5.03, 3.56 Hz, thiophene CH), 7.10 (1H, d, *J*HH 3.52 Hz, thiophene CH), 7.29 (1H, s, NH), 7.31 (1H, dd, JHH 5.07, 1.12 Hz, thiophene CH); ^{13}C NMR (100 MHz, $CDCl_3$): δC 14.5 (Me), 15.4 (Me), 55.9, 60.8 (C4), 81.0 (C5), 101.7 (C3), 125.7, 126.1, 127.1, 143.0, 166.7 (C2), 169.7 (C=O), 172.9 (C=O); HRMS (ESI^+): *m/z* $(M+Na)^+$ calcd for $C_{13}H_{15}NO_4SNa$: 304.06139; found: 304.06149.

***trans*-4-Acetyl-5-methyl-2-(thiophen-2-yl)-2,3-dihydrofuran-3-carboxamide (7h).** Yellow oil, yield 52%, 130 mg; IR (ν_{max}, cm^{-1}): 704, 750, 935, 827, 1207, 1384, 1578 (C=C), 1670 (C=O), 2914, 3006, 3190, 3415; ^{1}H NMR (400 MHz, $CDCl_3$): δH 2.36 (3H, s, Me), 2.43 (3H, s,

Me), 4.16 (1H, d, *J* HH 4.00 Hz, H3), 5.64 (1H, s, NH), 6.47 (1H, d, *J*HH 4.10 Hz, H2), 7.00 (1H, t, *J*HH 4.52 Hz, thiophene CH), 7.08 (1H, d, *J*HH 3.15 Hz, thiophene CH), 7.15 (1H, s, NH), 7.30 (1H, d, *J* 5.09 Hz, thiophene CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ C 16.5 (Me), 29.5 (Me), 55.7 (C3), 80.8 (C2), 114.0 (C4), 125.9, 126.2, 127.1, 142.5, 169.5 (C5), 172.9 (C=O), 194.6 (C=O); HRMS (ESI^+): *m/z* $(M+H)^+$ calcd for $C_{12}H_{14}NO_3S$: 252.06889; found: 252.06908.

***trans*-6,6-Dimethyl-2-(5-methylfuran-2-yl)-4-oxo-2,3,4,5,6,7-hexahydro-1-benzofuran-3-carboxamide (7i).** Yellow solid, yield 80%, 231 mg, mp 143-145 °C; IR (ν_{max}, cm^{-1}): 621, 665, 781, 879, 1020, 1070, 1251, 1388, 1591 (C=C), 1614 (C=O), 1683 (C=O), 2920, 2964, 3175, 3383; ^{1}H NMR (400 MHz, $CDCl_3$): δH 1.11 (6H, s, Me), 2.26 (3H, s, Me), 2.32 (2H, d, *J*HH 1.60 Hz, H5), 2.35 (2H, d, *J*HH 1.20 Hz, H7), 4.25 (1H, d, *J*HH 6.0 Hz, H3), 5.53 (1H, s, NH), 5.94 (1H, dq, *J*HH 3.60, 0.40 Hz, furan CH), 6.34 (1H, d, *J*HH 3.2 Hz, furan CH), 6.35 (1H, d, *J*HH 6.0 Hz, H2), 7.84 (1H, s, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δC 13.9, 28.6, 28.8, 34.5, 38.3, 48.7, 51.1 (C3), 81.3 (C2), 106.9, 110.3, 111.0, 149.2, 154.1, 171.9 (C7a), 178.2 (C=O), 196.2 (C=O); HRMS (ESI^+): *m/z* $(M+H)^+$ calcd for $C_{16}H_{20}NO_4$: 290.13868; found: 290.13923.

Ethyl *trans*-3-carbamoyl-5,5'-dimethyl-2,3-dihydro-[2,2'-bifuran]-4-carboxylate (7j). Yellow solid, yield 67%, 186 mg, mp 133-135 °C; IR (ν_{max}, cm^{-1}): 653, 796, 962, 1124, 1217, 1319, 1381, 1635 (C=C), 1654 (C=O), 1678 (C=O), 2918, 2985, 3165, 3352; ^{1}H NMR (400 MHz, $CDCl_3$): δH 1.32 (3H, t, *J*HH 7.20 Hz, Me), 2.23 (3H, s, Me), 2.27 (3H, s, 5.84 (1H, s, NH), Me), 4.14 (1H, d, *J*HH 5.60 Hz, H3´),4.23 (2H, q, *J*HH 7.20 Hz, –OCH_2-),5.92 (1H, d, *J*HH 3.20 Hz, furan CH), 6.08 (1H, d, *J*HH 5.60 Hz, H2´),6.28 (1H, d, *J*HH 3.20 Hz, furan CH), 6.95 (1H, s, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δC 13.9 (Me), 14.6(Me), 15.3(Me), 52.1, 60.6, 78.6, 102.0, 106.7, 110.4, 149.8, 153.7, 166.8 (C=O), 169.8 (C5´), 173.3 (C=O); HRMS (ESI^+): *m/z* $(M+Na)^+$ calcd for $C_{14}H_{17}NO_5Na$: 302.09989; found: 302.10051.

***trans*-4-Acetyl-5,5'-dimethyl-2,3-dihydro-[2,2'-bifuran]-3-carboxamide (7k).** Pale yellow solid, yield 70%, 174 mg, mp 150-152 °C; IR (ν_{max}, cm^{-1}): 663, 796, 900, 943, 1213, 1392, 1595 (C=C), 1672 (C=O), 1681 (C=O), 2848, 2918, 3153, 3327; ^{1}H NMR (400 MHz, $CDCl_3$): δH 2.26 (3H, s, Me), 2.29 (3H, s, Me), 2.37 (3H, d, *J*HH 0.8 Hz, Me), 4.24 (1H, d, *J*HH 5.2 Hz, H3´),5.70 (1H, s, NH), 5.91 (1H, dq, *J*HH 3.2, 0.8 Hz, furan CH), 6.11 (1H, d, *J*HH 5.2 Hz, H2´),6.26 (1H, d, *J*HH 3.2 Hz, furan CH), 7.14 (1H, s, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δC 13.9 (Me), 16.5 (Me), 29.6 (Me), 52.0, 78.4, 106.7, 110.5, 114.7, 149.6, 153.8, 169.9 (C5´), 173.1 (C=O), 194.5 (C=O); HRMS (ESI^+): *m/z* $(M+Na)^+$ calcd for $C_{13}H_{15}NO_4Na$: 272.08932; found: 272.08976.

***trans*-6,6-Dimethyl-4-oxo-2-(thiophen-3-yl)-2,3,4,5,6,7-hexahydrobenzofuran-3-carboxamide (7l).** Colorless solid, yield 36%, 104 mg, mp 148-150 °C; IR (ν_{max}, cm^{-1}): 700, 965, 1095, 1212, 1618 (C=C), 1675 (C=O), 1703 (C=O), 2920, 2983, 3194, 3362; ^{1}H NMR (400 MHz, $CDCl_3$): δH 1.14 (6H, s), 2.32 (2H, s), 2.42 (2H, s), 4.00 (1H, d, *J*HH 6.0 Hz, H3), 5.94 (1H, s, NH), 6.50 (1H, d, *J*HH 6.0 Hz, H2), 7.01 (1H, dd, *J*HH 4.8, 0.8 Hz, thiophene CH), 7.28 (1H, d, *J*HH 7.2 Hz, thiophene CH), 7.35 (1H, dd, *J*HH 5.2, 4.8 Hz, thiophene CH), 7.80 (1H, s, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δC 28.3, 28.6, 34.2, 38.1, 50.9, 51.8, 84.1, 109.6, 122.2,

124.9, 127.3, 140.6, 171.9 (C=O), 178.1 (C7a), 196.0 (C=O); HRMS (ESI^+): *m/z* $(M+Na)^+$ calcd for $C_{15}H_{17}NO_3SNa$: 314.08213; found: 314.08881.

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Supplementary Material

Copies of NMR spectra for all compounds, X-ray crystal data for compounds **7b**, **7i** and **7j** (CCDC nos. 997073, 997070 and 997071, respectively). Supplementary data and crystallographic data associated with this article can be found in the online version, at http://dx.doi.org/

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