Green Chemistry

PAPER

View Article Online
View Journal | View Issue

Cite this: *Green Chem.*, 2014, **16**, 3237

Group-assisted purification (GAP) chemistry for dihydrofurans: water as a medium for catalyst free synthesis in a one pot four component reaction†

Madhu Chennapuram,[a] Narender Reddy Emmadi,[a] Chiranjeevi Bingi,[a] Jagadeesh Babu Nanubolu[b] and Krishnaiah Atmakur*[a,c]

Received 5th March 2014,
Accepted 2nd April 2014

DOI: 10.1039/c4gc00388h

www.rsc.org/greenchem

A simple, catalyst free, water mediated, one pot four component, green protocol was developed for title compounds **7** starting from aromatic aldehydes (**1**), malononitrile (**2**), 1,3-diones (**3**) and *N*-chlorosuccinimide (NCS) in a sequential addition reaction at ambient temperature. The approach presented herein, for the first time, is through an unusual rearrangement where NCS was reacted with 2-amino-7,7-dimethyl-5-oxo-4-aryl-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**4**), which was formed by the Knoevenagel condensation of aldehyde and malononitrile followed by the Michael addition of **3**. In addition, this novel protocol is compatible with various aldehydes and active C–H functional derivatives, accomplishes high yields and follows the GAP chemistry principle. Interestingly, compound **4** when reacted with NCS in alcohol medium gave 2-cyano-6,6-dimethyl-4-oxo-3-aryl-2,3,4,5,6,7-hexahydrobenzofuran-2-carboxylate (**5**).

Introduction

In modern heterocyclic chemistry furan scaffolds occupy a prominent position principally because of their presence in many natural products and biologically active compounds.[1] Among this class of compounds, dihydrofurans are one of the important compounds commonly found in a large variety of naturally occurring substances.[2] Furthermore, dihydrofurans are subunits of a range of biologically active compounds[3] and also serve as extremely important intermediates in organic synthesis[4] as they can be transformed into an array of highly functionalized tetrahydrofurans.[5] In fact, a number of synthetic strategies have been reported[6,7] for synthesis of functionalized dihydrofuran derivatives including the Feist–Benary and the interrupted Feist–Benary (FB) reaction,[8] CAN mediated oxidative cycloaddition of 1,3-dicarbonyls to conjugated compounds,[9] DABCO promoted reaction of pyridinium salts with enones,[10,11] olefin metathesis,[12] Pd catalyzed coupling–cyclization of 2-(2′,3′-allenyl)acetylacetates,[13] copper catalyzed asymmetric cycloaddition,[14] and the ionic liquid promoted interrupted Feist–Benary reaction.[15] However, most of the strategies require using a base or a metal catalyst and an organic solvent and follow a traditional approach. Usually, traditional organic syntheses adopt a "stop-and-go" approach, which involves the purification of intermediates to avoid the compatibility issues of the consecutive reactions.

On the other hand, purification processes are often time consuming and expensive. In addition, organic solvents contribute the lion's share to the pollution problem in practical organic synthesis.[16] In this instance, water is the solvent of choice as an ideal organic reaction demands that it would proceed neat, that is, without any solvent or preferably in an environmentally benign solvent such as water. Moreover, water is considered as a cheap, safe, natural, non-flammable, environmentally benign and abundantly available green solvent.[17] Additionally, multicomponent reactions (MCRs) effectively answer the issues of traditional approaches and have become an increasingly powerful tool[18] in organic, combinatorial and medicinal chemistry because of their atom economy, convergence, multiple bond forming efficiency[19] and other suitable characteristics from the green chemistry point of view.[20] These features make MCRs well suited for easy construction of diversified heterocyclic scaffolds.[21] With this background, and also as a part of our research programme on the synthesis of bioactive molecules in a multicomponent one pot reaction,[22] herein we report the synthesis of functionalized 2,3-dihydrofurans for the first time by a green, novel and efficient, water mediated, catalyst free one pot four component reaction.

[a]*Division of Crop Protection Chemicals, CSIR-Indian Institute of Chemical Technology, Tarnaka, Hyderabad 500 007, India*
[b]*Laboratory of X-ray crystallography, CSIR-Indian Institute of Chemical Technology, Tarnaka, Hyderabad 500 007, India*
[c]*AcSIR-Indian Institute of Chemical Technology, Tarnaka, Hyderabad 500 007, India. E-mail: srikrishnua@yahoo.com; Fax: +91 40 27193382; Tel: +91 40 27191436*
†CCDC 979361 and 982398. For crystallographic data in CIF or other electronic format see DOI: 10.1039/c4gc00388h

Results and discussion

Before embarking on preparation of the title compounds **7** by water mediated reaction, 2-amino-7,7-dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**4**) was prepared in higher yield (84%) by reacting benzaldehyde (**1**), malononitrile (**2**) and 5,5-dimethylcyclohexane-1,3-dione (**3**) in water at reflux temperature (Scheme 1).[23]

In an effort to construct further a ring system over **4**, it was treated with *N*-chlorosuccinimide (NCS) in ethanol at room temperature (Table 1) and ethyl 2-cyano-6,6-dimethyl-4-oxo-3-phenyl-2,3,4,5,6,7-hexahydrobenzofuran-2-carboxylate (**5a**) was obtained in high yields within 0.5 h. Surprised over the unusual formation of the ring contraction product **5a** in contrast to a similar literature report,[24] the same reaction was repeated in methanol and gratifyingly obtained a methyl ester (**5b**). The structure of **5** was well characterized by NMR and mass spectra. However, IR spectra indicated a very low intense signal for the –CN functional group. Finally, the structure of a representative compound **5h** was unambiguously confirmed by single crystal X-ray diffraction analysis (Fig. 1).

In order to establish the optimum reaction conditions for **5**, catalyst screening studies were conducted in ethanol at room temperature employing NBS, NIS, I_2 and sodium chlorite, and sodium hypochlorite and aqueous *tert*-butyl hydroperoxide (TBHP) in combination with sodium chlorite. It is interesting to mention that the reaction with NBS (Table 1, entry 2) resulted in formation of two products, *i.e.* **5a** (50%) and **6a** (33%), whereas with NIS (Table 1, entry 3), compound **6b** was obtained in poor yields. However, reaction with I_2 (Table 1, entry 4) afforded **5a** in 33%, whereas the reaction of **4** with sodium chlorite independently, as well as in combination with TBHP and also with sodium hypochlorite, at ambient and reflux temperature could not give any product. With these results in hand, the NCS reaction was further studied using *n*-propanol, isopropanol, *n*-butanol, and isobutanol as the solvent and obtained the corresponding esters (**5c–f**). Furthermore, this method was generalised by reacting different chromenes **4** with NCS, varying substitution on the phenyl ring, in ethanol and the results **5g–m** are shown in Table 2.

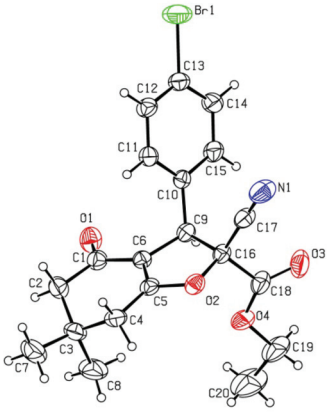
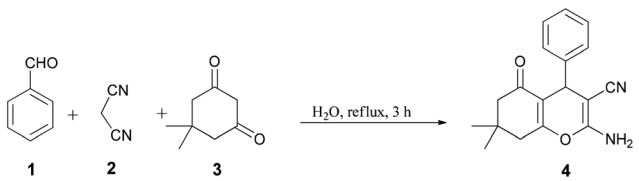
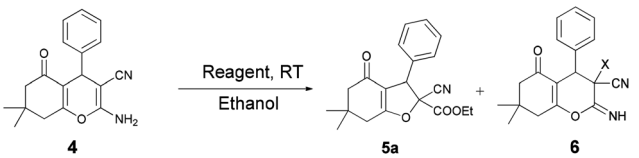


Fig. 1 ORTEP diagram of compound **5h**.[25]



Scheme 1

Table 1 Optimization of reaction conditions[a]



Entry	Reagent	Time (h)	Product **5a** (%)	Product **6** (%)
1	NCS	0.5	79	—
2	NBS	1.0	50	33 (**6a**: X = Br)
3	NIS	1.0	—	20 (**6b**: X = I)
4	I_2	1.0	33	—
5	$NaClO_2$	6.0	—	—
6	NaOCl	6.0	—	—
7	$NaClO_2$–TBHP	6.0	—	—

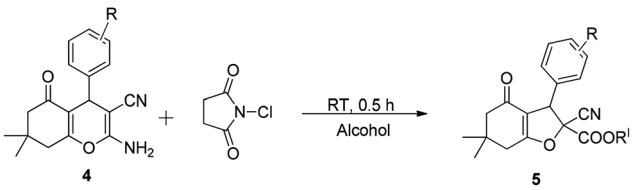
[a] Unless otherwise indicated, the reaction was performed by treating **4** (1.7 mmol) and the corresponding reagent (1.7 mmol) in ethanol at room temperature.

At this stage, attention was directed to treat compound **4** with NCS in water as a solvent presuming to yield a carboxylic acid **8** instead of an ester **5**.

Accordingly compound **4** was treated with NCS (1 equiv.) in water at room temperature and surprisingly **7** was obtained, at variance with the expected product in 7 h (Scheme 2). However, 1.2 equivalents of NCS could bring down the reaction time to 3 h. Having obtained compound **7** in water mediated reaction, we next scrutinized the solvent ratio in combination with 25% and also with 50% ethanolic water independently and obtained the combination of products **5** and **7** in 30%, 35% and 29%, and 42% yields respectively. Similar yields were also observed with 25% and 50% methanolic water.

The structure of **7** was confirmed by NMR, IR, and mass spectroscopy and also by X-ray crystallography analyses (Fig. 2). Next, our studies were directed to prepare **7** by four component one pot reaction in water. Thus a model reaction was attempted with benzaldehyde (**1**) (1 mmol), malononitrile (**2**) (1 mmol), and dimedone (**3**) (1 mmol) in water at reflux temperature followed by NCS (1.2 mmol) in sequential addition at ambient temperature. Amazingly, this reaction resulted in product **7** in high yields (Table 3).

Table 2 Scope of alcohols and the R functional group on **4** to synthesize compound **5**[a]



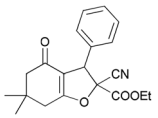
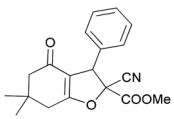
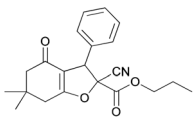
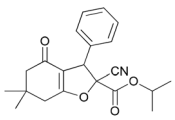
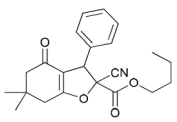
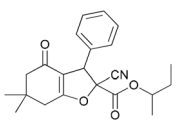
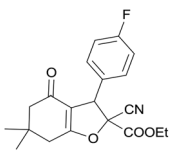
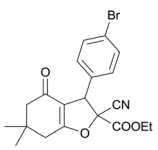
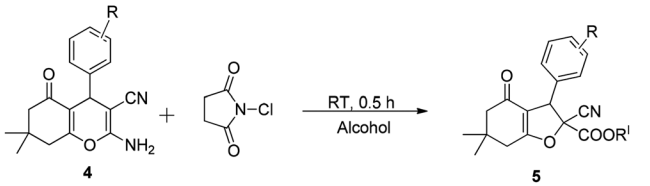
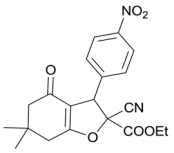
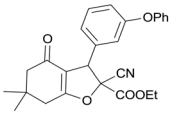
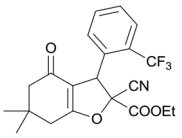
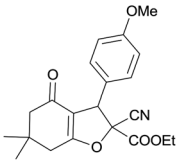
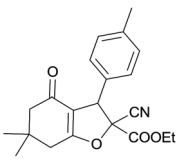
Entry	R	Alcohol	Product (**5**)	Yield[b] (%)
1	H	Ethanol	 **5a**	79
2	H	Methanol	 **5b**	70
3	H	*n*-Propanol	 **5c**	72
4	H	Isopropanol	 **5d**	62
5	H	*n*-Butanol	 **5e**	58
6	H	Isobutanol	 **5f**	68
7	4-F	Ethanol	 **5g**	69
8	4-Br	Ethanol	 **5h**	76

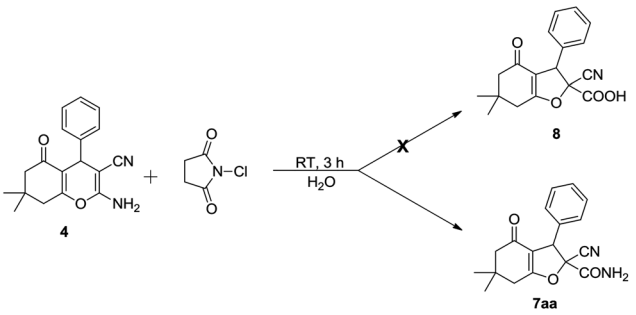
Table 2 *(Contd.)*



Entry	R	Alcohol	Product (**5**)	Yield[b] (%)
9	4-NO2	Ethanol	 **5i**	80
10	3-OPh	Ethanol	 **5j**	65
11	2-CF_3	Ethanol	 **5k**	63
12	4-OMe	Ethanol	 **5l**	69
13	4-Me	Ethanol	 **5m**	71

[a] Unless otherwise indicated, the reaction was performed with compound **4** (1.7 mmol) and NCS (1.7 mmol) in the corresponding alcohol at room temperature open to air for 0.5 h. [b] Yields are given for isolated products.

Captivated by the exceptional formation of **7** in a water mediated, four component, one pot, catalyst free, eco-friendly reaction in high yields, the generality and scope of this protocol were demonstrated by synthesizing a series of dihydrofuran derivatives (**7aa–7am** & **7b–d**). A wide range of aldehydes including an aliphatic aldehyde (**7am**) and different active C–H functional derivatives such as **3a**, **3b**, and **3c** were well tolerated under this set of reaction conditions and furnished **7** in good yields (Table 4). Pure products were obtained by simple filtration and washed with water and hexanes. It is noteworthy



Scheme 2

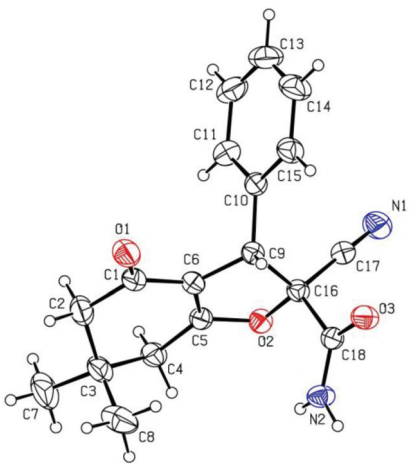
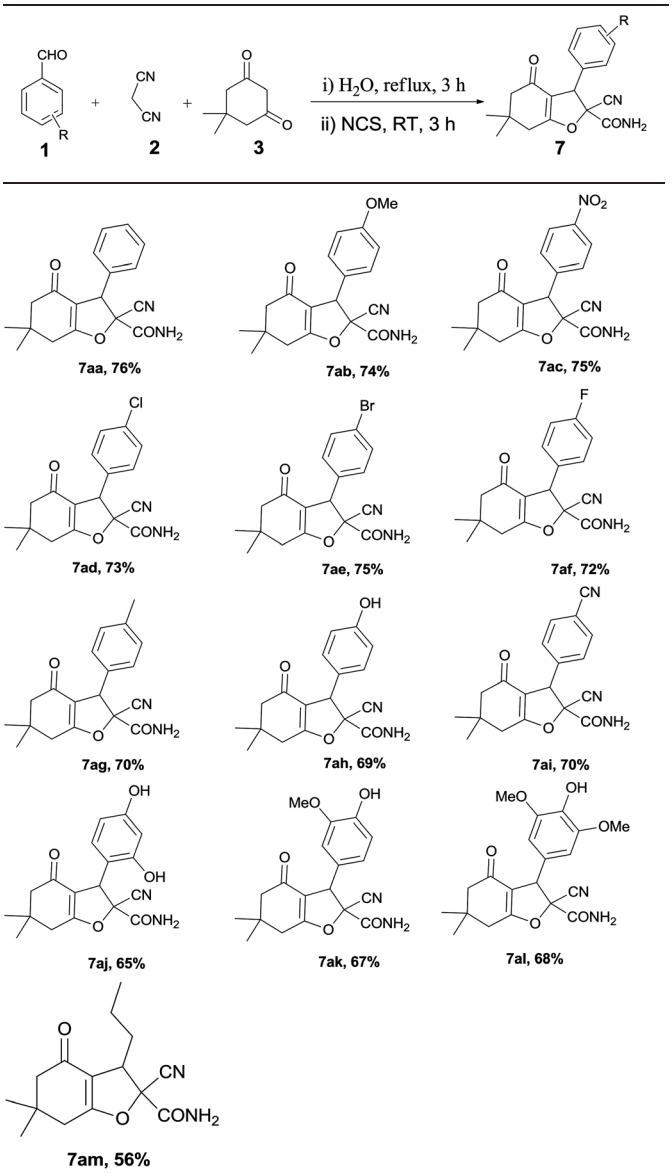


Fig. 2 ORTEP diagram of compound **7aa**.[25]

Table 3 Scope of aldehydes to synthesize compound **7**[a,b]



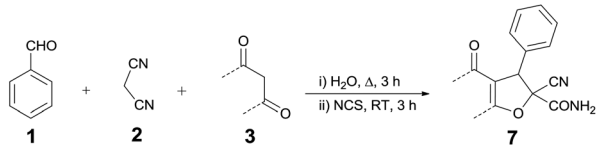
[a] Unless otherwise indicated, the reaction was performed with aldehyde **1** (3.7 mmol), malononitrile **2** (3.7 mmol) and dimedone **3** (3.7 mmol) in water (40 mL) at reflux temperature for 3 h followed by addition of NCS (4.5 mmol) at RT and stirred for 3 h. [b] Yields are given for isolated pure products.

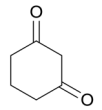
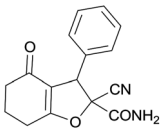
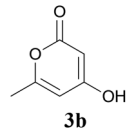
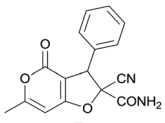
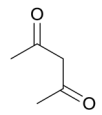
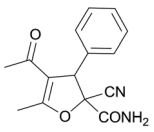
that this protocol followed the GAP chemistry process, which avoids traditional purification methods such as column chromatography and recrystallization.

Furthermore, compound **7** was subjected to hydrolysis with concentrated HCl and also with sulphuric acid to get an acid **8**. However, these studies were unsuccessful. In the light of sequential formation of **4**, followed by the unexpected ring contraction product **7** in one pot reaction, a plausible mechanism has been proposed for the title compounds. As per the established chemistry, the reaction begins with the formation of the Knoevenagel product **A** followed by the Michael addition of C–H functional derivatives leading to **B** which on intramolecular cyclization followed by a 1,3 proton shift provides the aminonitrile compound (**4**). This, on treatment with NCS gives C, which on C–O bond dissociation propelled by water, leads to intermediate **D**. Then the subsequent attack of the hydroxyl functional group on nitrile carbon and elimination of HCl facilitate the formation of the five member ring **E**, which tautomerises to the desired product **7**.

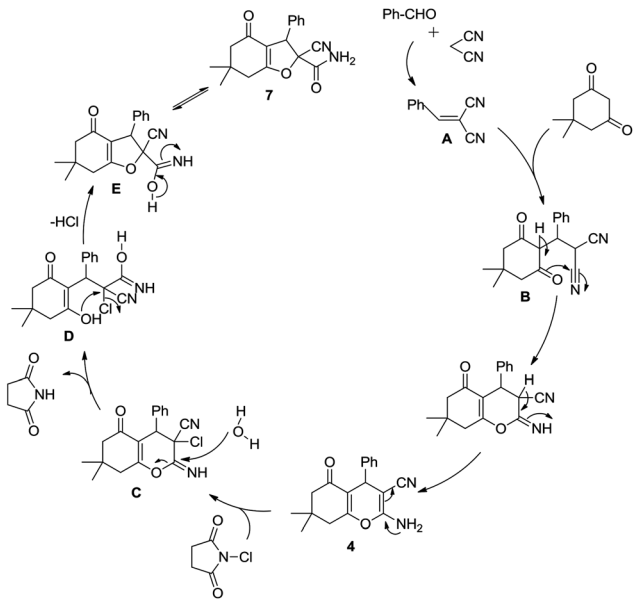
Furthermore, the presence of succinimide protons at 9.32 and 2.75 ppm in the ^{1}H NMR spectrum of the crude product **7**, which had disappeared on washing with water and hexanes, is evidence for the proposed mechanism. On the other hand, formation of **5** is presumably attributable to the hydrolysis of alkoxyimine (similar to **E**) due to the increase in acidity during the course of the reaction, as the pH of the alcoholic medium changed from 4.95 (before addition of NCS) to 1.23 on completion of the reaction and also there was no possibility for tautomerism. A similar situation was observed in water mediated reaction of **7**, where the pH changed from 5.02 to 1.60 at the end of the reaction. Nevertheless, the possible tautomerism of hydroxy imine **E** probably leads to **7** (Scheme 3).

Table 4 Scope of active methylene compounds to synthesize 7[a]



Entry	3	Product 7	Yield (%)
1	 3a	 7b	69
2	 3b	 7c	58
3	 3c	 7d	52

[a] Unless otherwise indicated, the reaction conditions are the same as in Table 3.



Scheme 3 Plausible reaction mechanism for compound 7.

Conclusions

In summary, we have improved the yields of **4** up to 84% in water mediated reaction at reflux temperature and developed a simple, efficient, catalyst free green protocol for the synthesis of dihydrofurans (**7**) for the first time in water mediated one pot four component reaction following GAP chemistry. High yields and compatibility are the added advantages of this protocol which can be exploited further.

Experimental section

General

Melting points were measured by CINTEX programmable melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra of samples in $CDCl_3$ and DMSO-d_6 were recorded on AVANCE-300 MHz and 500 MHz spectrometers. Chemical shifts (δ) are reported relative to TMS (δ = 0.0) as the internal standard. Mass spectra were recorded on ESI spectrometers. All high resolution mass spectra were recorded on the QSTAR XL Hybrid MS/MS System (Applied Biosystems/MDS Sciex, Foster City, USA), equipped with an ESI source (IICT, Hyderabad). IR were recorded on Thermo Nicolet nexus 670 spectrometer using KBr pellets. pH of the reaction medium was recorded on an EI digital pH meter (model no. 112) using standardised buffers 4 and 9. TLC was performed on Merck 60 F-254 silica gel plates. The chemicals used in this work were obtained from commercial channels and were used without purification.

General procedure for the preparation of ethyl 2-cyano-6,6-dimethyl-4-oxo-3-phenyl-2,3,4,5,6,7-hexahydrobenzofuran-2-carboxylate (5)

To a suspension of 2-amino-7,7-dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**4**) (500 mg, 1.7 mmol) in 5 mL of ethanol in a round bottomed flask was added *N*-chlorosuccinimide (226 mg, 1.7 mmol) and the homogeneous solution was stirred at room temperature, open to air. After completion of the reaction as indicated by TLC, the separated solid was filtered, washed with (2 × 2 mL) cold ethanol and dried to yield the pure product **5**.

Ethyl 2-cyano-6,6-dimethyl-4-oxo-3-phenyl-2,3,4,5,6,7-hexahydrobenzofuran-2-carboxylate (5a). Isolated as a yellow solid; yield 79%; m.p. 110–112 °C; IR (KBr): 3002, 2963, 2937, 2274, 1764, 1660, 1387, 1230, 1126, 1036, 971, 730, 700 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42–7.33 (m, 3H), 7.20 (d, J = 8.24 Hz, 2H), 4.71 (s, 1H), 4.44–4.35 (m, 2H), 2.62–2.50 (m, 2H), 2.34–2.22 (m, 2H), 1.38 (t, J = 7.17 Hz, 3H), 1.22 (s, 3H), 1.16 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 193.0, 175.0, 164.0, 135.2, 129.0, 128.0, 113.3, 112.4, 85.4, 64.3, 55.2, 51.0, 37.1, 34.2, 28.5, 28.4, 14.0 ppm; ESI-MS: m/z 340 $[M + H]^+$; HRMS (ESI) Anal. calcd for $C_{20}H_{22}NO_4$ m/z 340.1543 $[M + H]^+$, found 340.1585.

Methyl 2-cyano-6,6-dimethyl-4-oxo-3-phenyl-2,3,4,5,6,7-hexahydrobenzofuran-2-carboxylate (5b). Isolated as a colourless solid; yield 70%; m.p. 125–127 °C; IR (KBr): 3027, 2961, 2932, 2877, 2189, 1771, 1651, 1455, 1390, 1251, 1223, 1128, 1031, 972, 727, 697 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41 (d, J = 6.79 Hz, 3H), 7.22 (d, J = 7.55 Hz, 2H), 4.73 (s, 1H), 3.99 (s, 3H), 2.60 (s, 2H), 2.32 (s, 2H), 1.26 (s, 3H), 1.19 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 193.0, 175.0, 165.0, 135.2, 129.0, 128.0, 112.4, 85.4, 55.3, 55.0, 51.0, 37.2, 34.3, 30.0, 28.5 ppm;

ESI-MS: *m/z* 326 $[M + H]^+$; HRMS (ESI) Anal. calcd for $C_{19}H_{20}NO_4$ *m/z* 326.1392 $[M + H]^+$, found 326.1392.

Propyl 2-cyano-6,6-dimethyl-4-oxo-3-phenyl-2,3,4,5,6,7-hexahydrobenzofuran-2-carboxylate (5c). Isolated as a yellow solid; yield 72%; m.p. 149–153 °C; IR (KBr): 2983, 2937, 2140, 1764, 1660, 1387, 1230, 1126, 730, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.45–7.32 (m, 3H), 7.19 (d, J = 9.06 Hz, 2H), 4.70 (s, 1H), 4.32 (t , J = 6.60 Hz, 2H), 2.65–2.49 (m, 2H), 2.29 (s, 2H), 1.87–1.72 (m, 2H), 1.23 (s, 3H), 1.17 (s, 3H), 1.01 (t, J = 7.36 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 198.0, 175.0, 164.1, 135.3, 129.0, 128.0, 113.3, 112.4, 85.4, 70.0, 55.3, 51.0, 37.1, 34.2, 28.5, 28.4, 20.0, 10.0 ppm; ESI-MS: *m/z* 354 $[M + H]^+$; HRMS (ESI) Anal. calcd for $C_{21}H_{24}NO_4$ *m/z* 354.1707 $[M + H]^+$, found 354.1707.

Isopropyl 2-cyano-6,6-dimethyl-4-oxo-3-phenyl-2,3,4,5,6,7-hexahydrobenzofuran-2-carboxylate (5d). Isolated as a yellow solid; yield 62%; m.p. 121–123 °C; IR (KBr): 2989, 2964, 2168, 1762, 1650, 1386, 1261, 1226, 1105, 729, 699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.43–7.34 (m, 3H), 7.19 (d, J = 9.30 Hz, 2H), 5.25–5.17 (m, 1H), 4.67 (s, 1H), 2.63–2.52 (m, 2H), 2.34–2.26 (m, 2H), 1.41 (d, J = 6.25 Hz, 3H), 1.37 (d, J = 6.25 Hz, 3H), 1.24 (s, 3H), 1.17 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 193.0, 175.0, 163.5, 137.0, 135.3, 129.0, 128.0, 113.2, 112.5, 86.0, 73.0, 55.3, 51.0, 37.2, 34.2, 29.0, 21.3 ppm; ESI-MS: *m/z* 354 $[M + H]^+$; HRMS (ESI) Anal. calcd for $C_{21}H_{24}NO_4$ *m/z* 354.1715 $[M + H]^+$, found 354.1705.

Butyl 2-cyano-6,6-dimethyl-4-oxo-3-phenyl-2,3,4,5,6,7-hexahydrobenzofuran-2-carboxylate (5e). Isolated as a yellow liquid; yield 58%; IR (KBr): 2964, 2874, 2181, 1763, 1658, 1460, 1389, 1221, 1123, 730, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.43–7.34 (m, 3H), 7.19 (d, J = 6.56 Hz, 2H), 4.69 (s, 1H), 4.36 (t, J = 6.56 Hz, 2H), 2.68–2.50 (m, 2H), 2.35–2.25 (m, 2H), 1.79–1.71 (m, 2H), 1.49–1.36 (m, 2H), 1.23 (s, 3H), 1.17 (s, 3H), 0.98 (t, J = 7.35 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 192.8, 174.0, 164.0, 135.2, 129.0, 127.7, 113.2, 112.3, 67.9, 64.2, 55.1, 50.56, 37.0, 34.0, 30.3, 28.9, 18.5, 13.4 ppm; ESI-MS: *m/z* 368 $[M + H]^+$; HRMS (ESI) Anal. calcd for $C_{22}H_{26}NO_4$ *m/z* 368.1856 $[M + H]^+$, found 368.1878.

***sec*-Butyl 2-cyano-6,6-dimethyl-4-oxo-3-phenyl-2,3,4,5,6,7-hexahydrobenzofuran-2-carboxylate (5f).** Isolated as a yellow liquid; yield 68%; IR (KBr): 3031, 2963, 2875, 2230, 1753, 1720, 1655, 1389, 1221, 757, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.42–7.34 (m, 3H), 7.19 (d, J = 8.24 Hz, 2H), 4.70 (s, 1H), 4.18–4.90 (m, 2H), 2.63–2.52 (m, 2H), 2.33–2.25 (m, 2H), 2.12–2.03 (m, 1H), 1.24 (s, 3H), 1.17 (s, 3H), 1.01 (s, 3H), 1.00 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 193.1, 175.0, 164.0, 135.2, 129.0, 128.0, 113.3, 112.3, 85.4, 77.1, 74.0, 55.2, 51.0, 37.1, 34.1, 28.4, 28.0, 19.0 ppm; ESI-MS: *m/z* 368 $[M + H]^+$; HRMS (ESI) Anal. calcd for $C_{22}H_{26}NO_4$ *m/z* 368.1867 $[M + H]^+$, found 368.1868.

Ethyl 2-cyano-3-(4-fluorophenyl)-6,6-dimethyl-4-oxo-2,3,4,5,6,7-hexahydrobenzofuran-2-carboxylate (5g). Isolated as a colourless solid; yield 74%; m.p. 137–138 °C; IR (KBr): 2962, 2937, 2187, 1751, 1657, 1490, 1387, 1299, 964, 853 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.17 (q, J = 5.2 Hz, 2H), 7.09 (t, J = 8.49 Hz, 2H), 4.70 (s, 1H), 4.43 (q, J = 7.17 Hz, 2H), 2.59 (s, 2H), 2.30 (s, 2H), 1.41 (t, J = 7.16 Hz, 3H), 1.24 (s, 3H), 1.17 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 193.1, 175.0, 162.0, 130.0, 116.0, 113.3, 112.5, 85.4, 64.5, 55.0, 51.0, 37.31, 34.3, 29.5, 28.5, 14.0 ppm; ESI-MS: *m/z* 358 $[M + H]^+$; HRMS (ESI) Anal. calcd for $C_{20}H_{21}FNO_4$ *m/z* 358.1455 $[M + H]^+$, found 358.1454.

Ethyl 3-(4-bromophenyl)-2-cyano-6,6-dimethyl-4-oxo-2,3,4,5,6,7-hexahydrobenzofuran-2-carboxylate (5h). Isolated as a colourless solid; yield 76%; m.p. 141–144 °C; IR (KBr): 2959, 2897, 2873, 2185, 1919, 1764, 1649, 1391, 1250, 1218, 1208, 837, 544 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.53 (d, J = 8.30 Hz, 2H), 7.08 (d, J = 8.49 Hz, 2H), 4.67 (s, 1H), 4.48–4.37 (m, 2H), 2.68–2.48 (m, 2H), 2.28 (s, 2H), 1.40 (t, J = 7.17 Hz, 3H), 1.22 (s, 3H), 1.17 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 193.0, 175.0, 164.0, 134.3, 132.2, 130.0, 123.1, 113.1, 112.4, 85.2, 64.5, 55.0, 51.0, 37.2, 34.3, 28.4, 29.0, 14.0 ppm; ESI-MS: *m/z* 440 $[M + Na]^+$; HRMS (ESI) Anal. calcd for $C_{20}H_{20}BrNO_4Na$ *m/z* 440.0467 $[M + Na]^+$, found 440.0474.

Ethyl 2-cyano-6,6-dimethyl-3-(4-nitrophenyl)-4-oxo-2,3,4,5,6,7-hexahydrobenzofuran-2-carboxylate (5i). Isolated as a colourless solid; yield 80%; m.p. 152–154 °C; IR (KBr): 2963, 2877, 2214, 1771, 1659, 1526, 1348, 1224, 1111, 985, 730 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.27 (d, J = 8.30 Hz, 2H), 7.39 (d, J = 8.30 Hz, 2H), 4.82 (s, 1H), 4.45 (q, J = 6.79 Hz, 2H), 2.72–2.51 (m, 2H), 2.31 (s, 2H), 1.42 (t, J = 6.79 Hz, 3H), 1.25 (s, 3H), 1.19 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 193.0, 175.4, 163.5, 149.0, 142.3, 130.0, 113.0, 112.2, 85.0, 65.0, 55.0, 51.0, 37.2, 34.4, 29.0, 28.5, 13.86 ppm; ESI-MS: *m/z* 385 $[M + H]^+$; HRMS (ESI) Anal. calcd for $C_{20}H_{21}N_2O_6$ *m/z* 385.1394 $[M + H]^+$, found 385.1401.

Ethyl 2-cyano-6,6-dimethyl-4-oxo-3-(3-phenoxyphenyl)-2,3,4,5,6,7-hexahydrobenzofuran-2-carboxylate (5j). Isolated as a brown viscous liquid; yield 65%; IR (KBr): 2959, 2897, 2873, 2222, 1919, 1764, 1649, 1391, 1250, 1218, 1208, 837, 544 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.43–7.20 (m, 3H), 7.13–6.89 (m, 5H), 6.80 (d, J = 7.36 Hz, 1H), 4.68 (s, 1H), 4.37 (q, J = 6.98 Hz, 2H), 2.51 (s, 2H), 2.26 (s, 2H), 1.34 (t, J = 5.66 Hz, 3H), 1.12 (s, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 193.1, 175.3, 175.2, 164.0, 158.0, 157.2, 155.3, 137.2, 130.4, 129.5, 123.2, 119.0, 118.0, 113.0, 112.3, 85.3, 64.3, 55.0, 51.0, 37.0, 34.1, 28.3, 28.2, 14.0 ppm; ESI-MS: *m/z* 432 $[M + H]^+$; HRMS (ESI) Anal. calcd for $C_{26}H_{26}NO_5$ *m/z* 432.1811 $[M + H]^+$, found 432.1812.

Ethyl 2-cyano-6,6-dimethyl-4-oxo-3-(2-(trifluoromethyl)phenyl)-2,3,4,5,6,7-hexahydrobenzofuran-2-carboxylate (5k). Isolated as a yellow liquid; yield 63%; IR (KBr): 2962, 2937, 2222, 1751, 1657, 1490, 1387, 1299, 964, 853 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.74 (d, J = 7.78 Hz, 1H), 7.57 (t, J = 7.62 Hz, 1H), 7.46 (t, J = 7.62 Hz, 1H), 7.25 (d, J = 7.93 Hz, 1H), 5.19 (s, 1H), 4.43–4.33 (m, 2H), 2.63–2.50 (m, 2H), 2.29 (s, 2H), 1.36 (t, J = 8.08 Hz, 3H), 1.22 (s, 3H), 1.16 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 192.3, 175.0, 163.5, 134.1, 132.4, 129.1, 129.0, 126.4, 126.4, 114.0, 112.2, 86.0, 64.4, 51.0, 50.2, 37.1, 34.3, 30.0, 29.0, 28.3, 13.5 ppm; ESI-MS: *m/z* 408 $[M + H]^+$; HRMS (ESI) Anal. calcd for $C_{21}H_{21}NO_4F_3$ *m/z* 408.1423 $[M + H]^+$, found 408.1424.

Ethyl 2-cyano-3-(4-methoxyphenyl)-6,6-dimethyl-4-oxo-2,3,4,5,6,7-hexahydrobenzofuran-2-carboxylate (5l). Isolated as a brown solid; yield 69%; m.p. 128–130 °C; IR (KBr): 2973, 2943, 2245, 1889, 1735, 1646, 1456, 1232, 1122, 1037, 876, 756 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.12 (d, J = 8.69 Hz, 2H), 6.91 (d, J = 8.69 Hz, 2H), 4.66 (s, 1H), 4.45–4.34 (m, 2H), 3.79 (s, 3H), 2.62–2.49 (m, 2H), 2.28 (s, 2H), 1.32 (t, J = 7.17 Hz, 3H), 1.22 (s, 3H), 1.15 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 193.0, 174.6, 164.1, 160.0, 129.0, 127.2, 114.3, 113.4, 85.6, 64.2, 55.1, 54.8, 51.0, 34.2, 28.5, 28.4, 13.8 ppm; ESI-MS: m/z 370 $[M + H]^+$; HRMS (ESI) Anal. calcd for $C_{21}H_{24}NO_5$ m/z 370.1649 $[M + H]^+$, found 370.1653.

Ethyl 2-cyano-6,6-dimethyl-4-oxo-3-*p*-tolyl-2,3,4,5,6,7-hexahydrobenzofuran-2-carboxylate (5m). Isolated as a pale yellow solid; yield 71%; m.p. 122–125 °C; IR (KBr): 2962, 2935, 2225, 1898, 1749, 1653, 1608, 1465, 1251, 1120, 1027, 836, 763 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.14 (d, J = 7.62 Hz, 2H), 6.92 (d, J = 8.69 Hz, 2H), 4.66 (s, 1H), 4.46–4.34 (t, J = 6.25 Hz, 2H), 2.65–2.48 (m, 2H), 2.34 (s, 3H), 2.29 (s, 2H), 1.42 (t, J = 6.56 Hz, 3H), 1.23 (s, 3H), 1.16 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 193.0, 174.7, 164.1, 138.7, 132.2, 129.6, 127.6, 113.4, 112.5, 85.5, 64.2, 55.0, 51.0, 37.1, 34.2, 28.5, 28.4, 21.1, 13.8 ppm; ESI-MS: m/z 354 $[M + H]^+$; HRMS (ESI) Anal. calcd for $C_{21}H_{24}NO_4$ m/z 354.1699 $[M + H]^+$, found 354.1702.

General procedure for the preparation of 2-cyano-6,6-dimethyl-4-oxo-3-phenyl-2,3,4,5,6,7-hexahydrobenzofuran-2-carboxamide (7)

To a round bottomed flask equipped with a reflux condenser and a stopper were added benzaldehyde **1** (400 mg, 3.7 mmol), malononitrile **2** (248 mg, 3.7 mmol), and water (40 mL) and stirred for around 15 min at room temperature. To this was added 5,5-dimethylcyclohexane-1,3-dione (**3**) (527 mg, 3.7 mmol), and the reaction mixture was heated to reflux while stirring for 3 h. The reaction completion was monitored by TLC. Then the heterogeneous reaction mixture mass was allowed to cool down to room temperature, and to it *N*-chlorosuccinimide (603 mg, 4.5 mmol) was added under continued stirring. After completion of the reaction (by TLC, in 3 h), the separated solid was collected on a Buchner funnel after washing with water (2 × 10 mL) and hexanes (10 mL) to yield the pure product **7**.

2-Cyano-6,6-dimethyl-4-oxo-3-phenyl-2,3,4,5,6,7-hexahydrobenzofuran-2-carboxamide (7aa). Isolated as a colourless solid; yield 76%; m.p. 203–205 °C; IR (KBr): 3368, 3151, 2966, 2798, 2217, 1718, 1649, 1223, 641 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$ + DMSO-d_6): δ 7.65 (s, 2H), 7.41–7.23 (m, 5H), 4.88 (s, 1H), 2.65–2.55 (m, 2H), 2.28 (s, 2H), 1.24 (s, 3H), 1.17 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$ + DMSO-d_6): δ 192.2, 178.5, 174.0, 166.0, 136.4, 128.2, 127.9, 127.0, 113.5, 112.6, 86.1, 54.1, 50.5, 36.4, 36.2, 29.1, 28.1, 28.0 ppm; ESI-MS: m/z 311 $[M + H]^+$; HRMS (ESI) Anal. calcd for $C_{18}H_{19}N_2O_3$ m/z 311.1390 $[M + H]^+$, found 311.1395.

2-Cyano-3-(4-methoxyphenyl)-6,6-dimethyl-4-oxo-2,3,4,5,6,7-hexahydrobenzofuran-2-carboxamide (7ab). Isolated as a colourless solid; yield 74%; m.p. 233–235 °C; IR (KBr): 3365, 3197, 2960, 2262, 1711, 1646, 1246, 851 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + DMSO-d_6): δ 7.89 (s, 2H), 7.16 (d, J = 8.68 Hz, 2H), 6.88 (d, J = 8.68 Hz, 2H), 4.79 (s, 1H), 3.79 (s, 3H), 2.68–2.61 (m, 2H), 2.68 (s, 2H), 1.23 (s, 3H), 1.16 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6): δ 192.5, 178.4, 173.4, 166.2, 159.0, 129.0, 128.1, 113.5, 113.4, 113.0, 86.3, 54.6, 54.5, 53.1, 50.6, 36.0, 29.1, 28.2, 28.0 ppm; ESI-MS: m/z 341 $[M + H]^+$; HRMS (ESI) Anal. calcd for $C_{19}H_{21}N_2O_4$ m/z 341.1495 $[M + H]^+$, found 341.1496.

2-Cyano-6,6-dimethyl-3-(4-nitrophenyl)-4-oxo-2,3,4,5,6,7-hexahydrobenzofuran-2-carboxamide (7ac). Isolated as a colourless solid; yield 75%; m.p. 250–252 °C; IR (KBr): 3345, 3185, 2964, 2876, 2213, 1712, 1656, 1494, 1114, 976, 733, 682 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + DMSO-d_6): δ 8.26 (s, 1H), 8.24 (s, 1H), 7.95 (d, J = 7.74 Hz, 2H), 7.50 (d, J = 7.74 Hz, 2H), 4.93 (s, 1H), 2.80–2.59 (m, 2H), 2.31 (s, 2H), 1.23 (s, 3H), 1.16 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6): δ 193.2, 175.5, 166.0, 148.0, 144.1, 130.0, 124.0, 114.0, 112.4, 86.0, 54.1, 51.0, 37.0, 34.1, 28.4, 28.3 ppm; ESI-MS: m/z 356 $[M + H]^+$, HRMS (ESI) Anal. calcd for $C_{18}H_{18}N_3O_5$ 356.1241 $[M + H]^+$, found 356.1251.

3-(4-Chlorophenyl)-2-cyano-6,6-dimethyl-4-oxo-2,3,4,5,6,7-hexahydrobenzofuran-2-carboxamide (7ad). Isolated as a colourless solid; yield 73%; m.p. 278–280 °C; IR (KBr): 3360, 3172, 2965, 2873, 2283, 1713, 1651, 1223, 975, 657 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + DMSO-d_6): δ 8.16 (s, 1H), 8.02 (s, 1H), 7.36 (d, J = 8.30 Hz, 2H), 7.21 (d, J = 8.30 Hz, 2H), 4.78 (s, 1H), 2.67–2.53 (m, 2H), 2.26 (s, 2H), 1.22 (s, 3H), 1.15 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6): δ 192.1, 174.0, 166.0, 135.0, 133.2, 133.0, 129.1, 113.3, 112.3, 86.0, 53.5, 50.4, 36.4, 33.5, 30.2, 28.0 ppm; ESI-MS: m/z 345 $[M + H]^+$; HRMS (ESI) Anal. calcd for $C_{18}H_{18}N_2O_3Cl$ m/z 345.1000 $[M + H]^+$, found 345.1007.

3-(4-Bromophenyl)-2-cyano-6,6-dimethyl-4-oxo-2,3,4,5,6,7-hexahydrobenzofuran-2-carboxamide (7ae). Isolated as a colourless solid; yield 75%; m.p. 296–298 °C; IR (KBr): 3356, 3168, 2964, 2869, 2222, 1715, 1651, 1468, 1386, 1222, 975, 975, 656 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + DMSO-d_6): δ 8.19 (s, 1H), 8.06 (s, 1H), 7.51 (d, J = 8.12 Hz, 2H), 7.15 (d, J = 8.30 Hz, 2H), 4.75 (s, 1H), 2.80–2.59 (m, 2H), 2.25 (s, 2H), 1.22 (s, 3H), 1.17 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6): δ 193.0, 175.0, 166.4, 136.4, 132.0, 130.4, 122.1, 114.2, 113.0, 86.4, 54.2, 51.1, 37.0, 34.2, 29.0, 28.0 ppm; ESI-MS: m/z 388 $[M + H]^+$; HRMS (ESI) Anal. calcd for $C_{18}H_{18}O_3N_2Br$ m/z 389.0495 $[M + H]^+$, found 389.0504.

2-Cyano-3-(4-fluorophenyl)-6,6-dimethyl-4-oxo-2,3,4,5,6,7-hexahydrobenzofuran-2-carboxamide (7af). Isolated as a colourless solid; yield 72%; m.p. 265–267 °C; IR (KBr): 3367, 3184, 2963, 2874, 2262, 1649, 1222, 843, 655 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + DMSO-d_6): δ 7.94 (s, 1H), 7.64 (s, 1H) 7.25 (q, J = 5.28 Hz, 2H), 7.07 (t, J = 8.68 Hz, 2H), 4.85 (s, 1H), 2.65–2.55 (m, 2H), 2.27 (s, 2H), 1.23 (s, 3H), 1.16 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6): δ 192.2, 174.1, 166.1, 160.2, 133.1, 130.0, 129.1, 115.2, 114.1, 113.4, 86.0, 53.5, 50.5, 36.3, 34.0, 28.1, 27.1, 27.0 ppm; ESI-MS: m/z 329 $[M + H]^+$;

HRMS (ESI) Anal. calcd for $C_{18}H_{18}FN_2O_3$ *m*/*z* 329.1296 $[M + H]^+$, found 329.1299.

2-Cyano-6,6-dimethyl-4-oxo-3-*p*-tolyl-2,3,4,5,6,7-hexahydrobenzofuran-2-carboxamide (7ag). Isolated as a colourless solid; yield 70%; m.p. 242–246 °C; IR (KBr): 3338, 2960, 2869, 2218, 1715, 1651, 1469, 1396, 1268, 975, 656 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + DMSO-d_6): δ 8.11 (s, 1H), 7.96 (s, 1H), 7.17 (d, *J* = 7.93 Hz, 2H), 7.10 (d, *J* = 8.12 Hz, 2H), 4.72 (s, 1H), 2.80–2.50 (m, 2H), 2.34 (s, 3H), 2.29 (s, 2H), 1.27 (s, 3H), 1.18 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6): δ 192.3, 174.1, 166.1, 137.3, 133.5, 130.3, 129.0, 128.7, 127.5, 127.0, 115.3, 114.1, 113.0, 54.0, 50.0, 36.4, 28.1, 28.0, 26.6 ppm; ESI-MS: *m*/*z* 325 $[M + H]^+$; HRMS (ESI) Anal. calcd for $C_{19}H_{21}N_2O_3$ *m*/*z* 325.1546 $[M + H]^+$, found 325.1552.

2-Cyano-3-(4-hydroxyphenyl)-6,6-dimethyl-4-oxo-2,3,4,5,6,7-hexahydrobenzofuran-2-carboxamide (7ah). Isolated as a yellow solid; yield 69%; m.p. 264–266 °C; IR (KBr): 3471, 3329, 3289, 2984, 2873, 2274, 1719, 1641, 1514, 1219, 976, 536 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + DMSO-d_6): δ 8.08 (s, 1H), 7.95 (s, 1H) 7.00 (d, *J* = 8.30 Hz, 2H), 6.77 (d, *J* = 8.30 Hz, 2H), 6.54 (s, 1H), 4.65 (s, 1H), 2.68–2.61 (m, 2H), 2.26 (s, 2H), 1.21 (s, 3H), 1.13 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6): δ 192.3, 173.5, 166.2, 157.2, 129.0, 128.2, 127.0, 115.1, 114.1, 113.0, 112.0, 86.5, 54.0, 51.0, 36.4, 33.5, 28.1, 28.0 ppm; ESI-MS: *m*/*z* 327 $[M + H]^+$; HRMS (ESI) Anal. calcd for $C_{18}H_{19}N_2O_4$ *m*/*z* 327.1344 $[M + H]^+$, found 327.1343.

2-Cyano-3-(4-cyanophenyl)-6,6-dimethyl-4-oxo-2,3,4,5,6,7-hexahydrobenzofuran-2-carboxamide (7ai). Isolated as a colourless solid; yield 70%; m.p. 235–237 °C; IR (KBr): 3339, 3167, 2965, 2225, 2199, 1714, 1654, 1503, 1389, 1224, 1114, 977, 666 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + DMSO-d_6): δ 8.33 (s, 2H), 7.82 (d, *J* = 8.12 Hz, 2H), 7.43 (d, *J* = 8.12 Hz, 2H), 4.83 (s, 1H), 2.80–2.61 (m, 2H), 2.35–2.15 (m, 2H), 1.19 (s, 3H), 1.11 (s, 3H) ppm; ^1H NMR (300 MHz, $CDCl_3$ + DMSO-d_6) (D_2O exchange): δ 7.81 (d, *J* = 7.36 Hz, 2H), 7.44 (d, *J* = 7.55 Hz, 2H), 4.84 (s, 1H), 2.76–2.53 (m, 2H), 2.38–2.13 (m, 2H), 1.19 (s, 3H), 1.12 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6): δ 192.4, 175.0, 166.0, 142.0, 132.2, 129.1, 118.1, 114.0, 112.0, 111.2, 86.0, 54.0, 50.5, 36.3, 34.0, 28.2, 28.0 ppm; ESI-MS: *m*/*z* 336 $[M + H]^+$; HRMS (ESI) Anal. calcd for $C_{19}H_{18}N_3O_3$ *m*/*z* 336.1362 $[M + H]^+$, found 336.1341.

2-Cyano-3-(2,4-dihydroxyphenyl)-6,6-dimethyl-4-oxo-2,3,4,5,6,7-hexahydrobenzofuran-2-carboxamide (7aj). Isolated as a brown solid; yield 65%; m.p. 234–236 °C; IR (KBr): 3399, 3259, 2962, 2217, 1708, 1653, 1520, 1393, 1213, 968, 618 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + DMSO-d_6): δ 8.01 (s, 1H), 7.93 (s, 1H), 6.63 (d, *J* = 7.93 Hz, 1H), 6.52 (d, *J* = 1.88 Hz, 1H), 6.36 (d, *J* = 8.12 Hz, 1H), 4.43 (s, 1H), 2.80–2.50 (m, 2H), 2.17 (s, 2H), 1.21 (s, 3H), 1.12 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6): δ 193.0, 174.0, 166.5, 145.1, 145.0, 128.0, 119.0, 115.5, 115.3, 113.0, 87.0, 54.0, 50.1, 36.5, 34.0, 28.4, 28.1 ppm; ESI-MS: *m*/*z* 343 $[M + H]^+$; HRMS (ESI) Anal. calcd for $C_{18}H_{19}N_2O_5$ *m*/*z* 343.1294 $[M + H]^+$, found 343.1294.

2-Cyano-3-(4-hydroxy-3-methoxyphenyl)-6,6-dimethyl-4-oxo-2,3,4,5,6,7-hexahydrobenzofuran-2-carboxamide (7ak). Isolated as a brown solid; yield 67%; m.p. 201–204 °C; IR (KBr): 3365, 2964, 2201, 1744, 1658, 1517, 1389, 1211, 762, 631 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + DMSO-d_6): δ 9.02 (s, 1H), 7.38 (s, 2H), 6.83 (d, *J* = 7.91 Hz, 1H), 6.66 (d, *J* = 6.98 Hz, 2H), 4.70 (s, 1H), 3.82 (s, 3H), 2.80–2.61 (m, 2H), 2.26 (s, 2H), 1.23 (s, 3H), 1.16 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6): δ 192.2, 174.1, 164.1, 147.4, 126.5, 120.5, 115.4, 113.0, 112.5, 111.4, 85.3, 55.4, 54.4, 36.5, 43.0, 28.1, 28.0 ppm; ESI-MS: *m*/*z* 357 $[M + H]^+$; HRMS (ESI) Anal. calcd for $C_{19}H_{21}O_5N_2$ *m*/*z* 357.1445 $[M + H]^+$, found 357.1456.

2-Cyano-3-(4-hydroxy-3,5-dimethoxyphenyl)-6,6-dimethyl-4-oxo-2,3,4,5,6,7-hexahydrobenzofuran-2-carboxamide (7al). Isolated as a brown solid; yield 68%; m.p. 162–165 °C; IR (KBr): 3422, 3268, 2960, 2200, 1708, 1648, 1517, 1118, 972, 616 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + DMSO-d_6): δ 8.08 (s, 2H), 7.95 (s, 1H), 6.42 (s, 2H), 4.67 (s, 1H), 3.81 (s, 6H), 2.80–2.61 (m, 2H), 2.26 (s, 2H), 1.24 (s, 3H), 1.16 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6): δ 192.4, 174.0, 162.2, 146.0, 135.3, 126.0, 114.0, 113.0, 105.0, 86.4, 56.0, 51.0, 37.0, 35.5, 28.5, 28.0 ppm; ESI-MS: *m*/*z* 387 $[M + H]^+$; HRMS (ESI) Anal. calcd for $C_{20}H_{23}N_2O_6$ *m*/*z* 387.1564 $[M + H]^+$, found 387.1563.

2-Cyano-6,6-dimethyl-4-oxo-3-propyl-2,3,4,5,6,7-hexahydrobenzofuran-2-carboxamide (7am). Isolated as a colourless solid; yield 56%; m.p. 120–125 °C; IR (KBr): 3316, 3166, 2961, 2874, 2243, 1774, 1710, 1641, 1393, 1206, 1106, 650 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 6.68 (s, 1H), 6.47 (s, 1H), 3.66 (s, 1H), 2.44 (s, 2H), 2.26 (s, 2H), 2.09–1.70 (m, 2H), 1.63–1.35 (m, 2H), 1.14 (s, 3H), 1.11 (s, 3H), 0.96 (t, *J* = 7.17 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 193.8, 171.5, 166.9, 114.5, 113.7, 85.2, 51.2, 48.9, 37.3, 34.2, 33.6, 28.6, 20.0, 13.8 ppm; ESI-MS: *m*/*z* 277 $[M + H]^+$; HRMS (ESI) Anal. calcd For $C_{15}H_{21}N_2O_3$ *m*/*z* 277.1546 $[M + H]^+$, found 277.1543.

2-Cyano-4-oxo-3-phenyl-2,3,4,5,6,7-hexahydrobenzofuran-2-carboxamide (7b). Isolated as a colourless solid; yield 69%; m.p. 189–191 °C; IR (KBr): 3368, 3156, 2955, 2192, 1716, 1650, 1385, 1177, 1128, 961, 698 ppm; ^1H NMR (300 MHz, $CDCl_3$ + DMSO-d_6): δ 8.15 (s, 2H), 7.32 (d, *J* = 6.42 Hz, 3H), 7.18 (d, *J* = 6.79 Hz, 2H), 4.67 (s, 1H), 2.87–2.59 (m, 2H), 2.38 (q, *J* = 6.78 Hz, 2H), 2.10 (q, *J* = 5.85 Hz, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6): δ 193.0, 175.4, 166.1, 136.5, 128.3, 128.2, 128.0, 114.0, 113.6, 86.1, 54.3, 36.3, 23.0, 21.0 ppm; ESI-MS: *m*/*z* 283 $[M + H]^+$; HRMS (ESI) Anal. calcd for $C_{16}H_{15}N_2O_3$ *m*/*z* 283.1077 $[M + H]^+$, found 283.1080.

2-Cyano-6-methyl-4-oxo-3-phenyl-3,4-dihydro-2*H*-furo[3,2-*c*]-pyran-2-carboxamide (7c). Isolated as a colourless solid; yield 58%; m.p. 251–253 °C; IR (KBr): 3323, 3274, 3166, 2198, 1695, 1589, 1250, 1123, 701, 577 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + DMSO-d_6): δ 8.19 (s, 1H), 8.09 (s, 1H), 7.40 (q, *J* = 6.98 Hz, 3H), 7.27 (d, *J* = 9.06 Hz, 2H), 6.33 (s, 1H), 4.99 (s, 1H), 2.35 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6): δ 169.0, 167.0, 165.2, 159.0, 135.1, 128.4, 128.3, 113.2, 100.0, 95.1, 87.0, 53.5, 20.0 ppm; ESI-MS: *m*/*z* 297 $[M + H]^+$; HRMS (ESI) Anal. calcd for $C_{16}H_{13}N_2O_4$ *m*/*z* 297.0487 $[M + H]^+$, found 297.0876.

4-Acetyl-2-cyano-5-methyl-3-phenyl-2,3-dihydrofuran-2-carboxamide (7d). Isolated as a colourless solid; yield 52%; m.p. 157–159 °C; IR (KBr): 3399, 3164, 2257, 1719, 1679, 1601, 1381, 1319, 1223, 1191, 939, 637 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$ +

DMSO-d_6): δ 11.14 (s, 2H), 7.67–7.45 (m, 5H), 5.14 (s, 1H), 2.68 (s, 3H), 2.14 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$ + DMSO-d_6): δ 193.0, 178.5, 167.0, 165.3, 138.0, 129.0, 128.1, 114.2, 114.0, 84.0, 57.0, 29.2, 14.1 ppm; ESI-MS: m/z 271 $[M + H]^+$; HRMS (ESI) Anal. calcd for $C_{15}H_{15}N_2O_3$ m/z 271.1077 $[M + H]^+$, found 271.1082.

Acknowledgements

We thank Dr V. J. Rao, Head Crop Protection Chemicals Division for encouragement and Director CSIR-IICT for support. We are grateful to SERB-DST, New Delhi for financial support (grant no. SB/EMEQ-075/2013).

Notes and references

1 (*a*) B. H. Lipshutz, *Chem. Rev.*, 1986, **86**, 795; (*b*) G. D. McCallion, *Curr. Org. Chem.*, 1999, **3**, 67; (*c*) A. Goel, A. Kumar and A. Raghuvanshi, *Chem. Rev.*, 2013, **113**, 1614; (*d*) D. S. Mortensen, A. L. Rodriguez, K. E. Carlson, J. Sun, B. S. Katzenellenbogen and J. A. Katzenellenbogen, *J. Med. Chem.*, 2001, **44**, 3838.

2 (*a*) F. M. Dean and M. V. Sargent, in *Comprehensive Heterocyclic Chemistry*, ed. C. W. Bird and G. W. H. Cheeseman, Pergamon Press, New York, 1984, vol. 4, Part 3, p. 531; (*b*) Y. Sukpondma, V. Rukachaisirikul and S. Phongpaichit, *J. Nat. Prod.*, 2005, **68**, 1010; (*c*) G. Majetich, G. Zou and J. Grove, *Org. Lett.*, 2008, **10**, 85.

3 (*a*) S. S. Shin, Y. Byun, K. M. Lim, J. K. Choi, K.-W. Lee, J. H. Moh, J. K. Kim, Y. S. Jeong, J. Y. Kim, Y. H. Choi, H.-J. Koh, Y.-H. Park, Y. I. Oh, M.-S. Noh and S. Chung, *J. Med. Chem.*, 2004, **47**, 792; (*b*) S.-L. Vaittinen, H. Komulainen, V.-M. Kosma, A. Julkunen, J. Mäki-Paakkanen, K. Jansson, T. Vartiainen and J. Tuomisto, *J. Food Chem. Toxicol.*, 1995, **33**, 1027.

4 (*a*) R. S. Ward, *Tetrahedron*, 1990, **46**, 5029; (*b*) B. M. Fraga, *Nat. Prod. Rep.*, 1992, **9**, 217; (*c*) A. T. Merrit and S. V. Ley, *Nat. Prod. Rep.*, 1992, **9**, 243; (*d*) O. R. Gottlieb, *New Natural Products and Plant Drugs with Pharmacological, Biological, or Therapeutical Activity*, Springer-Verlag, Berlin, Heidelberg, Germany, 1987, p. 227; (*e*) U. Koert, *Synthesis*, 1995, 115.

5 (*a*) For leading references to the asymmetric synthesis of tetrahydrofurans, see: X.-L. Hou, Z. Yang, K.-S. Yeung and H. N. C. Wong, *Prog. Heterocycl. Chem.*, 2005, **17**, 142–171; (*b*) M. C. Elliott, *J. Chem. Soc., Perkin Trans. 1*, 2002, 2301; (*c*) M. M. Faul and B. E. Huff, *Chem. Rev.*, 2000, **100**, 2407.

6 (*a*) X. Liu, X. Xin, D. Xiang, Y. Liang, X. Xin, W. Li and D. Dong, *RSC Adv.*, 2013, **3**, 1346; (*b*) S. Ye and Z.-X. Yu, *Chem. Commun.*, 2011, **47**, 794; (*c*) S. C. Roy and P. K. Mandal, *Tetrahedron*, 1996, **52**, 2193; (*d*) S. C. Roy and P. K. Mandal, *Tetrahedron*, 1996, **52**, 12495; (*e*) Y. R. Lee, N. S. Kim and B. S. Kim, *Tetrahedron Lett.*, 1997, **38**, 5671; (*f*) Y. R. Lee, B. S. Kim and H. C. Wang, *Tetrahedron*, 1998, **54**, 12215; (*g*) G. Bar, A. F. Parson and C. B. Thomas, *Tetrahedron Lett.*, 2000, **41**, 7751; (*h*) Y. Zhang, A. J. Raines and R. A. Flowers, *Org. Lett.*, 2003, **5**, 2363; (*i*) R. M. Carlson and A. R. Oyler, *Tetrahedron Lett.*, 1975, **47**, 4099.

7 (*a*) K. S. Feldman and M. L. Wrobleski, *J. Org. Chem.*, 2000, **65**, 8659; (*b*) H. M. L. Davies, G. Ahmed, R. L. Calvo, M. R. Churchill and D. G. Churchill, *J. Org. Chem.*, 1998, **63**, 2641; (*c*) J. Ichikawa, M. Fujiwara, Y. Wada, T. Okauchi and T. Minami, *Chem. Commun.*, 2000, 1887; (*d*) K. Pravia, R. White, R. Fodda and D. F. Maynard, *J. Org. Chem.*, 1996, **61**, 6031; (*e*) E. A. Lund, I. A. Kennedy and A. G. Fallis, *Can. J. Chem.*, 1996, **74**, 2401.

8 (*a*) F. Feist, *Chem. Ber.*, 1902, **35**, 1537; (*b*) E. Benary, *Chem. Ber.*, 1911, **44**, 489; (*c*) M. A. Calter and Z. Cheng, *Org. Lett.*, 2002, **4**, 205.

9 L. R. Yong, K. S. Byung and K. H. Dae, *Tetrahedron*, 2000, **56**, 8845.

10 H. Ying, H. Hong, Y. Rong, F. Qin and Y. Chao-Guo, *Synthesis*, 2010, 4061.

11 C. Che-Ping and T. An-I, *Synthesis*, 2006, 0675.

12 B. Schmidt, *Eur. J. Org. Chem.*, 2003, 816.

13 M. Shengming, Z. Zilong and J. Xuefeng, *Org. Lett.*, 2007, **9**, 529.

14 S. Sunghee and C. F. Gregory, *J. Am. Chem. Soc.*, 2007, **129**, 1046

15 C. R. Brindaban, A. Laksmikanta and B. Subhash, *Tetrahedron Lett.*, 2008, **49**, 4613.

16 (*a*) S. Das and A.J. Thakur, *Eur. J. Org. Chem.*, 2011, 2301; (*b*) C. J. Li and L. Chen, *Chem. Soc. Rev.*, 2006, **35**, 68.

17 (*a*) A. K. Arya and M. Kumar, *Green Chem.*, 2011, **13**, 1332; (*b*) A. Dieguez-Vazquez, C. C. Tzschucke, W. Y. Lam and S. V. Ley, *Angew. Chem., Int. Ed.*, 2008, **47**, 209; (*c*) H. Waldmann, M. Kuhn, W. Liu and K. Kumar, *Chem. Commun.*, 2008, 1211; (*d*) M. Malacria, *Chem. Rev.*, 1996, **96**, 289; (*e*) T. Schwier, A. W. Sromek, D. M. Yap, D. Chernyak and V. J. Gevorgyan, *J. Am. Chem. Soc.*, 2007, **129**, 9868; (*f*) J. Barluenga, A. Jimenez-Aquino, C. Valdes and F. Aznar, *Angew. Chem., Int. Ed.*, 2007, **46**, 1529.

18 (*a*) L. F. Tietze, *Chem. Rev.*, 1996, **96**, 115; (*b*) B. M. Trost, *Acc. Chem. Res.*, 2002, **35**, 695; (*c*) P. A. Wender, V. A. Verma, T. J. Paxton and T. H. Pillow, *Acc. Chem. Res.*, 2008, **41**, 40.

19 (*a*) G. Shore, W.-J. Yoo, C.-J. Li and M. G. Organ, *Chem. – Eur. J.*, 2010, **16**, 126; (*b*) B. Ganem, *Acc. Chem. Res.*, 2009, **42**, 463; (*c*) A. Padwa, *Chem. Soc. Rev.*, 2009, **38**, 3072; (*d*) A. Domling, *Chem. Rev.*, 2006, **106**, 17; (*e*) D. M. D'Souza and T. J. J. Mueller, *Chem. Soc. Rev.*, 2007, **36**, 1095; (*f*) V. Polshettiwar and R. S. Varma, *Chem. Soc. Rev.*, 2008, **37**, 1546.

20 (*a*) P. Tundo, P. Anastas, D. S. Black, J. Breen, T. Collins, S. Memoli, J. Miyamoto, M. Polyakoff and W. Tumas, *Pure Appl. Chem.*, 2000, **72**, 1207; (*b*) K. Munabe, S. Limura, X. Sun and S. Kobayashi, *J. Am. Chem. Soc.*, 2002, **124**, 11971; (*c*) P. Anastas and J. C. Warner, in *Green Chemistry: Theory and Practice*, Oxford University Press, Oxford, 1998; (*d*) T. Tsukinoki, S. Nagashima, Y. Mitoma and M. Tashiro,

Green Chem., 2000, 2, 117; (*e*) F. Bigi, M. L. Conforti, R. Maggi, A. Piccinno and G. Sartori, *Green Chem.*, 2000, **2**, 101.

21 (*a*) B. Willy and T. J. J. Mueller, *Curr. Org. Chem.*, 2009, **13**, 1777; (*b*) J. Zhu, *J. Org. Chem.*, 2003, **7**, 1133; (*c*) D. Bello, R. Ramon and R. Lavilla, *Curr. Org. Chem.*, 201, **14**, 332.

22 (*a*) E. N. Reddy, A. Krishnaiah, B. Chiranjeevi, G. N. Reddy, C.G. Kumar and N. J. Babu, *Bioorg. Med. Chem. Lett.*, 2014, **24**, 485; (*b*) E. N. Reddy, A. Krishnaiah, P. Sujita, C. G. Kumar and N. J. Babu, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 7261; (*c*) E. N. Reddy, A. Krishnaiah, Ch. Madhu and N. J. Babu, *RSC Adv.*, 2014, **4**, 14501.

23 S. Hamid Reza, S. Mohsen, R. Sudabeh and S. Athar, *Green Chem.*, 2012, **14**, 1696.

24 M. S. Reddy, A. Manjula, B. Vittal Rao, N. J. Babu, L. S. Kumar and Y. Soujanya, *J. Org. Chem.*, 2012, **77**, 10648.

25 CCDC 979361 and 982398 contain the supplementary crystallographic data for this paper.

