

A facile regio- and stereoselective synthesis of *trans*-ethyl 5-aryl-4-aryl-2-[(arylsulfonyl)methyl]-4,5-dihydrofuran-3-carboxylates

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Abstract

A library of novel *trans*-ethyl 5-aryl-4-aryl-2-[(arylsulfonyl)methyl]-4,5-dihydrofuran-3-carboxylates were synthesized regio- and stereoselectively in good yields by a three-component domino reaction of ethyl-3-oxo-4-(arylsulfonyl)butanoates, aromatic aldehydes and *N*-phenacylpyridinium bromide in presence of triethylamine in acetonitrile under heating. This transformation generates C–O, C–C and C=C bonds and presumably proceeds via an α,β -unsaturated ketosulfonyl ester generation/Michael addition/intramolecular cyclisation domino sequence.

Keywords: Domino reaction, ethyl-3-oxo-4-(arylsulfonyl)butanoates, aromatic aldehyde, dihydrofuran

Introduction

Multicomponent reactions (MCRs) have emerged as an important synthetic strategy for generating complex scaffolds of structural diversity from simple molecules. In this protocol, three or more reactants are assembled together in a one pot operation to form a new product comprising substantial portions of all the components.¹⁻³ MCRs, besides generating complex structures, provide operational simplicity and synthetic efficiency over conventional linear multistep reactions. The most useful MCRs have additional advantages of selectivity, synthetic convergence, atom-economy and green credentials.⁴⁻⁹ Further, MCRs are perfectly amenable for automation to generate combinatorial libraries of biologically relevant heterocyclic scaffolds and hence play a pivotal role in lead identification and drug development programmes.

Furan and di-/tetrahydrofuran sub-structures are prevalent in diverse classes of natural products and biologically active heterocycles, besides serving as versatile building blocks in organic synthesis¹⁰⁻¹² and several synthetically derived sulfones also show interesting biological activities (Figure 1). For instance, dapsone **1** is an important drug currently used for the treatment of leprosy in conjunction with other drugs.¹³ 1-(4-Trifluoromethyl)-phenyl-2-(phenylsulfonyl)ethanone **2** inhibits of 11 β -hydroxysteroid dehydrogenase activity,¹⁴ whilst substituted (*E*)-(2-chloro-2-(phenylsulfonyl)vinyl)benzenes **3** show antiplasmodial activity.¹⁵ Sulfones appended to furan moiety also show important biological activities. For example, functionalized vinyl dihydrofuryl sulfones **4** and tetrahydrofuryl sulfones **5** show antiprotozoal¹⁶ and antimycobacterial activity¹⁷ respectively. Consequently, in the present work, we report the regio- and stereoselective synthesis of highly functionalized biologically relevant dihydrofurans bearing arylsulfonyl moiety **6**.

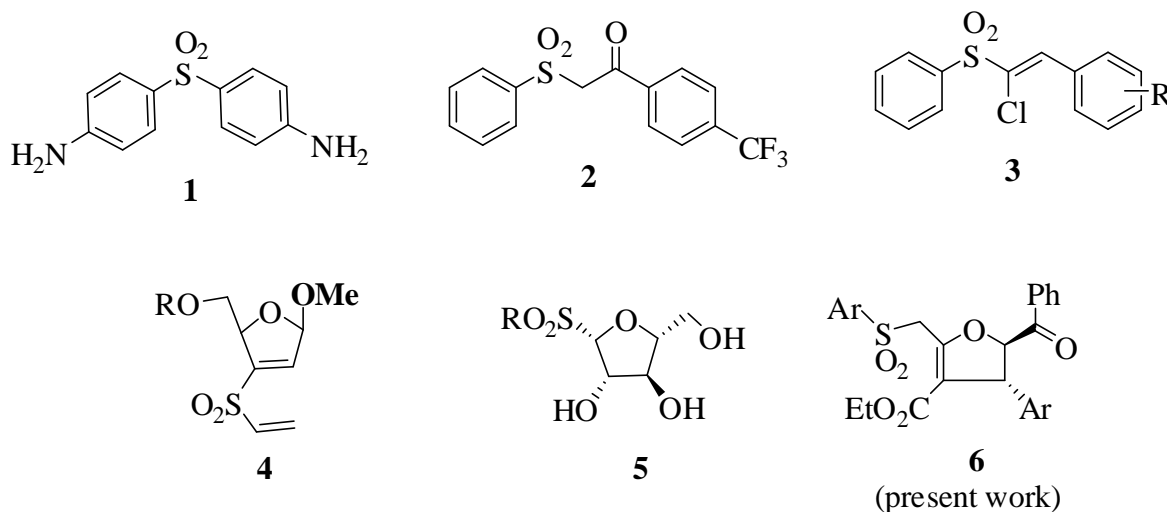


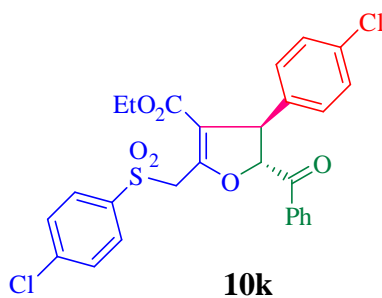
Figure 1

Previously reported synthesis of dihydrofuran derivatives include the reactions of sulfur ylide with α -ylidene- β -diketones via [4+1] annulation reaction,^{18,19} one-step cyclization of β -ketosulfides of benzothiazole and aldehydes in ionic liquids,²⁰ reaction of β -ketopolyfluoroalkane sulfones with aldehydes,²¹ reactions of 1,3-dicarbonyl compounds with appropriate olefins,²²⁻²⁴ or α -bromonitroalkenes.²⁵ Cyclization as well as ring enlargement reaction are mostly used for the construction of dihydrofurans.²⁶⁻²⁹ The reaction of pyridinium ylides with α,β -unsaturated carbonyl systems,³⁰⁻³³ is one of the most familiar and frequently used synthetic methods for the construction of dihydrofurans, the ylides, in turn, can be easily prepared by deprotonation of the α -halogenocarbonyl compounds. Present study constitutes a part of our ongoing research program launched on the exploration of tandem/domino/sequential multi-component reactions for the assembly of novel heterocycles.³⁴⁻³⁸

Results and Discussion

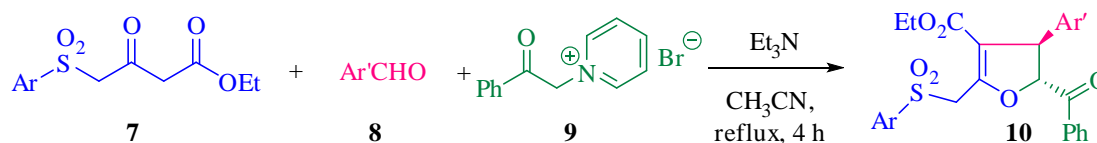
In the present investigation, a library of novel *trans*-ethyl 5-aryyl-4-aryl-2-[(arylsulfonyl)methyl]-4,5-dihydrofuran-3-carboxylates **10** were synthesized regio- and stereoselectively in good yields by a three-component domino reaction of ethyl-3-oxo-4-(arylsulfonyl)butanoates **7**, aromatic aldehydes **8** and *N*-phenacylpyridinium bromide **9** in the presence of triethylamine in acetonitrile under heating. The base- and solvent-screen for the model reaction leading to **10k** was studied and the results are presented in Table 1. The model reaction was carried out with ethyl 3-oxo-4-(4-chlorophenylsulfonyl)butanoate **7n** (1 mmol), *p*-chlorobenzaldehyde **8n** (1 mmol) and *N*-phenacylpyridinium bromide **9** (1 mmol) in presence of base (2.5 mmol) in various solvents under heating to reflux. It is found that Et₃N is more efficient for this transformation than either DBU or piperidine. A maximum yield of **10k** (82%) was obtained, when Et₃N was employed as the base and CH₃CN as the solvent.

Table 1. Base- and solvent-screen for the synthesis of **10k**



Entry	Base	Solvent	Reaction time (h)	Yield of 10k (%)
1	NH ₄ OAc	CH ₃ CN	4	45
2	K ₂ CO ₃	CH ₃ CN	4	60
3	Et ₃ N	CH ₃ CN	4	82
4	DBU	CH ₃ CN	4	52
5	Et ₃ N	CH ₂ Cl ₂	4	30
6	Et ₃ N	MeOH	4	55
7	Et ₃ N	DMF	4	65
8	Et ₃ N	THF	4	68
9	Piperidine	THF	4	48

This optimized procedure was used for preparing a series of dihydrofuran derivatives employing substituted ethyl-3-oxo-4-(arylsulfonyl)butanoates, *N*-phenacylpyridinium bromide and aromatic aldehydes (Scheme 1. Table 2). Typically, the reaction was carried out by refluxing the reaction mixture of ethyl-3-oxo-4-(arylsulfonyl)butanoates **7** (1 mmol), aromatic aldehyde **8** (1 mmol) and *N*-phenacylpyridinium bromide **9** (1 mmol) in presence of Et₃N (2.5 mmol) in



Scheme 1. Synthesis of *trans*-ethyl-5-aryl-4-aryl-2-[(arylsulfonyl)methyl]-4,5-dihydrofuran-3-carboxylates **10**.

Table 2. Yield and m.p. of **10**

Entry	Comp.	Ar	Ar'	M.p (°C)	Yield of 10 (%)
1	10a	<i>p</i> -MeC ₆ H ₄	C ₆ H ₅	126-127	70
2	10b	<i>p</i> -MeC ₆ H ₄	<i>p</i> -MeC ₆ H ₄	112-113	75
3	10c	<i>p</i> -MeC ₆ H ₄	<i>p</i> -ClC ₆ H ₄	148-149	72
4	10d	<i>p</i> -MeC ₆ H ₄	<i>p</i> -O ₂ NC ₆ H ₄	137-138	71
5	10e	<i>p</i> -MeC ₆ H ₄	<i>o</i> -MeOC ₆ H ₄	115-116	74
6	10f	<i>p</i> -MeC ₆ H ₄	<i>o</i> -BrC ₆ H ₄	132-133	70
7	10g	<i>p</i> -MeC ₆ H ₄	<i>m</i> -FC ₆ H ₃	118-119	77
8	10h	<i>p</i> -MeC ₆ H ₄	<i>o,p</i> -Cl ₂ C ₆ H ₄	123-124	75
9	10i	<i>p</i> -ClC ₆ H ₄	<i>p</i> -MeC ₆ H ₄	104-105	80
10	10j	<i>p</i> -ClC ₆ H ₄	<i>p</i> -Pr ⁱ C ₆ H ₄	127-128	72
11	10k	<i>p</i> -ClC ₆ H ₄	<i>p</i> -ClC ₆ H ₄	139-140	82
12	10l	<i>p</i> -ClC ₆ H ₄	<i>p</i> -MeOC ₆ H ₄	120-121	73
13	10m	<i>p</i> -ClC ₆ H ₄	<i>o</i> -BrC ₆ H ₄	128-129	75
14	10n	<i>p</i> -ClC ₆ H ₄	<i>m</i> -BrC ₆ H ₃	130-131	77
15	10o	<i>p</i> -ClC ₆ H ₄	<i>m</i> -FC ₆ H ₃	115-116	72
16	10p	<i>p</i> -ClC ₆ H ₄	<i>o,p</i> -Cl ₂ C ₆ H ₄	139-140	70

CH₃CN. After the completion of the reaction (TLC), the solvent was removed in a rotary evaporator and the residue was purified by column chromatography using ethyl acetate-pet.ether (1:4 v/v) to give *trans*-ethyl 5-aryl-4-aryl-2-[(arylsulfonyl)methyl]-4,5-dihydrofuran-3-carboxylates **10** in good yields (70-82%).

The structure of the *trans*-4,5-dihydrofurans is in accord with elemental analyses and ^1H , ^{13}C and 2D NMR spectroscopic data as illustrated for a representative example, **10n** (Figure 2). In the ^1H NMR spectrum of **10n**, H-4 appearing as a doublet at 4.52 ppm (J 5.2 Hz) shows a H,H-COSY correlation with H-5 appearing as a doublet at 5.69 ppm (J 5.2 Hz). The J value shows that these H-4 and H-5 are in *trans* relationship. The H-4 shows a C,H-COSY correlation with the carbon signal at 50.2 ppm and also shows HMBCs with the C-5, C-3, C-2', C-1' ipso, C-2 and ketocarbonyl at 89.5, 112.4, 129.1, 139.8, 156.9 and 192.0 ppm respectively (Figures 2 and 3).

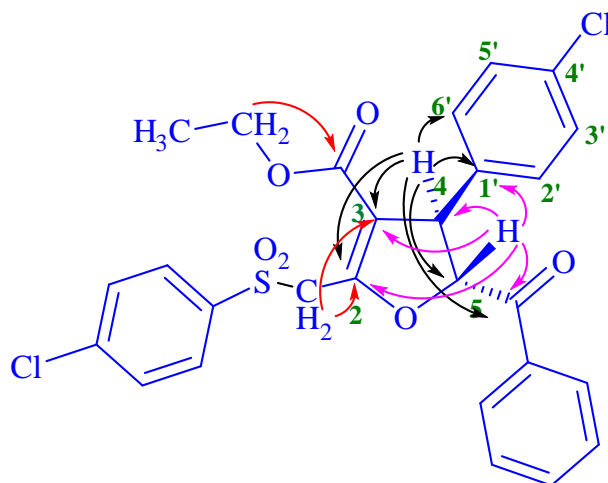


Figure 2. Selected HMBCs of **10n**.

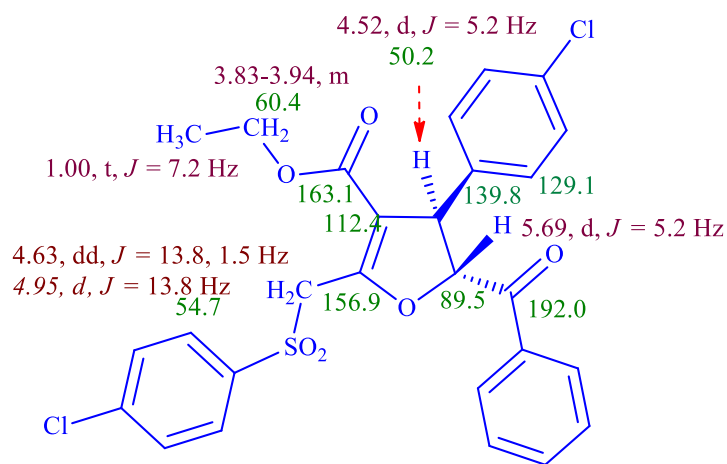
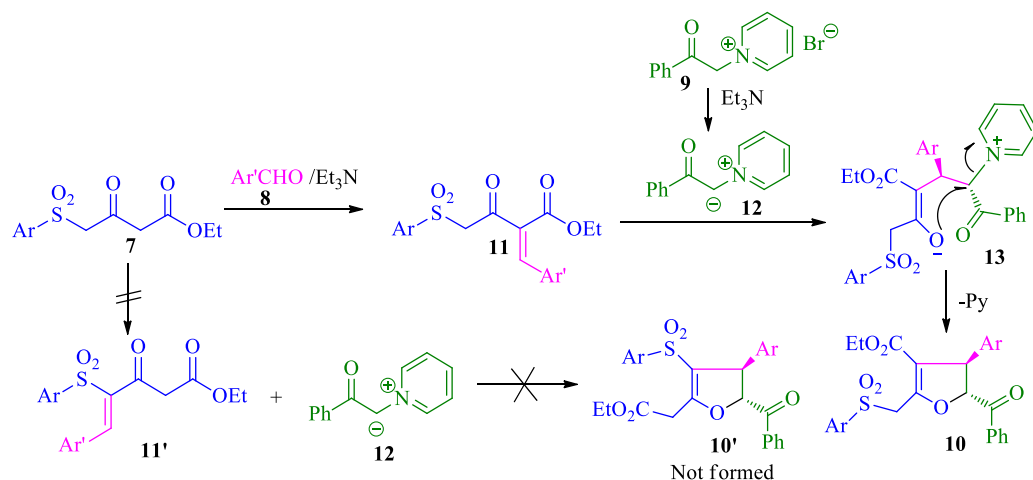


Figure 3. Selected NMR data of **10n**.

The H-5 shows a C,H-COSY correlation with the carbon signal at 89.5 ppm and shows HMBCs with C-4, C-3, C-1' and C-2 at 50.2, 112.4, 139.8 and 156.9 ppm respectively. The diastereotopic methylene hydrogens attached to the sulfonyl group give a doublet at 4.95 ppm (J 13.8 Hz) and a doublet of doublets at 4.63 ppm (J 13.8, 1.5 Hz) and these hydrogens show C,H-



Scheme 2. Plausible mechanism for the formation of *trans*-ethyl 5-aryl-4-aryl-2-[(arylsulfonyl)methyl]-4,5-dihydrofuran-3-carboxylates **10**.

Conclusions

In conclusion, the present work describes the synthesis of a series of novel *trans*-ethyl 5-aryl-4-aryl-2-[(arylsulfonyl)methyl]-4,5-dihydrofuran-3-carboxylates in a regio- and stereoselective manner in good yields via three-component domino reactions of ethyl-3-oxo-4-(arylsulfonyl)butanoates, aromatic aldehydes and N-phenacylpyridinium bromides in presence of triethylamine in acetonitrile under heating. This transformation generates C–O, C–C and C=C bonds and presumably proceeds via an α,β -unsaturated ketosulfonyl ester generation/Michael addition/intramolecular cyclisation domino sequence.

Experimental Section

General. Melting points were measured in open capillary tubes and are uncorrected. The ^1H NMR, ^{13}C NMR, DEPT, H,H-COSY, C,H-COSY and HMBC spectra were recorded on a Bruker (Avance) 300 MHz NMR instrument using TMS as internal standard and CDCl_3 as solvent. Standard Bruker software was used throughout. Chemical shifts are given in parts per million (δ scale) and the coupling constants are given in Hertz. Silica gel-G plates (Merck) were used for TLC analysis with a mixture of pet. ether (60–80 °C) and ethyl acetate as eluent. Elemental analyses were performed on a Perkin Elmer 2400 Series II Elemental CHNS analyzer.

General synthesis of *trans*-ethyl 5-aryl-4-aryl-2-[(arylsulfonyl)methyl]-4,5-dihydro-furan-3-carboxylates **10.** A mixture of ethyl 3-oxo-4-(arylsulfonyl)butanoate **7** (1 mmol), aromatic aldehyde **8** (1 mmol) and N-phenacylpyridinium bromide **9** (1 mmol) in the presence of Et_3N

(2.5 mmol) in CH₃CN was heated to reflux for 4 h. After completion of the reaction (TLC), the solvent was removed in a rotavapor and was purified by flash column chromatography with pet. ether-ethyl acetate (4:1 v/v) mixture to afford pale yellow solid (**10a-t**). Spectroscopic data for all the compounds are given below.

trans-Ethyl5-benzoyl-4-phenyl-2-((p-methylphenylsulfonyl)methyl)-4,5-dihydrofuran-3-carboxylate (10a). Pale yellow solid, yield 70%, mp 126 – 127 °C. ¹H NMR (300 MHz, CDCl₃) δ_H: 0.97 (t, 3H, *J* 7.2 Hz, CH₃), 2.41(s, 3H, CH₃) 3.82- 3.94 (m, 2H, CH₂), 4.51 (d, 1H, *J* 5.1 Hz), 4.55 (d, 1H, *J* 13.8 Hz), 5.01 (d, 1H, *J* 13.8 Hz,), 5.44 (d, 1H, *J* 5.1 Hz), 7.22-7.38 (m, 7H, Ar-H), 7.45 (t, 2H, *J* 7.1 Hz, Ar-H), 7.61 (t, 1H, *J* 7.1 Hz, Ar-H), 7.28 (d, 2H, *J* 7.1 Hz, Ar-H), 7.86 (d, 2H, *J* 7.1 Hz, Ar-H). ¹³C NMR (75 MHz, CDCl₃) δ_C: 13.7, 21.5, 50.9, 54.8, 60.0, 89.7, 112.3, 127.5, 128.5, 128.7, 129.0, 129.5, 133.3, 134.0, 136.2, 141.3, 144.8, 156.9, 163.2, 192.3. Anal. Calcd for C₂₈H₂₆O₆S : C, 68.55. H, 5.34% Found C, 68.67; H, 5.25%.

trans-Ethyl5-benzoyl-4-p-tolyl-2-((p-methylphenylsulfonyl)methyl)-4,5-dihydrofuran-3-carboxylate (10b). Pale yellow solid; yield 68%, mp 112-113 °C. ¹H NMR (300 MHz, CDCl₃) δ_H: 0.99 (t, 3H, *J* 7.2 Hz, CH₃), 2.36 (s, 3H, CH₃), 2.41(s, 3H, CH₃) 3.81- 3.91 (m, 2H, CH₂), 4.45 (d, 1H, *J* 5.1 Hz), 4.55 (d, 1H, *J* 13.8 Hz), 4.99 (d, 1H, *J* 13.8 Hz,), 5.71 (d, 1H, *J* 5.1 Hz), 7.13 (d, 2H, *J* 8.1 Hz, Ar-H), 7.16 (d, 2H, *J* 8.1 Hz, Ar-H), 7.26-7.30 (m, 2H, Ar-H) 7.45 (t, 2H, *J* 7.8 Hz, Ar-H), 7.61 (t, 1H, *J* 7.8 Hz, Ar-H), 7.82 (d, 2H, *J* 7.2 Hz, Ar-H), 7.87 (d, 2H, *J* 8.1 Hz, Ar-H). ¹³C NMR (75 MHz, CDCl₃) δ_C: 13.7, 21.0, 21.5, 50.6, 54.9, 60.0, 89.8, 112.4, 127.4, 128.1, 128.5, 129.0, 129.4, 129.9, 133.3, 133.9, 136.3, 137.2, 138.3, 144.7, 156.8, 163.2, 192.4. Anal. Calcd for C₂₉H₂₈O₆S : C, 69.03; H, 5.59% Found C, 69.13; H, 5.65%.

trans-Ethyl5-benzoyl-4-(4-chlorophenyl)-2-((p-methylphenylsulfonyl)methyl)-4,5-dihydrofuran-3-carboxylate (10c). Pale yellow solid; yield 72%, mp 148-149 °C ¹H NMR (300 MHz, CDCl₃) δ_H: 1.01 (t, 3H, *J* 7.2 Hz, CH₃), 2.43 (s, 3H, CH₃), 3.82- 3.95 (m, 2H, CH₂), 4.50 (d, 1H, *J* 5.1 Hz), 4.54 (d, 1H, *J* 13.8 Hz), 5.02 (d, 1H, *J* 13.8 Hz,), 5.68 (d, 1H, *J* 5.1 Hz), 7.26 – 7.35 (m, 5H, Ar-H), 7.46 (t, 2H, *J* 7.1 Hz, Ar-H), 7.63 (t, 2H, *J* 7.1 Hz, Ar-H), 7.80 – 7.87 (m, 4H, Ar-H). ¹³C NMR (75 MHz, CDCl₃) δ_C: 13.8, 21.6, 50.2, 54.8, 60.2, 89.5, 112.1, 126.6, 127.5, 128.4, 128.8, 129.0, 129.0, 129.6, 133.4, 134.1, 136.4, 139.9, 144.9, 157.2, 163.9, 192.6. Anal. Calcd for : C₂₈H₂₅ClO₆S: C, 64.06; H, 4.80% Found C, 63.95; H, 4.87%.

trans-Ethyl5-benzoyl-4-(4-nitrophenyl)-2-((p-methylphenylsulfonyl)methyl)-4,5-dihydrofuran-3-carboxylate (10d). Pale yellow solid; yield 71%, mp 137-138 °C. ¹H NMR (300 MHz, CDCl₃) δ_H: 1.04 (t, 3H, *J* 7.2 Hz, CH₃), 2.47 (s, 3H, CH₃), 3.90- 3.99 (m, 2H, CH₂), 4.52 (d, 1H, *J* 13.8 Hz), 4.80 (d, 1H, *J* 5.1 Hz), 5.07 (d, 1H, *J* 13.8 Hz,), 5.70 (d, 1H, *J* 5.1 Hz), 7.33 – 7.53 (m, 6H, Ar-H), 7.67 (t, 1H, *J* 7.1 Hz, Ar-H), 7.85 – 7.88 (m, 4H, Ar-H), 8.26 (d, 2H, *J* 7.1 Hz Ar-H). ¹³C NMR (75 MHz, CDCl₃) δ_C: 13.8, 21.6, 26.8, 54.8, 60.4, 89.1, 111.7, 124.1, 128.3, 128.6, 128.9, 129.1, 129.7, 133.2, 134.3, 136.4, 145.1, 147.4, 148.7, 157.7, 162.8, 191.6 Anal. Calcd for C₂₈H₂₅NO₈S: C, 62.79; H, 4.71; N, 2.62% Found C, 62.88; H, 4.61; N 2.71%.

trans-Ethyl5-benzoyl-4-(2-methoxyphenyl)-2-((p-methylphenylsulfonyl)methyl)-4,5-dihydrofuran-3-carboxylate (10e). Pale yellow solid; yield 74%, mp 115-116 °C. ¹H NMR (300 MHz, CDCl₃) δ_H: 0.99 (t, 3H, *J* 7.2 Hz, CH₃), 2.42(s, 3H, CH₃), 3.61 (s, 3H, OCH₃), 3.84- 3.97

(m, 2H, CH₂), 4.58 (d, 1H, *J* 13.8 Hz), 4.94 (d, 1H, *J* 5.1 Hz), 4.97 (d, 1H, *J* 13.8 Hz), 5.67 (d, 1H, *J* 5.1 Hz), 6.85 – 7.61 (m, 9H, Ar-H), 7.83 – 7.89 (m, 4H, Ar-H). ¹³C NMR (75 MHz, CDCl₃) δ_C: 13.8, 21.5, 44.7, 54.8, 55.0, 59.9, 89.2, 111.0, 120.7, 126.2, 127.3, 128.5, 128.8, 129.0, 129.2, 129.5, 133.6, 134.0, 135.8, 136.2, 140.3, 144.7, 156.5, 163.5, 192.8. Anal. Calcd for : C₂₉H₂₈O₇S : C, 66.91; H, 5.42% Found C, 69.98; H, 5.33%.

trans-Ethyl5-benzoyl-4-(2-bromophenyl)-2-((*p*-methylphenylsulfonyl)methyl)-4,5-dihydrofuran-3-carboxylate (10f). Pale yellow solid; yield 69%, mp 132-133 °C. ¹H NMR (300 MHz, CDCl₃) δ_H: 0.99 (t, 3H, *J* 7.2 Hz, CH₃), 2.42(s, 3H, CH₃), 3.84- 3.97 (m, 2H, CH₂), 4.54 (d, 1H, *J* 13.8 Hz), 5.01 (d, 1H, *J* 13.8 Hz), 5.22 (d, 1H, *J* 5.1 Hz), 5.68 (d, 1H, *J* 5.1 Hz), 7.27 – 7.64 (m, 9H, Ar-H), 7.83 – 7.87 (m, 4H, Ar-H). ¹³C NMR (75 MHz, CDCl₃) δ_C: 13.8, 21.6, 49.1, 54.7, 60.1, 88.8, 112.2, 123.8, 126.3, 127.4, 127.9, 128.5, 128.8, 129.0, 129.6, 132.8, 133.6, 134.0, 136.4, 140.4, 144.9, 157.5, 163.2, 191.6 Anal. Calcd for C₂₈H₂₅BrO₆S : C, 59.06; H, 4.42% Found C, 59.18; H, 4.52%.

trans-Ethyl5-benzoyl-4-(3-fluorophenyl)-2-((*p*-methylphenylsulfonyl)methyl)-4,5-dihydrofuran-3-carboxylate (10g). Pale yellow solid; yield 64%, mp 118-119 °C. ¹H NMR (300 MHz, CDCl₃) δ_H: 0.99 (t, 3H, *J* 7.2 Hz, CH₃), 2.41(s, 3H, CH₃), 3.79- 3.97 (m, 2H, CH₂), 4.53 (d, 1H, *J* 13.8 Hz), 4.56 (d, 1H, *J* 5.1 Hz), 5.02 (d, 1H, *J* 13.8 Hz), 5.68 (d, 1H, *J* 5.1 Hz), 6.88 – 7.05 (m, 2H, Ar-H), 7.28 – 7.38 (m, 4H, Ar-H), 7.46 (t, 2H, *J* 8.1 Hz, Ar-H), 7.62 (t, 1H, *J* 8.1 Hz, Ar-H), 7.83 (d, 2H, *J* 8.1 Hz, Ar-H), 7.86 (d, 2H, *J* 8.1 Hz, Ar-H). ¹³C NMR (75 MHz, CDCl₃) δ_C: 13.8, 21.6, 50.3, 54.8, 60.2, 89.4, 111.9, 123.3, 126.4, 127.6, 128.2, 128.5, 128.8, 129.1, 129.6, 130.0, 130.4, 133.3, 134.2, 136.5, 145.0, 157.3, 163.0, 192.1. Anal. Calcd for: C₂₈H₂₅FO₆S : C, 66.13; H, 4.95% Found C, 66.06; H, 5.05%.

trans-Ethyl5-benzoyl-4-(2,4-dichlorophenyl)-2-((*p*-methylphenylsulfonyl)methyl)-4,5-dihydrofuran-3-carboxylate (10h). Pale yellow solid; yield 75%, mp 123-124 °C. ¹H NMR (300 MHz, CDCl₃) δ_H: 1.06 (t, 3H, *J* 7.2 Hz, CH₃), 2.46 (s, 3H, CH₃), 3.91- 3.98 (m, 2H, CH₂), 4.52 (d, 1H, *J* 13.8 Hz), 5.04 (d, 1H, *J* 13.8 Hz), 5.22 (d, 1H, *J* 5.1 Hz), 5.67 (d, 1H, *J* 5.1 Hz), 7.33 – 7.41 (m, 5H, Ar-H), 7.49 (t, 2H, *J* 8.1 Hz, Ar-H), 7.65 (t, 1H, *J* 8.1 Hz, Ar-H), 7.87 (d, 2H, *J* 8.1 Hz, Ar-H), 7.88 (d, 2H, *J* 8.1 Hz, Ar-H). ¹³C NMR (75 MHz, CDCl₃) δ_C: 13.8, 21.6, 49.2, 54.7, 60.3, 88.4, 111.7, 123.2, 127.9, 128.3, 128.8, 129.1, 129.3, 129.6, 130.0, 133.9, 134.1, 136.4, 145.0, 157.7, 163.0, 191.4. Anal. Calcd for C₂₈H₂₄Cl₂O₆S : C, 60.11; H, 4.32% Found C, 60.23; H, 4.40%.

trans-Ethyl5-benzoyl-2-((4-chlorophenylsulfonyl)methyl)-4-(4-methylphenyl)-4,5-dihydrofuran-3-carboxylate (10i). Pale yellow solid; yield 67%, mp 104-105 °C. ¹H NMR (300 MHz, CDCl₃) δ_H: 0.99 (t, 3H, *J* 7.2 Hz, CH₃), 2.37 (s, 3H, CH₃), 3.81- 3.89 (m, 2H, CH₂), 4.44 (d, 1H, *J* 5.1 Hz), 4.65 (d, 1H, *J* 13.8 Hz), 4.95 (d, 1H, *J* 13.8 Hz), 5.74 (d, 1H, *J* 5.1 Hz), 7.09 (d, 2H, *J* = 8.1 Hz, Ar-H), 7.16 (d, 2H, *J* 8.1 Hz, Ar-H), 7.44 – 7.48 (m, 4H, Ar-H), 7.62 (t, 1H, *J* 7.2, Ar-H), 7.81 (d, 2H, *J* 8.1 Hz, Ar-H), 7.94 (d, 2H, *J* 8.1 Hz, Ar-H). ¹³C NMR (75 MHz, CDCl₃) δ_C: 13.8, 21.1, 50.6, 54.9, 60.2, 89.9, 112.8, 127.5, 128.9, 129.1, 129.2, 129.6, 130.3, 133.5, 134.1, 137.4, 137.7, 138.3, 140.7, 156.5, 163.3, 192.4. Anal. Calcd for : C₂₈H₂₅ClO₆S : C, 64.06; H, 4.80% Found C, 64.17; H, 4.68%.

trans-Ethyl5-benzoyl-2-((4-chlorophenylsulfonyl)methyl)-4-(4-isopropylphenyl)-4,5-dihydrofuran-3-carboxylate (10j). Pale yellow solid; yield 60%; mp 127-128 °C. ¹H NMR (300 MHz, CDCl₃) δ_H: 0.98 (t, 3H, *J* 7.2 Hz, CH₃), 1.26 (s, 3H, CH₃), 1.28 (s, 3H, CH₃), 2.91 – 2.96 (m, 1H, CH), 3.83- 3.90 (m, 2H, CH₂), 4.47 (d, 1H, *J* 5.1 Hz), 4.65 (d, 1H, *J* 13.8 Hz), 4.95 (d, 1H, *J* 13.8 Hz), 5.76 (d, 1H, *J* 5.1 Hz), 7.12 (d, 2H, *J* 8.1 Hz, Ar-H) 7.22 (d, 2H, *J* 8.1 Hz, Ar-H), 7.42 – 7.48 (m, 4H, Ar-H), 7.59 - 7.62 (m, 1H, Ar-H), 7.83 (d, 2H, *J* 8.1 Hz, Ar-H), 7.93 (d, 2H, *J* 8.1 Hz, Ar-H). ¹³C NMR (75 MHz, CDCl₃) δ_C: 13.8, 23.9, 26.9, 33.8, 50.5, 54.8, 60.2, 89.8, 112.9, 126.9, 127.5, 128.5, 128.9, 129.1, 130.2, 133.3, 134.1, 137.4, 138.1, 140.6, 148.4, 156.4, 163.3, 192.0. Anal. Calcd for C₃₀H₂₉ClO₆S : C, 65.15; H, 5.29% Found C, 65.08; H, 5.38%

trans-Ethyl5-benzoyl-4-(4-chlorophenyl)-2-((4-chlorophenylsulfonyl)methyl)-4,5-dihydrofuran-3-carboxylate (10k). Pale yellow solid; yield 67%, mp 139-140 °C. ¹H NMR (300 MHz, CDCl₃) δ_H: 1.00 (t, 3H, *J* 7.2 Hz, CH₃), 3.84- 3.94 (m, 2H, CH₂), 4.52 (d, 1H, *J* 5.1 Hz), 4.63 (d, 1H, *J* 13.8 Hz), 4.95 (d, 1H, *J* 13.8 Hz), 5.69 (d, 1H, *J* 5.1 Hz), 7.16 (d, 2H, *J* 8.1 Hz, Ar-H), 7.34 (d, 2H, *J* 8.1 Hz, Ar-H), 7.44 – 7.49 (m, 4H, Ar-H), 7.63 (t, 1H, *J* 7.1 Hz, Ar-H), 7.81 (d, 2H, *J* 8.1 Hz, Ar-H), 7.91 (d, 2H, *J* 8.1 Hz, Ar-H). ¹³C NMR (75 MHz, CDCl₃) δ_C: 13.8, 50.2, 54.8, 60.3, 89.5, 112.4, 126.3, 127.4, 128.9, 129.1, 129.3, 130.1, 133.2, 133.6, 134.3, 137.5, 139.8, 140.7, 156.9, 163.1, 191.9. Anal. Calcd for C₂₇H₂₂Cl₂O₆S: C, 59.46; H, 4.07% Found C, 59.52; H, 4.18%.

trans-Ethyl5-benzoyl-2-((4-chlorophenylsulfonyl)methyl)-4-(4-methoxyphenyl)-4,5-dihydrofuran-3-carboxylate (10l). Pale yellow solid; yield 70%; mp 120-121 °C. ¹H NMR (300 MHz, CDCl₃) δ_H: 0.99 (t, 3H, *J* 7.2 Hz, CH₃), 3.80 (s, 3H, OCH₃), 3.82-3.94 (m, 2H, CH₂), 4.42 (d, 1H, *J* 5.1 Hz), 4.64 (d, 1H, *J* 13.8 Hz), 4.96 (d, 1H, *J* 13.8 Hz), 5.73 (d, 1H, *J* 5.1 Hz), 6.89 (d, 2H, *J* 8.1 Hz, Ar-H), 7.12 (d, 2H, *J* 8.1 Hz, Ar-H), 7.43 – 7.48 (m, 4H, Ar-H), 7.62 (t, 1H, *J* 7.1 Hz, Ar-H), 7.81 (d, 2H, *J* 8.1 Hz, Ar-H), 7.94 (d, 2H, *J* 8.1 Hz, Ar-H). ¹³C NMR (75 MHz, CDCl₃) δ_C: 13.8, 50.7, 54.8, 54.3, 60.2, 89.9, 112.8, 126.4, 127.8, 128.7, 128.9, 129.1, 129.2, 130.2, 133.3, 134.2, 137.5, 140.7, 156.4, 159.1, 163.3, 192.4. Anal. Calcd for C₂₈H₂₅ClO₇S : C, 62.16; H, 4.66% Found C, 62.08; H, 4.55%.

trans-Ethyl5-benzoyl-4-(2-bromophenyl)-2-((4-chlorophenylsulfonyl)methyl)-4,5-dihydrofuran-3-carboxylate (10m). Pale yellow solid; yield 70%; mp 128-129 °C. ¹H NMR (300 MHz, CDCl₃) δ_H: 0.99 (t, 3H, *J* 7.2 Hz, CH₃), 3.84 - 3.94 (m, 2H, CH₂), 4.66 (d, 1H, *J* 13.8 Hz), 4.93 (d, 1H, *J* 13.8 Hz), 5.21 (d, 1H, *J* 5.1 Hz), 5.69 (d, 1H, *J* 5.1 Hz), 7.27 – 7.64 (m, 9H, Ar-H), 7.83 – 7.87 (m, 4H, Ar-H). ¹³C NMR (75 MHz, CDCl₃) δ_C: 13.7, 48.9, 54.6, 60.3, 88.7, 112.4, 123.8, 126.4, 127.6, 128.2, 128.5, 128.8, 129.1, 130.1, 132.9, 133.5, 134.1, 136.2, 137.5, 140.7, 157.2, 163.2, 191.4. Anal. Calcd for C₂₇H₂₂BrClO₆S : C, 54.98; H, 3.76% Found C, 55.07; H, 3.65%.

trans-Ethyl5-benzoyl-4-(3-bromophenyl)-2-((4-chlorophenylsulfonyl)methyl)-4,5-dihydrofuran-3-carboxylate (10n). Pale yellow solid; yield 70%, mp 139-140 °C. ¹H NMR (300 MHz, CDCl₃) δ_H: 0.99 (t, 3H, *J* 7.2 Hz, CH₃), 3.78 - 3.96 (m, 2H, CH₂), 4.53 (d, 1H, *J* 5.1 Hz), 4.62 (d, 1H, *J* 13.8 Hz), 4.92 (d, 1H, *J* 13.8 Hz), 5.72 (d, 1H, *J* 5.1 Hz), 7.15 – 7.26 (m, 2H, Ar-H), 7.41 – 7.49 (m, 5H, Ar-H), 7.63 (t, 1H, *J* 8.1 Hz, Ar-H), 7.82 (t, 1H, *J* 8.1 Hz, Ar-H), 7.90 (d, 2H, *J* 8.1

Hz, Ar-H), 7.86 (d, 2H, *J* 8.1 Hz, Ar-H). ¹³C NMR (75 MHz, CDCl₃) δ_C: 13.8, 50.1, 54.7, 60.3, 89.3, 112.2, 122.9, 126.3, 128.9, 129.1, 129.3, 130.1, 130.5, 130.7, 130.9, 133.2, 134.3, 137.4, 140.7, 143.5, 156.9, 162.9, 191.8. Anal. Calcd for C₂₇H₂₂BrClO₆S : C, 54.98; H, 3.76% Found C, 55.05; H, 3.85%.

trans-Ethyl5-benzoyl-2-((4-chlorophenylsulfonyl)methyl)-4-(3-fluorophenyl)-4,5-dihydrofuran-3-carboxylate (10o). Pale yellow solid; yield 70%, mp 115-116 °C. ¹H NMR (300 MHz, CDCl₃) δ_H: 0.98 (t, 3H, *J* 7.2 Hz, CH₃), 3.81- 3.96 (m, 2H, CH₂), 4.55 (d, 1H, *J* 5.1 Hz), 4.64 (d, 1H, *J* 13.8 Hz), 4.93 (d, 1H, *J* 13.8 Hz), 5.71 (d, 1H, *J* 5.1 Hz), 6.91 – 7.02 (m, 3H, Ar-H), 7.26 – 7.65 (m, 8H, Ar-H), 7.81 (t, 1H, *J* 8.1 Hz, Ar-H), 7.91 (t, 1H, *J* 8.1 Hz, Ar-H). ¹³C NMR (75 MHz, CDCl₃) δ_C: 13.8, 50.3, 54.7, 60.3, 89.4, 112.4, 123.2, 123.5, 126.6, 127.4, 128.9, 129.1, 129.3, 130.1, 130.9, 133.2, 134.3, 137.4, 140.7, 143.8, 156.9, 162.7, 191.9. Anal. Calcd for C₂₇H₂₂ClFO₆S : C, 61.30; H, 4.19% Found C, 61.22; H, 4.30%.

trans-Ethyl5-benzoyl-2-((4-chlorophenylsulfonyl)methyl)-4-(2,4-dichlorophenyl)-4,5-dihydrofuran-3-carboxylate (10p). Pale yellow solid; yield 70%, mp 139-140 °C. ¹H NMR (300 MHz, CDCl₃) δ_H: 1.03 (t, 3H, *J* 7.2 Hz, CH₃), 3.85 - 3.95 (m, 2H, CH₂), 4.62 (d, 1H, *J* 13.8 Hz), 4.94 (d, 1H, *J* 13.8 Hz), 5.20 (d, 1H, *J* 5.1 Hz), 5.66 (d, 1H, *J* 5.1 Hz), 7.22 – 7.62 (m, 7H, Ar-H), 7.83 (d, 2H, *J* 8.1 Hz, Ar-H), 7.91 (d, 2H, *J* 8.1 Hz, Ar-H), 8.12 (d, 1H, *J* 7.2 Hz, Ar-H). ¹³C NMR (75 MHz, CDCl₃) δ_C: 13.8, 49.2, 54.7, 60.3, 88.4, 111.7, 123.2, 127.9, 128.3, 128.8, 129.1, 129.3, 129.6, 130.0, 133.9, 134.1, 136.4, 145.0, 157.7, 163.0, 191.4. Anal. Calcd for C₂₇H₂₁Cl₃O₆S : C, 55.92; H, 3.65% Found C, 56.04; H, 3.73%.

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39. Crystallographic data for the derivative **10n** in this paper is deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 912394. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk]