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

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Abstract

A library of novel *trans*-ethyl 5-aroyl-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 synthesis[10-12] 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 11β-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 antiprotozoal[16] and antimycobacterial activity[17] respectively. Consequently, in the present work, we report the regio- and stereoselective synthesis of highly functionalized biologically relevant dihydrofurans bearing arylsulfonyl moiety **6**.

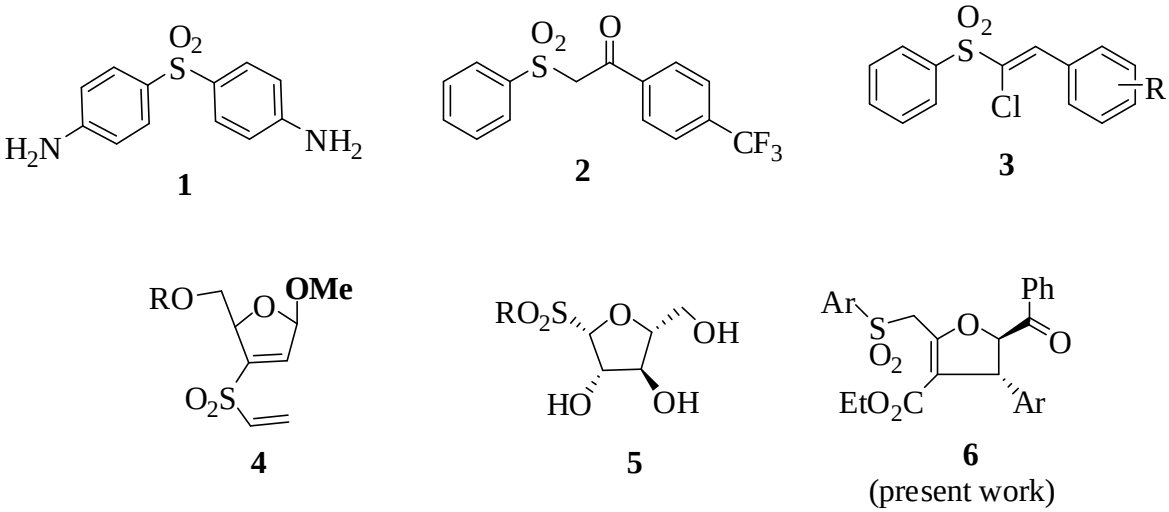


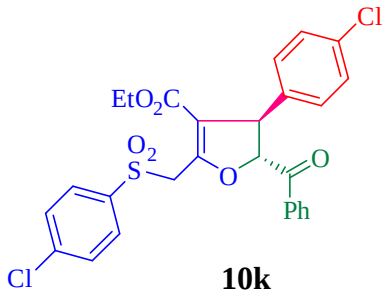
Figure 1

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-aroyl-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 sovent-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 Et_3N is more efficient for this transformation than either DBU or piperidine. A maximum yield of **10k** (82%) was obtained, when Et_3N was employed as the base and CH_3CN as the solvent.

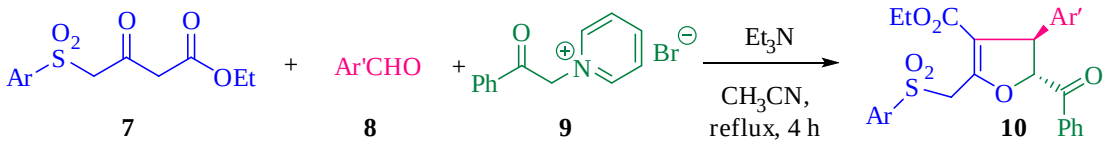
Table 1. Base- and solvent-screen for the synthesis of **10k**



10k

Entry	Base	Solvent	Reaction time (h)	Yield of 10k (%)
1	NH_4OAc	CH_3CN	4	45
2	K_2CO_3	CH_3CN	4	60
3	Et_3N	CH_3CN	4	82
4	DBU	CH_3CN	4	52
5	Et_3N	CH_2Cl_2	4	30
6	Et_3N	MeOH	4	55
7	Et_3N	DMF	4	65
8	Et_3N	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 Et_3N (2.5 mmol) in



Scheme 1. Synthesis of *trans*-ethyl-5-aroyl-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 (ºC)	Yield of **10** (%)
1	**10a**	*p*-MeC_6H_4	C_6H_5	126-127	70
2	**10b**	*p*-MeC_6H_4	*p*-MeC_6H_4	112-113	75
3	**10c**	*p*-MeC_6H_4	*p*-ClC_6H_4	148-149	72
4	**10d**	*p*-MeC_6H_4	*p*- $O_2NC_6H_4$	137-138	71
5	**10e**	*p*-MeC_6H_4	*o*-$MeOC_6H_4$	115-116	74
6	**10f**	*p*-MeC_6H_4	*o*-BrC_6H_4	132-133	70
7	**10g**	*p*-MeC_6H_4	*m*-FC_6H_3	118-119	77
8	**10h**	*p*-MeC_6H_4	*o,p*-$Cl_2C_6H_4$	123-124	75
9	**10i**	*p*-ClC_6H_4	*p*-MeC_6H_4	104-105	80
10	**10j**	*p*-ClC_6H_4	*p*-$Pr^iC_6H_4$	127-128	72
11	**10k**	*p*-ClC_6H_4	*p*-ClC_6H_4	139-140	82
12	**10l**	*p*-ClC_6H_4	*p*-$MeOC_6H_4$	120-121	73
13	**10m**	*p*-ClC_6H_4	*o*-BrC_6H_4	128-129	75
14	**10n**	*p*-ClC_6H_4	*m*-BrC_6H_3	130-131	77
15	**10o**	*p*-ClC_6H_4	*m*-FC_6H_3	115-116	72
16	**10p**	*p*-ClC_6H_4	*o,p*-$Cl_2C_6H_4$	139-140	70

CH_3CN. 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-aroyl-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 ^{1}H, ^{13}C and 2D NMR spectroscopic data as illustrated for a representative example, **10n** (Figure 2). In the ^{1}H 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).

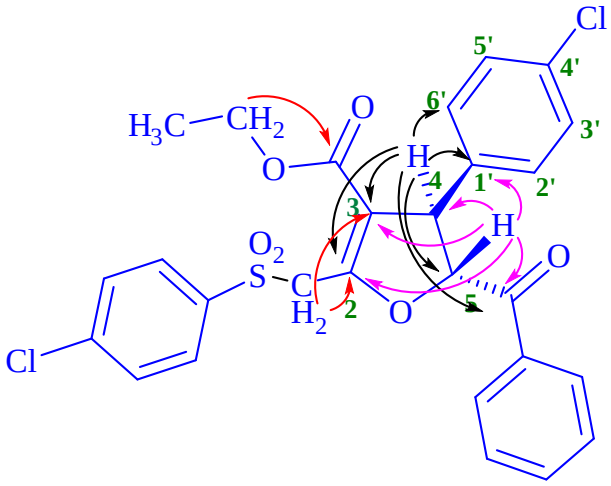


Figure 2. Selected HMBCs of **10n.**

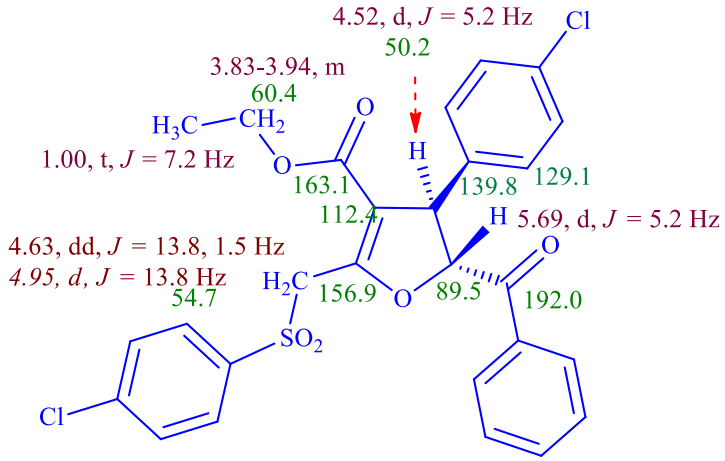


Figure 3. Selected NMR data of **10n.**

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-

COSY correlations with the carbon signal at 54.7 ppm and HMBCs with C-2 and C-3 carbons. Ester methylene hydrogens appeared as a multiplet in the region of 3.86-3.94 ppm and methyl hydrogens appeared as a triplet at 1.00 ppm (*J* 7.2 Hz). The structure of **10n** deduced from NMR spectroscopic data is in good accord with that determined from the X-ray crystallographic studies on a single crystal of **10n**[39] (Figure 4).

This transformation leading to the formation of dihydrofurans (Scheme 2) is presumably triggered by an initial regioselective condensation of ketosulfonyl ester **7** with aromatic aldehyde **8** affording **11**. This regioselectivity might probably arise from the steric hindrance posed by the bulky arylsulfonyl moiety to the condensation of the aromatic aldehyde with the methylene flanked by the sulfonyl and keto groups, which is likely to impede the formation of **11**'. Subsequent Michael addition of the pyridinium ylide **12** to the acceptor **11** furnishes the enolate **13**, which undergoes intramolecular cyclisation by the displacement of pyridine to afford exclusively the regioisomer **10**.

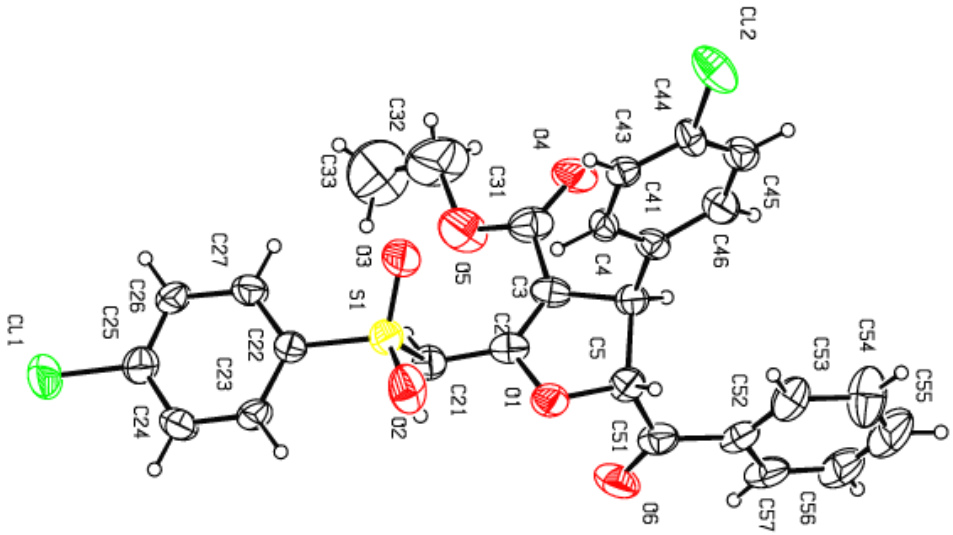
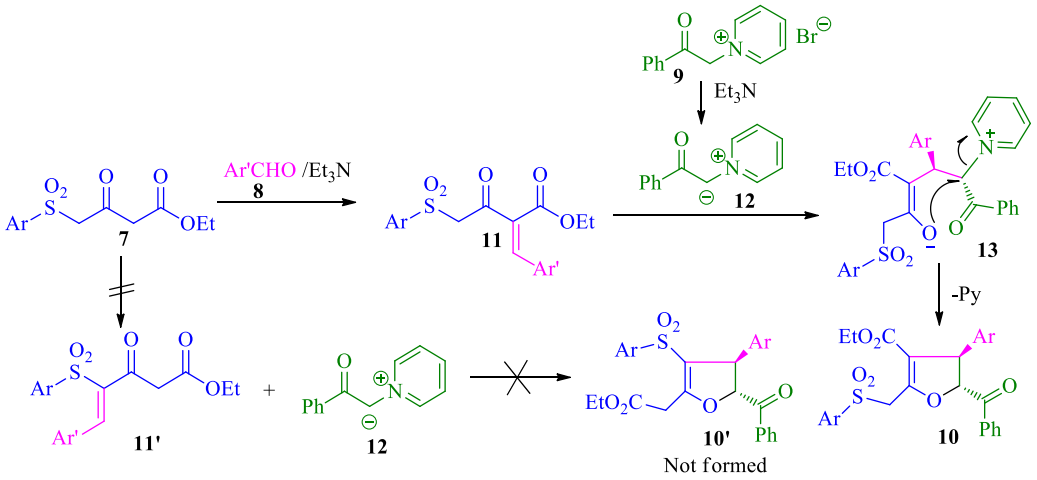


Figure 4. ORTEP diagram of **10n**.



Scheme 2. Plausible mechanism for the formation of *trans*-ethyl 5-aroyl-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-aroyl-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 ^{1}H 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 ^{o}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-aroyl-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 CH_3CN 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 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 0.97 (t, 3H, *J* 7.2 Hz, CH_3), 2.41(s, 3H, CH_3 ,) 3.82- 3.94 (m, 2H, CH_2), 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). ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{28}H_{26}O_6S$: 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 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 0.99 (t, 3H, *J* 7.2 Hz, CH_3), 2.36 (s, 3H, CH_3), 2.41(s, 3H, CH_3 ,) 3.81- 3.91 (m, 2H, CH_2), 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). ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{29}H_{28}O_6S$: 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 ºC ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.01 (t, 3H, *J* 7.2 Hz, CH_3), 2.43 (s, 3H, CH3), 3.82- 3.95 (m, 2H, CH_2), 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). ^{13}C NMR (75 MHz, $CDCl_3$) 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 : $C_{28}H_{25}ClO_6S$: 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 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.04 (t, 3H, *J* 7.2 Hz, CH_3), 2.47 (s, 3H, CH3), 3.90- 3.99 (m, 2H, CH_2), 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). ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{28}H_{25}NO_8S$: 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 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 0.99 (t, 3H, *J* 7.2 Hz, CH_3), 2.42(s, 3H, CH_3), 3.61 (s, 3H, OCH_3), 3.84- 3.97

(m, 2H, CH_2), 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). ^{13}C NMR (75 MHz, $CDCl_3$) 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 : $C_{29}H_{28}O_7S$: 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. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 0.99 (t, 3H, *J* 7.2 Hz, CH_3), 2.42(s, 3H, CH_3), 3.84- 3.97 (m, 2H, CH_2), 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). ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{28}H_{25}BrO_6S$: 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. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 0.99 (t, 3H, *J* 7.2 Hz, CH_3), 2.41(s, 3H, CH_3), 3.79- 3.97 (m, 2H, CH_2), 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). ^{13}C NMR (75 MHz, $CDCl_3$) 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**:** $C_{28}H_{25}FO_6S$: 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. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.06 (t, 3H, *J* 7.2 Hz, CH_3), 2.46 (s, 3H, CH3), 3.91- 3.98 (m, 2H, CH_2), 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). ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{28}H_{24}Cl_2O_6S$: 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. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 0.99 (t, 3H, *J* 7.2 Hz, CH_3), 2.37 (s,3H, CH_3), 3.81- 3.89 (m, 2H, CH_2), 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* 8.1Hz, Ar-H), 7.94 (d, 2H, *J* 8.1 Hz, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) 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 : $C_{28}H_{25}ClO_6S$: 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 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 0.98 (t, 3H, *J* 7.2 Hz, CH_3), 1.26 (s, 3H, CH_3), 1.28 (s, 3H, CH_3), 2.91 – 2.96 (m, 1H, CH) 3.83- 3.90 (m, 2H, CH_2), 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). ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{30}H_{29}ClO_6S$: 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 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.00 (t, 3H, *J* 7.2 Hz, CH_3), 3.84- 3.94 (m, 2H, CH_2), 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). ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{27}H_{22}Cl_2O_6S$: 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 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 0.99 (t, 3H, *J* 7.2 Hz, CH_3), 3.80 (s, 3H, OCH_3), 3.82-3.94 (m, 2H, CH_2), 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). ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{28}H_{25}ClO_7S$: 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 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 0.99 (t, 3H, *J* 7.2 Hz, CH_3), 3.84 - 3.94 (m, 2H, CH_2), 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). ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{27}H_{22}BrClO_6S$: 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 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 0.99 (t, 3H, *J* 7.2 Hz, CH_3), 3.78 - 3.96 (m, 2H, CH_2), 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). ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{27}H_{22}BrClO_6S$: 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-dihydro-furan-3-carboxylate (10o).** Pale yellow solid; yield 70%, mp 115-116 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 0.98 (t, 3H, *J* 7.2 Hz, CH_3), 3.81- 3.96 (m, 2H, CH_2), 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). ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{27}H_{22}ClFO_6S$: 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-dihyd-rofuran-3-carboxylate (10p).** Pale yellow solid; yield 70%, mp 139-140 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.03 (t, 3H, *J* 7.2 Hz, CH_3), 3.85 - 3.95 (m, 2H, CH_2), 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). ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{27}H_{21}Cl_3O_6S$: 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]

