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Efficient and mild synthesis of highly substituted 2,5-dihydrofuran and furan derivatives via stepwise reaction

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ABSTRACT

An efficient and mild synthesis of highly substituted 2,5-dihydrofuran and furan derivatives from a variety of alkylidene malonates and 1,4-butyne-diol via one-pot reaction was applied. With various conditions of base amount, temperature and time applied to the reaction, the 2,5-dihydrofuran and the furan derivatives could be selectively obtained. Moreover, the formation of furan derivatives with 2,5-dihydrofuran derivatives as intermediates was also investigated. Some of these 2,5-dihydrofuran derivatives showed potent in vitro anti-tumor activities against **HeLa** cells.

1. Introduction

Functionalized 2,5-dihydrofuran, an important class of heterocyclic compounds, represents common structural units in many natural products[1] and valuable intermediates for organic synthesis.[2] Although unsubstituted dihydrofurans can be straightforwardly derived from furan, preparation of functionalized 2,5-dihydrofurans is much more complex and difficult. Recently, several synthetic strategies for functionalized 2,5-dihydrofurans have been reported, which include RCM reaction, Ag(I)-catalyzed rearrangement–cyclization, Prins reaction, and Au(I)-, Ag(I)-, Hg(II)-, Pd(0)-, Ru(III)-, Au(III)-catalyzed cyclization reactions.[3–16] However, the synthesis is still sub-optimal because of difficulty in obtaining raw materials, expensive catalysts, harsh reaction conditions, and multi-step synthesis. As such, novel and more efficient methods for synthesis of functionalized 2,5-dihydrofurans are much needed.

Metal-catalyzed [3+2] cycloaddition reactions have been extensively applied to the synthesis of heterocycle derivatives. Also, propynol has been frequently used to prepare tetrahydrofuran derivatives.[17] In the reactions, both the hetero-atom and the alkyne moiety in the substrates are responsible for bond formation, thus producing highly functionalized 3-methylene-tetrahydrofurans.[18] The above synthetic strategies have been widely adopted, whereas only a small portion of studies reported the usage of other ring systems.[19] In the pursuit of an ongoing medicinal chemistry program, we have been recently interested in introducing a wide range of substituents on the 2-, 3- and 4-positions, especially carboxylic acid group on the 3-position, of 2,5-dihydrofuran. 1,4-Butyne-diol, with a propargyl alcohol structure but possessing two active hydroxyl functional groups, is a substrate suitable for preparing [3+2] cycloadditions. Moreover, it is known that when the Conia-ene reaction is performed upon the linear compounds in the presence of an excess of base, the cyclization is often followed by a decarboxylation reaction. In this respect, we conceive that 1,4-butyne-diol and alkylidene malonates might be cyclized to produce functionalized 2,5-dihydrofurans through a cascade reaction. In this paper, we describe an efficient and mild method for the synthesis of 2-aryl-4-vinyl-2,5-dihydrofuran-3-carboxylic acid (**3**) from the reaction of 1,4-butyne-diol (**2**) with alkylidene malonates (**1**). Meanwhile, 2-aryl-4-ethyl-furan-3-carboxylic acid (**4**) was also obtained through this reaction. Furthermore, with various conditions of base stoichiometry, temperature and time applied to the reaction, the 2,5-dihydrofuran and furan derivatives could be selectively obtained (Scheme 1).

2. Result and discussion

In a previous report we described that several tetrahydrofuran lignans, which 3,5-dimethoxyphenyl substitution at **C-2** position showed potent anti-tumor activity in vitro.[20] Hence, diethyl 2-(3,5-dimethoxybenzylidene) malonate (compound **1a**), which can be readily prepared through Knoevenagel condensation,[21] was used as the model substrate in this study. Compound **1a** (1 equiv) was

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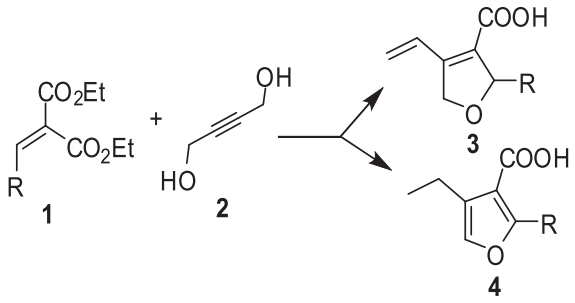


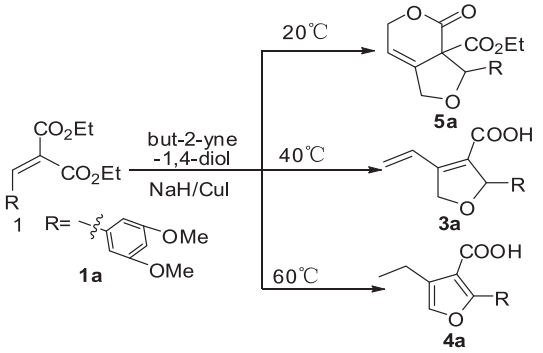
Scheme 1. Synthesis of 2,5-dihyodrofynan and furan derivatives.

reacted with 1,4-butyne-diol (1.5 equiv) in the presence of NaH (1.0 equiv) and CuI (0.1 equiv) at room temperature (25 °C) in THF, and 12 h later, compound **3a** was obtained as a major product (69%) in the presence of the side product **5a** (13%).

Next, the conditions of base stoichiometry, temperature and time were optimized for optimal reactions to produce compound **3a**. Data in Table 1 outline both the principle and the optimization of the reaction conditions. First, 1.2 equiv of NaH was applied to the reaction. When the reaction was undergone at a low temperature (10 °C), no valid product was obtained within 24 h (Table 1, entry 1). When the temperature was elevated to 20 °C, after 6 h, compound **5a** was afforded as the only product, while a lot of starting material **1a** was not consumed in the reaction (Table 1, entry 2). With a prolonged reaction time, however, not only the consumption of compound **1a** was completed, but also compound **3a** was produced (Table 1, entry 4). After 24 h, compound **3a** was obtained as the single product with 87% yield (Table 1, entry 5). Furthermore, with a higher temperature (40 or 60 °C) applied to the reaction, compound **3a** was easily obtained with good yield (Table 1, entries 5–10). Second, 3.0 equiv of NaH was used in the reaction. When the reaction was undergone at 40 or 60 °C for 24 or 6 h, respectively, compounds **3a** was obtained as the single product (Table 1, entries 10 and 11). However, when 3.0 equiv of NaH was used in a reaction at 60 °C for 12 h, compound **3a** was obtained in the presence of another product, which was subsequently identified as compound **4a** (Table 1, entry 12). To more surprise, under this condition (3.0 equiv NaH, 60 °C, and 24 h), only compound **4a** was obtained with a 67% yield (Table 1, entry 13). The structure of compound **3a** was unambiguously confirmed by X-ray crystallographic analysis as racemates (Fig. 1).

Although the reactions could directly afford compounds **3a**, **4a**, and **5a**, considering the relevance among the products obtained under various conditions (Table 1, entries 3, 4, and 11–13), it is rational to hypothesize that compound **4a** was formed sequentially after compound **5a** with compound **3a** as an intermediate. Hereby, a straightforward validation assay was performed (Scheme 2). When compound **5a** was reacted with NaH (1.1 equiv), however, at 40 °C in THF for 48 h, only a small amount of compound **3a** was produced and the majority of compound **5a** was not transformed. 1,4-Butyne-diol (1.1 equiv) was subsequently added, and compound **5a** disappeared in 6 h. When the temperature was further raised to 60 °C, compound **3a** was still not transformed to compound **4a**. However, when 1.1 equiv of NaH was added, after 12 h, compound **4a** was obtained as the single yielding compound with 75% yield. Furthermore, it was suggested that 1,4-butyne-diol is not essential in the transformation of compound **3a** to compound **4a** in this reaction. Hence, the reaction of compound **3a** with NaH (1.1 equiv) was performed at 60 °C in THF. Obviously, compound **4a** was obtained with the consumption of compound **3a** at 12 h. These observations suggest that compound **5a** would be converted to compound **4a** when NaH and 1,4-butyne-diol were presented in the reaction; while compound **3a** was transformed to compound **4a** in this reaction with only NaH needed.

Table 1
The various reaction conditions[a]



Entry	NaH equiv	Catalyst	Temp (°C)	Time (h)	Product[b]	Yield[c] (%)
1	1.2	CuI	10	24	**No**	No
2	1.2	CuI	20	6	**5a**	37
3	1.2	CuI	20	12	**3a**+**5a**	23+43
4	1.2	CuI	20	24	**3a**	87
5	1.2	CuI	40	6	**3a**	Not Cal[d]
6	1.2	CuI	40	12	**3a**	83
7	1.2	CuI	40	24	**3a**	79
8	1.2	CuI	60	6	**3a**	Not Cal[d]
9	1.2	CuI	60	12	**3a**	76
10	3.0	CuI	40	24	**3a**	73
11	3.0	CuI	60	6	**3a**	Not Cal[d]
12	3.0	CuI	60	12	**3a**+**4a**	57+11
13	3.0	CuI	60	24	**4a**	67

[a] Unless otherwise specified, the reaction was carried on 2.0 mmol scale in 5 ml of solvent.
[b] Monitored by TLC.
[c] Isolated yield.
[d] Lots of the starting material not involved in the reaction, the yields were not calculated.

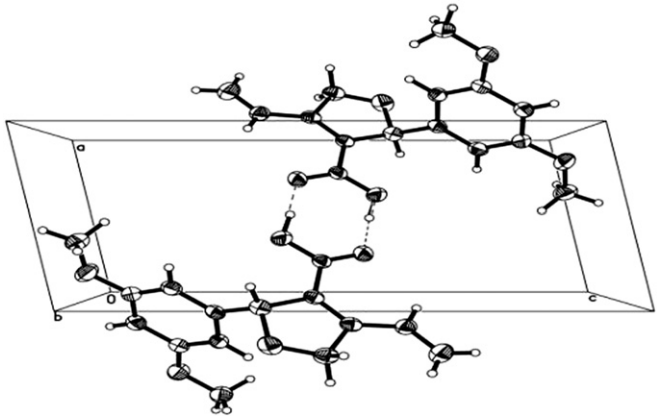
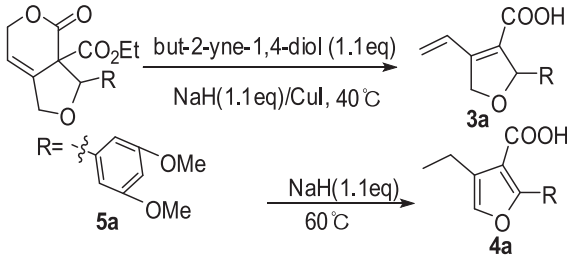


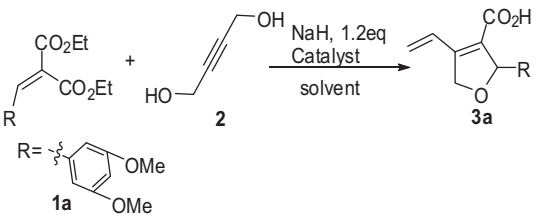
Fig. 1. X-ray crystal structures of 2-(3,5-dimethoxyphenyl)-4-vinyl-2,5-dihydrofuran-3-carboxylic acid (**3a**, ORTEP view, CCDC 756984).



Scheme 2. Validation assay.

The results above indicate that compound **5a** could be converted to compound **3a** and be further transformed to compound **4a**. Afterward, various solvents and Cu salt catalysts were tested to optimize the conditions for the synthesis of compound **3a** (Table 2). The reaction proceeded well in 1,4-dioxane or CH_2Cl_2, however, without enhanced speed and yield. Instead, when the reaction was performed in CH_2Cl_2, the speed was slowed down (Table 2, entry 1). Although the reaction could be performed in DMF or DMSO at 20 °C with the complete consumption of compound **1a** at 2 h or 1 h, respectively, the products were lousy (Table 2, entries 3 and 4). As for the catalysts, CuCl and CuBr had certain effects. However, the reactions would take much longer time, and meanwhile, the yield was significantly decreased (Table 2, entries 8 and 9). Except for $Cu(OAc)_2$, the Cu^{2+} salt almost had no effects. No matter $CuCl_2$, $CuBr_2$ $CuSO_4$ or $Cu(NO_3)_2$ was used in the reaction, the starting material compound **1a** could not be initiated to the reaction at 20–60 °C within 48 h (Table 2, entries 8–11). When $Cu(OAc)_2$ was added, an elevated temperature of 60 °C would be needed, whereas most of the starting material could not be reacted within 48 h (Table 2, entry 7). As such, CuI and THF were finally determined as the catalyst and the solvent, respectively.

Table 2
Optimization of the solvent and the catalysts[a]



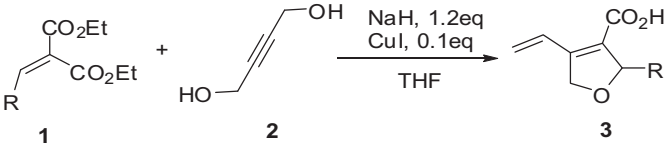
Entry	Catalyst	Solvent	Temp (°C)	Time (h)	Yield[b] (%)
1	CuI	CH_2Cl_2	Reflux	48	40
2	CuI	1,4-Dioxane	40	12	73
3	CuI	DMF	20	2	—
4	CuI	DMSO	20	1	—
5	CuCl	THF	40	24	48
6	CuBr	THF	40	24	59
7	$Cu(OAc)_2$	THF	60	48	10
8	$CuCl_2$	THF	60	48	—
9	$CuBr_2$	THF	60	48	—
10	$CuSO_4$	THF	60	48	—
11	$Cu(NO_3)_2$	THF	60	48	—

[a] Unless otherwise specified, the reaction was carried on 2.0 mmol scale in 5 ml of solvent.
[b] Isolated yield.

Under the optimized reaction conditions, the generality of the reaction was investigated by using 1,4-butyne-diol and a variety of alkylidene malonates to produce 2,5-dihydrofuran derivatives. The results are summarized in Table 3. The reaction was speedy with electron-deficient aryl-substituted substrates (Table 3, entry 12), while slow with electronrich aryl-substituted ones (Table 3, entries 7–9). Heteroaromatic and alkyl substituents could also be applied to promote conversions to the substituted 2,5-dihydrofurans (Table 3, entries 10–12).

Furans are one of the most important class of compounds in organic and synthetic chemistry, that exist in numerous natural products, such as kallolides,[22] combranolides,[23] pheromones,[24] and polyether antibiotics[25] with a variety of biological activities.[26] Recently, Zanatta et al. reported that a series of furan-3-carboxamides demonstrated potent anti-microbial activities.[27] Hence, we synthesized various 2-aryl-4-ethyl-furan-3-carboxylic acids, which were summarized in Table 4. The process was similar to the synthesis of 2,5-didydrofuran derivatives. No matter when an electron-withdrawing group or an electron-donating group on the aryl ring or heteroaromatic substitution was applied, the reaction could be smoothly performed, despite higher temperature and excess NaH

Table 3
Synthesis of 2,5-dihydrofuran derivatives[a]

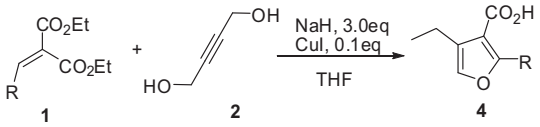


Entry	1	Substrate R=	Temp (°C)	Time (h)	Yield[b] (%)
1	**1b**	Ph	40	15	75
2	**1c**	2-F–Ph	40	15	73
3	**1d**	4-F–Ph	40	15	77
4	**1e**	3-Cl–Ph	40	15	71
5	**1f**	4-Cl–Ph	40	15	75
6	**1g**	4-Br–Ph	40	15	88
7	**1h**	4-OCH_3–Ph	40	22	82
8	**1i**	3,4-$(OCH_3)_2$–Ph	40	22	87
9	**1j**	3,4,5-$(OCH_3)_3$–Ph	40	22	79
10	**1k**	2-Furanyl	40	12	80
11	**1l**	2-Pyridyl	30	10	80
12	**1m**	$CH_3(CH_2)_8$	40	22	83
13	**1n**	4-NO_2–Ph	30	10	89

[a] Unless otherwise specified, the reaction was carried on 20.0 mmol scale in 50 ml of solvent.
[b] Isolated yield.

were needed. Meanwhile, an electron-withdrawing group on the aryl ring was slightly more favored than an electron-donating group. The structure of furan derivatives was determined by ^1H, ^{13}C NMR and MS spectra, and further unambiguously conformed by X-ray crystallographic analysis of compound **4l** (Fig. 2).

Table 4
Synthesis of furan derivatives[a]



Entry	1	Substrate R=	Temp (°C)	Time (h)	Yield[b] (%)
1	**1b**	Ph	50	22	73
2	**1c**	2-F–Ph	50	22	70
3	**1d**	4-F–Ph	60	22	71
4	**1e**	3-Cl–Ph	50	22	82
5	**1f**	4-Cl–Ph	50	22	71
6	**1g**	4-Br–Ph	50	22	75
7	**1h**	4-OCH_3–Ph	60	22	75
8	**1i**	3,4-$(OCH_3)_2$–Ph	60	22	68
9	**1j**	3,4,5-$(OCH_3)_3$–Ph	60	22	62
10	**1k**	2-Furanyl	40	22	66
11	**1l**	2-Pyridyl	40	22	57
12	**1m**	$CH_3(CH_2)_8$	60	28	—
13	**1o**	4-CF_3–Ph	20	16	85

[a] Unless otherwise specified, the reaction was carried on 20.0 mmol scale in 50 ml of solvent.
[b] Isolated yield.

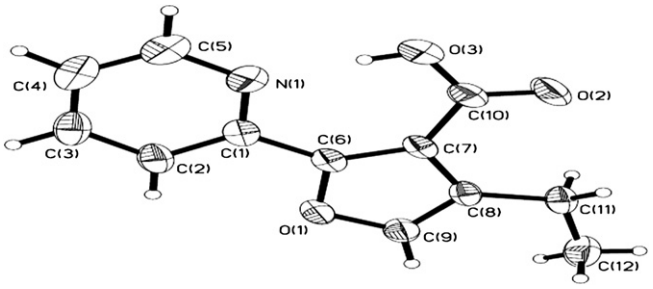
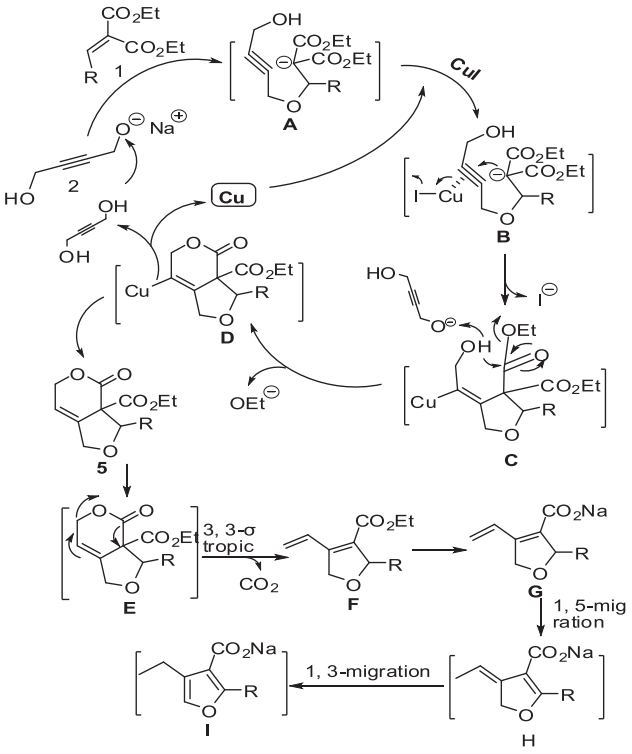


Fig. 2. X-ray crystal structures of 4-ethyl-5-(pyridin-2-yl)furan-3-carboxylic acid (**4l**, ORTEP views, CCDC 790041).

Based on the above results, a tentative mechanism for the tandem reaction is proposed in Scheme 3. First, 1,4-butyne-diol was treated with NaH to produce alcohol sodium. One of the oxygen anion of 1,4-butyne-diol conjugate was then added to the double bond of the substrate alkynylmalonate to form the intermediate **A**, followed by copper-promoted cyclization that yields intermediates **B** and **C**. Subsequently, an intramolecular ester exchange between another anion of 1,4-butyne-diol and one eater of alkynylmalonate yields intermediate **D**. The **Cu** atom then draws off to yield product **5**. Product **5** (compound **E**) is not very stable under this condition, and undergoes [3, 3]-sigmatropic reaction which releases one carbon dioxide to form intermediate **F**. Later on, a basic hydrolysis helps generate intermediate **G**. Finally, when the temperature was elevated and the excess base was used, the intermediate **G** consecutively undergoes [1,5] and [1,3] migration to produce the intermediate **H** and the final intermediate **I**, respectively. The intermediates **G** and **I** yield products **3** and **4**, respectively, through acidification.



Scheme 3. Tentative mechanism for final product formation.

All these newly synthesized 2,5-dihydrofuran derivatives were evaluated for their inhibitory effects against proliferation of human lung cancer (**A549**) cells, human hepatoma carcinoma (**QGY**) cells and human cervix carcinoma (**HeLa**) cells by MTT assays.[28] As showed in the Fig. 3, several of these 2,5-dihydrofuran derivatives showed potent in vitro anti-proliferative activities against **HeLa** cells. In particular, compound **3j** (IC_{50}=7.5 μM) exhibited the highest cytostatic activity again **HeLa** cells, with IC_{50} twofold lower than the control drug 5-fluorouracil (16.1 μM) (Fig. 3).

3. Conclusion

In summary, we have developed an efficient and mild stepwise reaction of 1,4-butyne-diol and alkylidene malonates that allows controlled acquisition of highly substituted 2,5-dihydrofurans and furans, with good to excellent yields. The furan derivatives obtained by continuous reactions via intermediates 3, 3*a*-dihydro-1*H*-furo [3,4-*c*]pyran-4(6*H*)-one and 2,5-dihydrofuran derivatives were also functionally characterized. Some of these 2,5-dihydrofuran

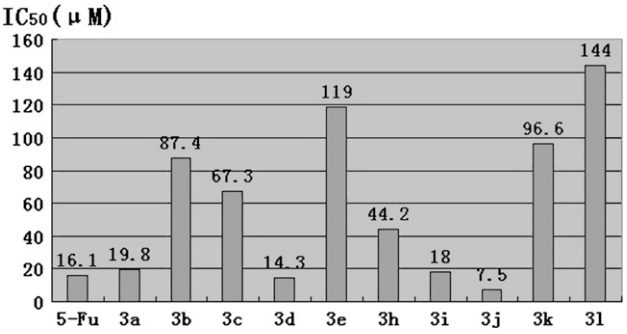


Fig. 3. Anti-tumor activity evaluation against **HeLa** cells in vitro.

derivatives showed potent in vitro anti-tumor activities against **HeLa** cells. Ongoing experiments are being carried out to further address these novel functions.

4. Experimental section

4.1. General

All reactions were carried out in oven-dried glassware. Progress of reactions was monitored by thin layer chromatography (TLC) while purification of crude compounds was done by column chromatography using silica gel (200–300 mesh). Melting points were recorded on a YUHUA X-5 melting point apparatus and are uncorrected. Elemental analysis was performed with a Carlo Erba 1106 elemental analyzer. NMR experiments were performed on Bruke Avance 300 and Bruke Avance 600 instruments and samples were obtained in $CDCl_3$ (referenced to residual $CHCl_3$ at 7.26 ppm for ^1H and 77.0 ppm for ^{13}C) or DMSO-d_6 (referenced to residual DMSO at 2.50 ppm for ^1H and 39.5 ppm for ^{13}C). Coupling constants (*J*) are in hertz. The multiplicities of the signals are described using the following abbreviations: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad. Mass spectra were recorded using Finigan LCQ Deca XP MAX mass spectrometer. IR spectra were recorded on Bruker Vector 22 series FT-IR spectrometer, absorbencies are reported in cm^{-1}. Yields refer to quantities obtained after chromatography.

4.2. General experimental procedure for synthesis of highly substituted 2,5-dihydrofurans (3) and furans (4)

NaH (60% in mineral oil, 24 mmol) was added to a solution of but-2-yne-1,4-diol (2.58 g, 30 mmol) in THF (50 mL) under nitrogen, and the solution was stirred for 5 min at room temperature. Alkylidene malonate (**1**, 20 mmol) and CuI (0.38 g, 2 mmol) were then added successively. When consumption of the starting materials was observed by TLC, the reaction mixture was quenched by dropwise addition of a 20% solution of HCl, immediately cooled to room temperature. The mixture was further diluted and extracted twice with CH_2Cl_2, and the organics washed successively with saturated solution of brine, and water. The organic extracts were dried over $MgSO_4$, filtered, concentrated, and the residue purified by flash column chromatography to afford compound **3**. Furthermore, 3.0 equiv (60 mmol) of NaH was used in the reaction to obtained compound **4**.

*4.2.1. 2-(3,5-Dimethoxyphenyl)-4-vinyl-2,5-dihydrofuran-3-carboxylic acid (**3a**).* Yield: 76%; white solid; mp: 140.5–140.7 °C. IR: 3440, 2986, 2957, 2887, 2847, 2661, 2622, 2580, 2530, 1869, 1681, 1633, 1609, 1593, 1463, 1431, 1408, 1384, 1367, 1344, 1315, 1279, 1198, 1157, 1067, 1014, 993, 930, 858, 820, 788, 741 cm^{-1}. ^1H NMR (DMSO, 300 MHz): δ 12.78 (br 1H), 7.40 (dd, *J*=18, 11.1 Hz, 1H), 6.40–6.42 (m, 3H), 5.79 (dd, *J*=5.4, 2.7 Hz, 1H), 5.60 (d, *J*=11.1 Hz, 1H), 5.48 (d, *J*=18.0 Hz, 1H), 5.11 (dd, *J*=14.4, 5.4 Hz, 1H), 5.91 (dd,

J=14.4, 2.7 Hz, 1H), 3.70 (s, 6H) ppm; ^{13}C NMR (DMSO, 75 MHz): δ 163.8, 160.3, 146.2, 143.7, 129.0, 127.6, 123.3, 105.2, 99.3, 88.0, 74.7, 55.0 ppm. ESIMS: *m*/*s* (%): 275.65 [M−H]$^-$. Anal. Calcd for $C_{15}H_{16}O_5$: C, 65.21; H, 5.84. Found: C, 65.27; H, 5.58%.

*4.2.2. 2-Phenyl-4-vinyl-2,5-dihydrofuran-3-carboxylic acid (**3b**).* Yield: 75%; white solid; mp: 165.7–166.2 °C. IR: 3414, 3027, 2895, 2852, 2618, 1575, 2525, 1999, 1952, 1880, 1666, 1586, 1492, 1442, 1407, 1384, 1321, 1276, 1127, 1083, 1066, 1027, 937, 839, 759, 742 cm^{-1}. ^{1}H NMR (DMSO, 300 MHz): δ 12.76 (br, 1H), 7.19–7.58 (m, 6H), 5.86 (dd, *J*=5.4, 3.0 Hz, 1H), 5.60 (d, *J*=10.8 Hz, 1H), 5.50 (d, *J*=18.0 Hz, 1H), 5.13 (dd, *J*=14.4, 5.4 Hz, 1H), 4.95 (dd, *J*=14.4, 3.0 Hz, 1H) ppm; ^{13}C NMR (DMSO, 75 MHz): δ 163.8, 146.3, 141.5, 129.2, 128.2, 127.9, 127.8, 127.2, 123.3, 88.3, 74.8 ppm. ESIMS: *m*/*s* (%): 215.53 [M−H]$^-$. Anal. Calcd for $C_{13}H_{12}O_3$: C, 72.21; H, 5.59. Found: C, 72.27; H, 5.63%.

*4.2.3. 2-(2-Fluorophenyl)-4-vinyl-2,5-dihydrofuran-3-carboxylic acid (**3c**).* Yield: 73%; white solid; mp: 154.7–154.9 °C. IR: 3446, 3072, 2927, 2853, 2622, 1670, 1635, 1590, 1558, 1540, 1507, 1491, 1455, 1408, 1384, 1319, 1279, 1227, 1178, 1129, 1101, 1065, 1012, 954, 934, 838, 805, 759, 745 cm^{-1}. ^{1}H NMR (DMSO, 300 MHz): δ 12.81 (s, 1H), 7.12–7.39 (m, 5H), 6.12 (dd, *J*=5.1, 3.0 Hz, 1H), 5.61 (d, *J*=10.8 Hz, 1H), 5.52 (d, *J*=18.0 Hz, 1H), 5.09 (dd, *J*=14.4, 5.1 Hz, 1H), 4.96 (dd, *J*=14.4, 3.0 Hz, 1H) ppm; ^{13}C NMR (DMSO, 75 MHz): δ 163.6, 161.8, 158.6, 147.4, 130.1, 129.4, 128.2, 127.7, 124.3, 123.6, 115.6, 82.2, 74.8 ppm. ESIMS: *m*/*s* (%): 233.53 [M−H]$^-$. Anal. Calcd for $C_{13}H_{11}FO_3$: C, 66.66; H, 4.73. Found: C, 66.81; H, 4.92%.

*4.2.4. 2-(4-Fluorophenyl)-4-vinyl-2,5-dihydrofuran-3-carboxylic acid (**3d**).* Yield: 77%; white solid; mp: 155.1–155.7 °C. IR: 3456, 2860, 2580, 2015, 1671, 1603, 1509, 1450, 1384, 1331, 1282, 1218, 1158, 1132, 1099, 1072, 1014, 946, 854, 824, 746 cm^{-1}. ^{1}H NMR (DMSO, 300 MHz): δ 12.83 (br, 1H), 7.24–7.34 (m, 3H), 7.11–7.18 (m, 2H), 5.87 (dd, *J*=5.1, 3.0 Hz, 1H), 5.60 (d, *J*=14.4 Hz, 1H), 5.50 (d, *J*=18.0 Hz, 1H), 5.13 (dd, *J*=14.4, 5.1 Hz, 1H), 4.95 (dd, *J*=14.4, 3.0 Hz, 1H) ppm; ^{13}C NMR (DMSO, 75 MHz): δ 163.8, 163.4, 160.2, 146.5, 137.9, 129.2, 127.7, 123.5, 115.1, 87.5, 74.8 ppm. ESIMS: *m*/*s* (%): 233.42 [M−H]$^-$. Anal. Calcd for $C_{13}H_{11}FO_3$: C, 66.66; H, 4.73. Found: C, 66.69; H, 4.76%.

*4.2.5. 2-(3-Chlorophenyl)-4-vinyl-2,5-dihydrofuran-3-carboxylic acid (**3e**).* Yield: 71%; white solid; mp: 158.4–158.7 °C. IR: 3428, 3062, 2941, 2849, 2618, 2519, 2360, 2340, 1903, 1683, 1634, 1588, 1475, 1430, 1404, 1384, 1363, 1317, 1270, 1189, 1131, 1097, 1077, 1010, 993, 932, 867, 849, 786, 744, 704 cm^{-1}. ^{1}H NMR (DMSO, 300 MHz): δ 12.90 (br, 1H), 7.31 (m, 5H), 5.88 (dd, *J*=5.1, 3.0 Hz, 1H), 5.60 (d, *J*=11.1 Hz, 1H), 5.50 (d, *J*=18.0 Hz, 1H), 5.16 (dd, *J*=14.4, 5.1 Hz, 1H), 4.95 (dd, *J*=14.4, 3.0 Hz, 1H) ppm; ^{13}C NMR (DMSO, 75 MHz): δ 163.7, 164.8, 144.1, 132.9, 130.1, 128.6, 127.8, 127.6, 127.0, 125.9, 123.7, 87.5, 75.1 ppm. ESIMS: *m*/*s* (%): 249.65 [M−H]$^-$. Anal. Calcd for $C_{13}H_{11}ClO_3$: C, 62.29; H, 4.42. Found: C, 62.28; H: 4.31%.

*4.2.6. 2-(4-Chlorophenyl)-4-vinyl-2,5-dihydrofuran-3-carboxylic acid (**3f**).* Yield: 75%, white solid; mp: 160.6–161.2 °C. IR: 3080, 3031, 2861, 2667, 2624, 2576, 2529, 1771, 1673, 1639, 1587, 1558, 1541, 1521, 1507, 1489, 1472, 1431, 1406, 1384, 1371, 1326, 1313, 1277, 1200, 1128, 1091, 1071, 1012, 999, 946, 918, 844, 810, 741 cm^{-1}. ^{1}H NMR (DMSO, 300 MHz): δ 12.86 (s, 1H), 7.26–7.39 (m, 5H), 5.88 (dd, *J*=5.1, 3.0 Hz, 1H), 5.60 (d, *J*=11.1 Hz, 1H), 5.51 (d, *J*=18.0 Hz, 1H), 5.13 (dd, *J*=14.4, 5.1 Hz, 1H), 4.94 (dd, *J*=14.4, 3.0 Hz, 1H) ppm; ^{13}C NMR (DMSO, 75 MHz): δ 163.7, 146.7, 140.6, 132.4, 129.1, 128.8, 128.2, 127.7, 123.6, 87.5, 74.9 ppm. ESIMS: *m*/*s* (%): 249.20 [M−H]$^-$. Anal. Calcd for $C_{13}H_{11}ClO_3$: C, 62.29; H, 4.42. Found: C, 62.33; H: 4.47%.

*4.2.7. 2-(4-Bromophenyl)-4-vinyl-2,5-dihydrofuran-3-carboxylic acid (**3g**).* Yield: 88%, white solid; mp: 144.7–145.2 °C. IR: 3445, 2894, 2854, 2663, 2615, 2574, 2360, 2340, 1892, 1676, 1636, 1589, 1488, 1470, 1435, 1414, 1384, 1364, 1311, 1280, 1255, 1124, 1106, 1073, 1009, 945, 860, 840, 811, 745 cm^{-1}. ^{1}H NMR (DMSO, 300 MHz): δ 12.84 (br, 1H), 7.47–7.51 (m, 2H), 7.19–7.31 (m, 3H), 5.83 (s, 1H), 5.58 (d, *J*=10.8 Hz, 1H), 5.48 (d, *J*=18.0 Hz, 1H), 5.14 (dd, *J*=14.4, 5.4 Hz, 1H), 4.95 (dd, *J*=14.4, 2.1 Hz, 1H) ppm; ^{13}C NMR (DMSO, 75 MHz): δ 163.7, 146.7, 141.0, 131.1, 129.4, 128.7, 127.7, 123.6, 121.0, 87.6, 74.9 ppm. ESIMS: *m*/*s* (%): 293.61 [M−H]$^{-\cdot}$ Anal. Calcd for $C_{13}H_{11}BrO_3$: C, 52.91; H, 3.76. Found: C, 52.39; H, 3.82%.

*4.2.8. 2-(4-Methoxyphenyl)-4-vinyl-2,5-dihydrofuran-3-carboxylic acid (**3h**).* Yield: 82%; white solid; mp: 160.1–160.4 °C. IR: 3446, 3035, 3964, 2889, 2855, 2839, 2670, 2621, 2574, 2360, 2340, 1672, 1612, 1588, 1440, 1384, 1513, 1440, 1384, 1320, 1303, 1273, 1248, 1174, 1125, 1113, 1073, 1034, 1019, 947, 852, 824, 809, 742 cm^{-1}. ^{1}H NMR (DMSO, 300 MHz): δ 12.71 (s, 1H), 7.29 (dd, *J*=18.0, 11.1 Hz, 1H), 7.14–7.19 (m, 2H), 6.84–6.89 (m, 2H), 5.82 (dd, *J*=5.4, 3.0 Hz, 1H), 5.58 (d, *J*=11.1 Hz, 1H), 5.48 (d, *J*=18.0 Hz, 1H), 5.07 (dd, *J*=14.4, 5.4 Hz, 1H), 4.89 (dd, *J*=14.4, 3.0 Hz, 1H), 3.72 (s, 3H) ppm; ^{13}C NMR (DMSO, 75 MHz): δ 163.8, 158.9, 146.0, 133.5, 129.3, 128.3, 127.7, 123.1, 113.5, 87.7, 74.3, 55.0 ppm. ESIMS: *m*/*s* (%): 245.7 [M−1]$^-$. Anal. Calcd for $C_{14}H_{14}O_4$: C, 68.28; H, 5.73. Found: C, 68.46; H, 7.89%.

*4.2.9. 2-(3,4-Dimethoxyphenyl)-4-vinyl-2,5-dihydrofuran-3-carboxylic acid (**3i**).* Yield: 87%; white solid; mp: 180.3–180.9 °C. IR: 3446, 3009, 2961, 2946, 2836, 1868, 1072, 1646, 1592, 1558, 1520, 1467, 1423, 1384, 1357, 1310, 1264, 1237, 1193, 1161, 1141, 1114, 1062, 1019, 932, 871, 807, 795, 768, 705 cm^{-1}. ^{1}H NMR (DMSO, 300 MHz): δ 12.76 (s, 1H), 7.30 (dd, *J*=18.0, 11.1 Hz, 1H), 6.76–6.91 (m, 3H), 5.82 (dd, *J*=5.4, 3.0 Hz, 1H), 5.60 (d, *J*=11.1 Hz, 1H), 5.50 (d, *J*=18.0 Hz, 1H), 5.09 (dd, *J*=14.4, 5.4 Hz, 1H), 4.90 (dd, *J*=14.4, 3.0 Hz, 1H), 3.72 (s, 3H), 3.71 (s, 3H) ppm; ^{13}C NMR (DMSO, 75 MHz): δ 164.0, 152.7, 146.3, 137.2, 137.0, 129.0, 127.7, 123.3, 104.4, 88.3, 74.6, 59.9, 55.8 ppm. ESIMS: *m*/*s* (%): 275.7 [M−1]$^-$. Anal. Calcd for $C_{15}H_{16}O_5$: C, 65.21; H, 5.84. Found: C, 65.31; H, 5.90%.

*4.2.10. 2-(3,4,5-Trimethoxyphenyl)-4-vinyl-2,5-dihydrofuran-3-carboxylic acid (**3j**).* Yield: 79%; white solid; mp: 168.6–170.1 °C. IR: 3581, 3453, 2943, 2843, 2626, 2348, 2284, 1899, 1667, 1637, 1594, 1549, 1508, 1466, 1426, 1383, 1323, 1281, 1236, 1185, 1127, 1074, 1001, 942, 827, 799, 776, 747 cm^{-1}. ^{1}H NMR (DMSO, 300 MHz): δ 12.83 (br, 1H), 7.31 (dd, *J*=18.0, 11.1 Hz, 1H), 6.55 (s, 2H), 5.85 (dd, *J*=5.1, 3.0 Hz, 1H), 5.59 (d, *J*=11.1 Hz, 1H), 5.49 (d, *J*=18.0 Hz, 1H), 5.13 (dd, *J*=14.4, 5.1 Hz, 1H), 4.92 (dd, *J*=14.4, 3.0 Hz, 1H), 3.79 (s, 6H), 3.73 (s, 3H) ppm; ^{13}C NMR (DMSO, 75 MHz): δ 164.0, 152.7, 146.3, 137.2, 129.1, 127.8, 123.3, 104.4, 88.3, 74.6, 59.9, 55.8 ppm. ESIMS: *m*/*s* (%): 305.69 [M−H]$^-$. Anal. Calcd for $C_{16}H_{18}O_6$: C, 62.74; H, 5.92. Found: C, 62.81; H, 5.99%.

*4.2.11. 2-(Furan-2-yl)-4-vinyl-2,5-dihydrofuran-3-carboxylic acid (**3k**).* Yield: 80%; white solid; mp: 158.5–159.1 °C. IR: 3420, 3123, 2848, 2664, 2620, 2577, 2526, 1672, 1636, 1588, 1558, 1541, 1504, 1432, 1408, 1384, 1364, 1317, 1275, 1227, 1067, 1009, 932, 848, 818, 769, 743 cm^{-1}. ^{1}H NMR (DMSO, 300 MHz): δ 12.85 (s, 1H), 7.58 (dd, *J*=1.8, 0.6 Hz, 1H), 7.33 (dd, *J*=18.0, 11.1 Hz, 1H), 6.39 (dd, *J*=3.0, 1.8 Hz, 1H), 6.32 (dd, *J*=3.0, 0.6 Hz, 1H), 5.89 (dd, *J*=4.8, 3.0 Hz, 1H), 5.60 (d, *J*=11.1 Hz, 1H), 5.50 (d, *J*=18.0 Hz, 1H), 4.95 (dd, *J*=14.1, 4.8 Hz, 1H), 4.87 (dd, *J*=14.1, 3.0 Hz, 1H) ppm; ^{13}C NMR (DMSO, 75 MHz): δ 163.6, 153.4, 147.8, 142.7, 127.6, 125.9, 123.7, 110.5, 107.9, 80.5, 74.0 ppm. ESIMS: *m*/*s* (%): 205.77 [M−H]$^-$. Anal. Calcd for $C_{11}H_{10}O_4$: C, 64.07; H, 4.89. Found: C, 64.19; H: 4.97%.

*4.2.12. 2-(Pyridin-2-yl)-4-vinyl-2,5-dihydrofuran-3-carboxylic acid (**3l**).* Yield: 70%; blue solid; mp: 138.8–139.5 °C. IR: 3440, 3090, 2885, 2847, 1361, 2343, 1931, 1690, 1648, 1602, 1477, 1439, 1383, 1371, 1342, 1314, 1287, 1217, 1157, 1101, 1072, 1012, 998, 942, 907, 839, 775, 737 cm^{-1}. ^{1}H NMR (DMSO, 300 MHz): δ 12.80 (br, 1H), 8.50 (d, *J*=4.2 Hz, 1H), 7.74–7.80 (m, 1H), 7.28–7.39 (m, 3H), 5.91

(dd, *J*=4.8, 2.7 Hz, 1H), 5.60 (d, *J*=11.1 Hz, 1H), 5.50 (d, *J*=18.0 Hz, 1H), 5.05 (dd, *J*=14.1, 4.8 Hz, 1H), 4.95 (dd, *J*=14.1, 2.7 Hz, 1H) ppm; ^{13}C NMR (DMSO, 75 MHz): δ 163.8, 159.7, 148.9, 147.5, 136.9, 128.1, 127.7, 123.4, 123.2, 122.4, 89.0, 75.1 ppm. ESIMS: *m*/*s* (%): 218.30 $[M+H]^+$. Anal. Calcd for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.10; N, 6.45 found: C, 66.42; H, 5.22; N, 6.49%.

*4.2.13. 2-Nonyl-4-vinyl-2,5-dihydrofuran-3-carboxylic acid (**3m**).* Yield: 63%; colorless oil. IR: 2927, 2854, 2262, 2130, 1730, 1550, 1506, 1458, 1377, 1244, 1155, 1024, 818, 764, 721 cm^{-1}. ^{1}H NMR (DMSO, 300 MHz): δ 12.68–12.79 (br, 1H), 7.24 (q, *J*=18.0, 8.1 Hz, 1H), 5.50 (d, *J*=8.1 Hz, 1H), 5.55 (d, *J*=18.0 Hz, 1H), 4.87 (dd, *J*=9.9, 0.9 Hz, 1H), 4.11 (dd, *J*=10.2, 1.8 Hz, 1H), 1.40–1.46 (m, 2H),1.42–1.51 (m, 1H), 1.65–1.75 (m, 1H), 1.18–1.22 (m, 14H), 0.79–0.88 (m, 3H) ppm; ^{13}C NMR (DMSO, 75 MHz): δ 164.2, 146.1, 129.1, 127.3, 122.5, 86.2, 73.9, 40.3, 40.0, 31.2, 28.3, 29.5, 24.5, 22.0, 13.9 ppm. ESIMS: *m*/*s* (%): 205.58 $[M-H]^-$. Anal. Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found: C, 72.22; H, 9.72%.

*4.2.14. 2-(4-Nitrophenyl)-4-vinyl-2,5-dihydrofuran-3-carboxylic acid (**3n**).* Yield: 89%; yellow solid; mp: 169.7–169.9 °C. IR: 3440, 3078, 2864, 2575, 1912, 1677, 1606, 1587, 1519, 1445, 1415, 1384, 1346, 1280, 1126, 1108, 1072, 1011, 955, 824, 745 cm^{-1}. ^{1}H NMR (DMSO, 300 MHz): δ 12.87 (br, 1H), 8.18 (d, *J*=9.0 Hz, 2H), 7.58 (d, *J*=9.0 Hz, 2H), 7.32 (dd, *J*=18.0, 11.1 Hz, 1H), 6.02 (dd, *J*=5.4, 3.0 Hz, 1H), 5.64 (d, *J*=11.1 Hz, 1H), 5.54 (d, *J*=18.0 Hz, 1H), 5.21 (dd, *J*=14.4, 5.4 Hz, 1H), 5.01 (dd, *J*=14.4, 3.0 Hz, 1H) ppm; ^{13}C NMR (DMSO, 75 MHz): δ 163.6, 149.0, 147.2, 147.1, 128.5, 128.3, 127.5, 124.1, 123.5, 123.4, 87.2, 75.4 ppm. ESIMS: *m*/*s* (%): 260.09 $[M-H]^-$. Anal. Calcd for $C_{13}H_{11}NO_5$: C, 59.77; H, 4.24; N, 5.36. Found: C, 59.92; H, 4.27; N: 5.43%.

*4.2.15. 2-(3,5-Dimethoxyphenyl)-4-ethylfuran-3-carboxylic acid (**4a**).* Yield: 67%; white solid; mp: 105.3–105.6 °C. IR: 3441, 2996, 2963, 2941, 2833, 2623, 1686, 1610, 1588, 1549, 1481, 1446, 1384, 1344, 1327, 1307, 1261, 1194, 1157, 1135, 1094, 1062, 1042, 1008, 934, 838, 806, 765, 703 cm^{-1}. ^{1}H NMR (DMSO, 300 MHz): δ 12.86 (s,1H), 7.56 (t, *J*=2.1, 1.2 Hz, 1H), 6.91 (d, *J*=2.4 Hz, 1H), 6.54 (t, *J*=2.4, 2.1 Hz, 1H), 3.76 (s, 6H), 2.54–2.59 (m, 2H), 1.11–1.16 (m, 3H) ppm; ^{13}C NMR (DMSO, 75 MHz): δ 165.3, 160.1, 155.0, 131.5, 128.6, 114.8, 105.7, 100.9, 55.2, 17.6, 13.8 ppm. ESIMS: *m*/*s* (%): 275.68 $[M-H]^-$. Anal. Calcd for $C_{15}H_{16}O_5$: C, 65.21; H, 5.84. Found: C, 65.07; H, 5.66%.

*4.2.16. 4-Ethyl-2-phenylfuran-3-carboxylic acid (**4b**).* Yield: 73%; white solid; mp: 102.7–103.1 °C. IR: 2957, 2924, 2853, 2575, 1683, 1587, 1558, 1539, 1507, 1457, 1383, 1305, 1219, 1135, 1069, 1011, 928, 826, 773, 756, 710 cm^{-1}. ^{1}H NMR (DMSO, 300 MHz): δ 12.78 (br, 1H), 7.38–7.73 (m, 6H), 2.57 (q, *J*=7.5 Hz, 2H), 1.15 (t, *J*=7.5 Hz, 3H) ppm; ^{13}C NMR (DMSO, 75 MHz): δ 165.2, 156.0, 139.2, 134.0, 128.9, 128.6, 128.1, 127.8, 17.6, 13.8 ppm. ESIMS: *m*/*s* (%): 215.37 $[M-H]^-$. Anal. Calcd for $C_{13}H_{12}O_3$: C, 72.21; H, 5.59. Found: C, 72.33; H, 5.67%.

*4.2.17. 4-Ethyl-2-(2-fluorophenyl)furan-3-carboxylic acid (**4c**).* Yield: 70%; white solid; mp: 105.6–106.1 °C. IR: 2970, 2929, 2878, 2589, 2553, 1682, 1623, 1594, 1556, 1383, 1332, 1311, 1260, 1225, 1155, 1136, 1114, 1095, 1069, 1031, 933, 822, 807, 759, 704 cm^{-1}. ^{1}H NMR (DMSO, 300 MHz): δ 12.56 (s, 1H), 7.66 (s, 1H), 7.48–7.57 (m, 2H), 7.25–7.32 (m, 2H), 2.59 (q, *J*=7.5 Hz, 2H), 1.16 (t, *J*=7.5 Hz, 3H) ppm; ^{13}C NMR (DMSO, 75 MHz): δ 164.1, 160.9, 157.6, 151.1, 140.2, 131.5, 130.9, 128.4, 124.2, 119.0, 116.8, 115.9, 17.6, 13.8 ppm. ESIMS: *m*/*s* (%): 233.49$[M-H]^-$. Anal. Calcd for $C_{13}H_{11}FO_3$: C, 66.66; H, 4.73. Found: C, 66.74; H, 4.83%.

*4.2.18. 4-Ethyl-2-(4-fluorophenyl)furan-3-carboxylic acid (**4d**).* Yield 71%; white solid; mp: 114.6–116.7 °C. IR: 2971, 2924, 2877, 2691, 2621, 2545, 1676, 1610, 1587, 1550, 1473, 1445, 1383, 1331, 1304, 1265, 1250, 1223, 1140, 1090, 1063, 1046, 1036, 980, 933, 911, 805, 771, 726 cm^{-1}. ^{1}H NMR (DMSO, 300 MHz): δ 12.51 (s, 1H), 7.36–7.63 (m, 5H), 2.59–2.67 (m, 2H), 1.18 (t, *J*=7.5 Hz, 3H) ppm; ^{13}C NMR (DMSO, 75 MHz): δ 164.3, 154.6, 139.9, 133.1, 132.1, 131.0, 130.2, 129.3, 127.9, 126.8, 116.3, 17.6, 13.7 ppm. ESIMS: *m*/*s* (%): 265.35 $[M+Na]^+$. Anal. Calcd for $C_{13}H_{11}FO_3$: C, 66.66; H, 4.73. Found: C, 66.81; H, 4.92%.

*4.2.19. 2-(3-Chlorophenyl)-4-ethylfuran-3-carboxylic acid (**4e**).* Yield: 82%; white solid; mp: 132.3–133.0 °C. IR: 3069, 2970, 2936, 2882, 2682, 2650, 2617, 2573, 1733, 1681, 1602, 1588, 1574, 1558, 1539, 1478, 1443, 1382, 1330, 1299, 1252, 1221, 1146, 1089, 1069, 912, 890, 806, 777, 766, 745 cm^{-1}. ^{1}H NMR (DMSO, 300 MHz): δ 12.92 (s, 1H), 7.79 (s, 1H), 7.65–0.7.69 (m, 1H), 7.62 (s, 1H), 7.42–7.48 (m, 2H), 2.58 (q, *J*=7.5 Hz, 3H), 1.13 (t, *J*=7.5 Hz, 1 h) ppm; ^{13}C NMR (DMSO, 75 MHz): δ 164.9, 154.1, 139.6, 132.8, 131.8, 129.9, 128.8, 128.5, 127.3, 126.2, 115.2, 17.6, 13.6 ppm. ESIMS: *m*/*s* (%): 249.7 $[M-H]^-$. Anal. Calcd for $C_{13}H_{11}ClO_3$: C, 62.29; H, 4.42. Found: C, 62.17; H, 4.22%.

*4.2.20. 2-(4-Chlorophenyl)-4-ethylfuran-3-carboxylic acid (**4f**).* Yield 71%; white solid; mp: 139.7–141.2 °C. IR: 2965, 2936, 2876, 2633, 2578, 1771, 1733, 1683, 1601, 1570, 1558, 1540, 1507, 1484, 1456, 1436, 1384, 1333, 1307, 1295, 1223, 1136, 1096, 1075, 1014, 929, 928, 801, 775, 747, 715 cm^{-1}. ^{1}H NMR (DMSO, 300 MHz): δ 12.87 (s, 1H), 7.76 (d, *J*=6.9 Hz, 2H), 7.62 (s, 1H), 7.51 (d, *J*=7.5 Hz, 2H), 2.56 (q, *J*=7.5 Hz, 2H), 1.14 (t, *J*=7.5 Hz, 3H) ppm; ^{13}C NMR (DMSO, 75 MHz): δ 165.0, 154.8, 139.5, 133.6, 129.5, 128.8, 123.2, 114.7, 17.6, 13.7 ppm. ESIMS: *m*/*s* (%): 295.38 $[M-H]^-$. Anal. Calcd for $C_{13}H_{11}ClO_3$: C, 62.29; H, 4.42. Found: C, 62.19; H, 4.63%.

*4.2.21. 2-(4-Bromophenyl)-4-ethylfuran-3-carboxylic acid (**4g**).* Yield 75%; white solid; mp: 139.7–141.2 °C. IR: 2964, 2934, 2875, 2691, 2630, 2575, 1670, 1598, 1567, 1538, 1507, 1479, 1436, 1384, 1332, 1305, 1294, 1263, 1220, 1136, 1093, 1070, 1011, 928, 827, 801, 773, 754, 735, 711 cm^{-1}. ^{1}H NMR (DMSO, 300 MHz): δ 12.84 (s, 1H), 7.38–7.73 (m, 5H), 2.56 (m, 2H), 1.14 (t, *J*=7.5 Hz, 3H) ppm; ^{13}C NMR (DMSO, 75 MHz): δ 165.5, 155.3, 139.9, 131.5, 130.2, 129.6, 129.3, 128.5, 122.7, 115.2, 18.1, 14.1 ppm. ESIMS: *m*/*s* (%): 293.18 $[M-H]^-$. Anal. Calcd for $C_{13}H_{11}BrO_3$: C, 52.91; H, 3.76. Found: C, 52.89; H, 3.79%.

*4.2.22. 4-Ethyl-2-(4-methoxyphenyl)furan-3-carboxylic acid (4**h**).* Yield 75%; white solid; mp: 142.3–142.9 °C. IR:2973, 2918, 2875, 2843, 2681, 2583, 1672, 1611, 1589, 1575, 1543, 1497, 1437, 1384, 1370, 1335, 1305, 1286, 1254, 1220, 1176, 1138, 1080, 1024, 927, 837, 805, 759 cm^{-1}. ^{1}H NMR (DMSO, 300 MHz): δ 12.88 (s, 1H), 7.66 (d, *J*=6.9 Hz, 2H), 7.58 (s, 1H), 7.52 (d, *J*=6.9 Hz, 2H), 2.54 (q, *J*=7.5 Hz, 2H), 1.14 (t, *J*=7.5 Hz, 3H) ppm; ^{13}C NMR (DMSO, 75 MHz):δ 162.6, 158.7, 152.3, 143.5, 131.2, 125.8, 123.5, 115.8, 17.6, 13.9 ppm. ESIMS: *m*/*s* (%): 285.5 $[M]^+$. Anal. Calcd for $C_{13}H_{10}Cl_2O_3$: C, 54.76; H, 3.54. Found: C, 54.79; H, 3.58%.

*4.2.23. 2-(3,4-Dimethoxyphenyl)-4-ethylfuran-3-carboxylic acid (**4i**).* Yield: 68%; white solid; mp: 112.7–113.1 °C. IR: 3011, 2966, 2941, 2919, 2880, 2837, 2588, 1683, 1616, 1590, 1558, 1540, 1507, 1455, 1383, 1321, 1258, 1236, 1213, 1175, 1139, 1118, 1080, 1022, 942, 854, 808, 765 cm^{-1}. ^{1}H NMR (DMSO, 300 MHz): 12.77 (br, 1H), 7.53 (s, 1H), 7.38 (d, *J*=2.1 Hz, 1H), 7.32 (dd, *J*=18.3, 2.1 Hz, 1H), 6.92 (d, *J*=18.3 Hz, 1H), 3.70–3.79 (m, 6H), 2.57 (q, *J*=7.5 Hz, 2H), 1.14 (t, *J*=7.5 Hz, 3H) ppm; ^{13}C NMR (DMSO, 75 MHz): 163.3, 158.7, 153.7, 153.4, 133.7, 127.3, 125.4, 123.7, 121.6, 118.5, 116.5, 17.6, 14.2 ppm. ESIMS: *m*/*s* (%): 275.7 $[M-1]^-$. Anal. Calcd for $C_{15}H_{16}O_5$: C, 65.21; H, 5.84. Found: C, 65.31; H, 5.90%.

*4.2.24. 4-Ethyl-2-(3,4,5-trimethoxyphenyl)furan-3-carboxylic acid (**4j**).* Yield: 62%; white solid; mp: 142.6–143.1 °C. IR: 2963, 2944, 2882, 2838, 2625, 1691, 1588, 1551, 1498, 1471, 1455, 1417, 1384, 1347, 1305, 1260, 1244, 1212, 1178, 1134, 1088, 1003, 930, 853, 835, 821, 802, 766, 738, 711 cm^{-1}. ^{1}H NMR (DMSO, 300 MHz): δ 12.80 (s, 1H), 7.55 (s, 1H), 7.11 (s, 2H), 3.79 (s, 6H), 3.71 (s, 3H), 2.55 (q,

J=7.5 Hz, 2H), 1.15 (t,=7.5 Hz, 3H) ppm; ^{13}C NMR (DMSO, 75 MHz): δ 165.4, 155.6, 152.4, 138.7, 138.2, 128.7, 125.2, 114.1, 105.5, 60.0, 55.8, 17.6, 13.8 ppm. ESIMS: m/s (%): 305.53 $[M-H]^-$. Anal. Calcd for $C_{16}H_{18}O_6$: C, 62.74; H, 5.92. Found: C, 62.51; H, 5.67%.

*4.2.25. 4-Ethyl-2,2′-bifuran-3-carboxylic acid (**4k**).* Yield: 66%; white solid; mp: 136.8–137.1 °C. IR: 3143, 2966, 2938, 2877, 2610, 2580, 1733, 1681, 1599, 1558, 1530, 1489, 1457, 1422, 1384, 1322, 1298, 1268, 1233, 1162, 1140, 1091, 1076, 1022, 987, 937, 886, 809, 769, 751 cm^{-1}. ^{1}H NMR (DMSO, 300 MHz): δ 12.88 (s, 1H), 7.82 (q, J=1.8; 0.6 Hz, 1H), 7.58 (s, 1H), 7.26 (t, J=0.6 Hz, 1H), 6.32 (q, J=1.8 Hz, 1H), 2.57 (q, J=7.5 Hz, 2H), 1.16 (q, J=7.5 Hz, 3H) ppm; ^{13}C NMR (DMSO, 75 MHz): δ 164.3, 143.9, 139.1, 128.4, 133.1, 112.3, 111.8, 59.7, 17.6, 13.8 ppm. ESIMS: m/s (%): 205.29 $[M-H]^-$. Anal. Calcd for $C_{11}H_{10}O_4$: C, 64.07; H, 4.89. Found: C, 64.15; H: 4.93%.

*4.2.26. 4-Ethyl-2-(pyridin-2-yl)furan-3-carboxylic acid (**4l**).* Yield: 57%; white solid; mp: 119.0–119.4 °C. IR: 3159, 3131, 3086, 2966, 2929, 2871, 1360, 2341, 1699, 1652, 1635, 1603, 1575, 1558, 1539, 1507, 1456, 1429, 1382, 1219, 1282, 1260, 1217, 1153, 1080, 1019, 932, 817, 782, 749, 738 cm^{-1}. ^{1}H NMR (DMSO, 300 MHz): δ 8.69 (d, J=4.8 Hz, 1H), 8.16 (t, J=7.8 Hz, 1H), 7.99 (d, J=9.1 Hz, 3H), 7.78 (s, 1H), 7.59 (t, J=6.0 Hz, 1H), 2.68 (q, J=7.5 Hz, 2H), 1.14 (t, J=7.5 Hz, 3H) ppm; ^{13}C NMR (DMSO, 75 MHz): δ 162.4, 150.1, 146.1, 146.0, 141.1, 140.2, 131.4, 124.4, 121.0, 118.3, 17.7, 13.5 ppm. ESIMS: m/s (%): 216.19 $[M-H]^-$. Anal. Calcd for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.10; N, 6.45 found: C, 66.28; H, 5.17; N, 6.41%.

*4.2.27. 4-Ethyl-2-(4-(trifluoromethyl)phenyl)furan-3-carboxylic acid (**4o**).* Yield: 85%; white solid; mp: 159.9–161.0 °C. IR: 2974, 2942, 2882, 2678, 2633, 2583, 2526, 1683, 1620, 1594, 1549, 1507, 1449, 1427, 1384, 1322, 1227, 1170, 1132, 1080, 1064, 1017, 931, 847, 805, 763, 713 cm^{-1}. ^{1}H NMR (DMSO, 300 MHz): δ 12.02 (s, 1H), 7.95 (d, J=8.7 Hz, 2H), 7.75 (d, J=8.4 Hz, 2H), 7.63 (s, 1H), 2.57 (q, J=7.5 Hz, 2H), 1.15 (J=7.5 Hz, 3H) ppm; ^{13}C NMR (DMSO, 75 MHz): δ 165.3, 159.7, 156.0, 138.5, 129.5, 128.6, 126.6, 113.5, 113.0, 55.2, 17.8, 13.9 ppm. ESIMS: m/s (%): 283.10 $[M-H]^-$. Anal. Calcd for $C_{12}H_{11}NO_3$: C, 59.16; H, 3.90. Found: C, 59.32; H, 3.73%.

*4.2.28. Ethyl 3-(3,5-dimethoxyphenyl)-4-oxo-3,3a,4,6-tetra-hydro-1H-furo[3,4-c]pyran-3a-carboxylate (**5a**).* Yield: 51%; white solid; mp: 102.6–102.7 °C. IR: 3464, 3110, 3011, 2965, 2932, 2868, 2839, 1726, 1596, 1469, 1427, 1386, 1355, 1289, 1230, 1182, 1151, 1101, 1052, 974, 962, 913, 866, 851, 836, 813, 796, 778, 726, 700 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.91–6.92 (m, 2H), 6.37–6.39 (m, 1H), 6.04–6.06 (m, 1H), 4.97 (d, J=12.0 Hz, 1H), 4.81–4.85 (m, 2H), 4.64 (d, J=12.0 Hz, 1H), 3.78–3.87 (m, 8H), 0.91 (t, J=7.2 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 167.4, 164.8, 160.3, 141.9, 138.7, 115.6, 104.6, 100.7, 83.9, 68.8, 67.5, 64.3, 62.2, 55.3, 13.4 ppm. ESIMS: m/s (%): 371.93 $[M+Na]^+$. Anal. Calcd for $C_{18}H_{20}O_7$: C, 62.06; H, 5.79. Found: C, 62.13; H, 5.87%.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2011.03.038. This data include MOL file and InChIKey of the most important compound described in this article.

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