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One-pot synthesis of tetrahydrochromene derivatives catalyzed by lipase

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ABSTRACT

An efficient and green one-pot synthesis route for tetrahydrochromene derivatives was developed. Lipase from *Porcine pancreas* (PPL) shows excellent catalytic activity and exerts good adaptability to different substrates in the reaction. All the reactions go smoothly and provide tetrahydrochromene derivatives with isolate yield up to 97% under room temperature. This lipase-catalyzed multistep conversion method has provided a new strategy to synthesize chromene derivatives and expanded the application of enzyme in organic synthesis.

1. Introduction

Tetrahydrochromene moiety is an important class of benzopyran derivatives founded in many natural products.[1] The derivatives have biological activities such as antioxidant, spamolytic, anticancer, antibacterial, antianaphylactic, and anti-HIV activity.[2] Furthermore, these compounds exhibit unique pharmacological activities including treatment of human inflammatory TNFα-mediated diseases, Alzheimer's disease, amyotrophic lateral sclerosis, Huntington's disease, and Parkinson's disease.[3] Moreover, functionally substituted chromenes have played increasing roles in synthetic approaches to promising compounds in the field of medicinal chemistry.[1c,4] For example, 2-amino-4*H*-chromene derivatives bearing a nitrile functionality arise from their potential application in the treatment of psoriatic arthritis and rheumatoid, and in cancer therapy.[5]

Numerous methods have been reported for the synthesis of tetrahydrochromene derivatives.[6–10] However, the reported methods still have drawbacks such as long reaction time, high reaction temperature, using toxic organic solvents, and so on. To the best of our knowledge, there is no report about this reaction catalyzed by enzyme. The significant biological activity and recent synthetic advances of enzyme encouraged the development of biologically promising analogs that were more facile and clean than the original natural products.[11] Research in the area of biocatalytic promiscuity has attracted significant attention from chemists and biochemists recently.[12] The term 'promiscuity' refers to secondary activities of an enzyme in addition to its primary physiological activity. Enzyme promiscuity is hypothesised to contribute to the natural evolution of enzymes and provides new possibilities for exploiting enzymatic synthesis in organic chemistry.[13] The past few years we have seen significant advances related to this latest skill of certain enzymes. Several enzymes have fully been exhibited great advantages and potential in organic transformations like aldol reaction, Michael addition, Diels–Alder reaction, Knoevenagel reaction, Mannich reaction, and Hantzsch-type reaction.[14–19]

Following our interest in catalysis by enzymes, our research group has previously used enzymes as reusable catalyst for Knoevenagel condensation and esterification reactions,[20] Mannich reaction,[21] and synthesis of spirooxindole derivatives reactions.[22] However, natural enzymes, which are capable of catalyzing multiple reactions are very scarce, and only a few single-enzyme multistep conversions have been reported.[23] Furthermore, designing chemical reaction in aqueous medium attracts more and more attention in recent years.[24] Here we report the unprecedented efficient and convenient lipase (PPL)-catalyzed one-pot multiple reaction for synthesizing tetrahydrochromene derivatives in the presence of water, which expands the application of enzymes in organic synthesis.

2. Results and discussion

In order to find the most suitable enzyme for the envisaged one-pot synthesis of tetrahydrochromene derivatives reaction, we tested the reaction of benzaldehyde **1a**, malononitrile **2a**, and

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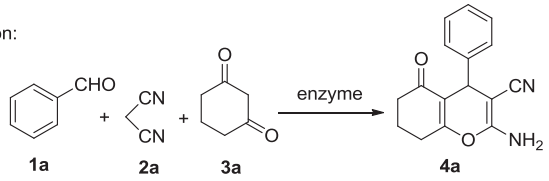
cyclohexane-1,3-dione **3a** (1 mmol, respectively) as model substrates with various additives using the EtOH as the reaction media. The results were summarized in Table 1.

Table 1
Optimization of the reaction conditions[a]

Model reaction:



Entry	Catalyst	Yield[b] (%)
1	No enzyme	Trace
2	Cellulase	Trace
3	Trypsin from Porcine pancreas	60
4	Pepsin from hog stomach	52
5	β-Amylase	Trace
6	α-Amylase from *Aspergillus oryzae*	5
7	α-Amylase from hog pancreas	76
8	α-Amylase from *Bacillus subtilis*	9
9	Amano lipase M from *Mucor javanicus*	18
10	Amano lipase AK from *Pseudomonas fluorescens*	Trace
11	Lipase AY30	Trace
12	Amano lipase A from *Aspergillus niger*	24
13	Lipase from Porcine pancreas	86
14	Lipase from Porcine pancreas[c]	Trace
15	Bovine serum albumin (BSA)	Trace

[a] Reaction conditions: benzaldehyde (1 mmol), malononitrile (1 mmol), cyclohexane-1,3-dione (1 mmol), enzyme (30 mg), and EtOH (4 mL) were shaken at 160 rpm at 35 °C for 1 h.
[b] Isolated yields.
[c] Lipase from Porcine pancreas predenatured with urea at 100 °C for 24 h.

We found that only trace product was detected (entry 1, Table 1), if no enzyme was added as catalyst. Several enzymes displayed detectable catalytic activities for this reaction, including α-amylase from *hog pancreas*, trypsin from *Porcine pancreas*, pepsin from *hog stomach*, amano lipase A from *Aspergillus niger*, amano lipase M from *Mucor javanicus*, α-amylase from *Bacillus subtilis*, and α-amylase from *Aspergillus oryzae* showed moderate catalytic activity for this reaction (entries 3, 4, 6–9, and 12, Table 1). Notably, lipase from *Porcine pancreas* (PPL) displayed an especially significant catalytic activity (entry 13, Table 1). When reactions were incubated with denatured PPL or bovine serum albumin (BSA), no product was detected (entries 14 and 15, Table 1). All the results suggest that the tertiary structure and the specific spatial conformation of PPL are responsible for the one-pot synthesis of chromene derivatives.

We screened the reaction in various organic solvents using PPL as catalyst (Table 2). The results revealed that solvent shows great effect on the catalytic activity of PPL. Among the tested solvents, including DMSO, CH_3CN, EtOH, acetone, THF, CH_2Cl_2, toluene, hexane, and water, EtOH leads to a highest yield of 86% (entry 3 vs entries 1–2 and 4–9, Table 2). This may be attributed to the proton nature of the solvent and that it accelerates the reaction compared to other solvents. However, pure water leads to trace yield, which may be due to the insolubility of the substrates in pure water.

In previous studies of enzymatic promiscuity, water has been considered to play an important role in enzymes' activity, generally leading to an improvement in their activity.[25] In order to optimize the water/ethanol ratio for this specific reaction, some experiments were performed (Fig. 1). It was found that the best ratio between EtOH and water was 4:1 (v/v). In this case, the yield is as high as 96%. However, once the water content surpassed 20%, the yield of tetrahydrochromene product declined sharply, which may be due to the insolubility of the substrates. All these results indicated obviously that water was essential in this promiscuous biocatalysis reaction.

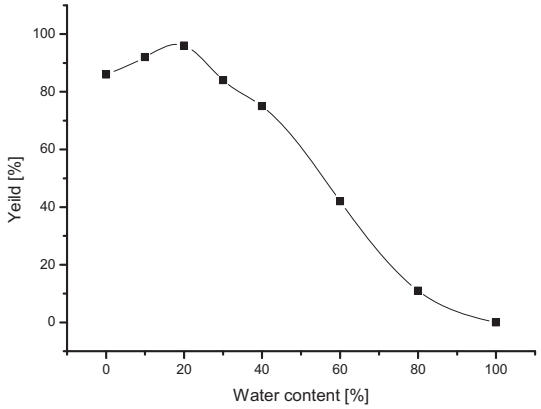


Fig. 1. Influence of water on the PPL-catalyzed one-pot synthesis of tetrahydrochromenes. Reaction conditions: benzaldehyde (1 mmol), malononitrile (1 mmol), cyclohexane-1,3-dione (1 mmol), PPL (30 mg), and solvent (5 mL) were shaken at 160 rpm at 35 °C for 1 h; deionized water from 0% to 100% [water/ethanol, v/v]; product yield was determined by HPLC.

In order to improve the activity of enzyme, other influencing factors such as temperature, concentration of catalyst, and reaction time have also been investigated (Table 3). The results showed that the desired products were obtained in yields up to 96% when 30 mg of PPL in 5 mL solvent at 35 °C/1 h were used.

Table 2
PPL-catalyzed reaction of benzaldehyde, malononitrile, and cyclohexane-1,3-dione in different solvents[a]

Entry	Solvent	Temp (°C)	Yield[b] (%)
1	DMSO	35	Trace
2	CH_3CN	35	20
3	Ethanol	35	86
4	Acetone	35	16
5	THF	35	23
6	CH_2Cl_2	35	Trace
7	Toluene	35	Trace
8	*n*-Hexane	35	Trace
9	Water	35	Trace

[a] Reaction conditions: benzaldehyde (1 mmol), malononitrile (1 mmol), cyclohexane-1,3-dione (1 mmol), PPL (30 mg), and solvent (5 mL) were shaken at 160 rpm at 35 °C.
[b] Isolated yields.

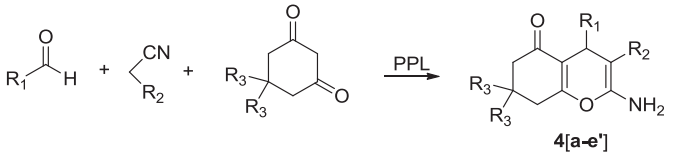
Table 3
Optimization of the reaction conditions[a]

Entry	PPL amount (mg)	Temp (°C)	Time (h)	Yield[b] (%)
1	30	20	1	56
2	30	30	1	89
3	30	35	1	96
4	30	40	1	94
5	30	50	1	84
6	10	35	1	60
7	20	35	1	84
8	40	35	1	95
9	50	35	1	95
10	30	35	0.25	52
11	30	35	0.5	82
12	30	35	0.75	94
13	30	35	2	95

[a] Reaction conditions: benzaldehyde (1 mmol), malononitrile (1 mmol), cyclohexane-1,3-dione (1 mmol), and solvent: EtOH (4 mL)/water (1 mL) were shaken at 160 rpm.
[b] Isolated yields.

We have also employed various different aromatic or aliphatic aldehydes, 1,3-dicarbonyl compounds, and malononitrile or cyanoacetic ester as substrates in order to investigate the generality for the scope of this new catalysis method. The results are summarized in Table 4. Gratifyingly, we found that nearly all of the corresponding products were obtained in excellent yields. But the reaction with cyanoacetic ester offered a lower yield compared to that with malononitrile, which is probably because of the lower reactivity of cyanoacetic ester. Although many substrates and conditions were applied in this reaction to measure the enantioselectivity, there is no obvious optical activity of obtained products and we will undertake related further research to improve it.

Table 4
Synthesis of different tetrahydrochromene derivatives **4** catalyzed by PPL[a]



Entry	Products	R_1	R_2	R_3	Yield[b] (%)
1	**4a**	Ph	CN	H	96
2	**4b**	Ph	CN	CH_3	94
3	**4c**	2-NO_2–C_6H_4	CN	H	95
4	**4d**	2-NO_2–C_6H_4	CN	CH_3	95
5	**4e**	3-NO_2–C_6H_4	CN	H	96
6	**4f**	3-NO_2–C_6H_4	CN	CH_3	94
7	**4g**	4-NO_2–C_6H_4	CN	H	96
8	**4h**	4-NO_2–C_6H_4	CN	CH_3	97
9	**4i**	2-CF_3–C_6H_4	CN	H	96
10	**4j**	2-CF_3–C_6H_4	CN	CH_3	96
11	**4k**	4-OH–C_6H_4	CN	H	93
12	**4l**	4-OH–C_6H_4	CN	CH_3	94
13	**4m**	3,4-Di-OCH_3–C_6H_4	CN	H	95
14	**4n**	3,4-Di-OCH_3–C_6H_4	CN	CH_3	93
15	**4o**	2-OCH_3–C_6H_4	CN	H	93
16	**4p**	2-OCH_3–C_6H_4	CN	CH_3	92
17	**4q**	3-CH_3–C_6H_4	CN	H	92
18	**4r**	3-CH_3–C_6H_4	CN	CH_3	91
19	**4s**	4-OCH_3–C_6H_4	CN	H	93
20	**4t**	4-OCH_3–C_6H_4	CN	CH_3	93
21	**4u**	2-Cl–C_6H_4	CN	H	91
22	**4v**	2-Cl–C_6H_4	CN	CH_3	89
23	**4w**	Furan-2-yl	CN	H	92
24	**4x**	Furan-2-yl	CN	CH_3	92
25	**4y**	*n*-Propyl	CN	H	93
26	**4z**	*n*-Propyl	CN	CH_3	92
27	**4a′**	4-NO_2–C_6H_4	COOEt	H	81
28	**4b′**	4-NO_2–C_6H_4	COOEt	CH_3	83
29	**4c′**	2-CF_3–C_6H_4	COOEt	H	78
30	**4d′**	4-OH–C_6H_4	COOEt	H	76
31	**4e′**	3-CH_3–C_6H_4	COOEt	H	78

[a] Reaction conditions: aromatic or aliphatic aldehydes (1 mmol), malononitrile or cyanoacetic ester (1 mmol), 1,3-dicarbonyl compounds (1 mmol), PPL (30 mg), ethanol (4 mL), and water (1 mL) were shaken at 160 rpm at 35 °C.
[b] Isolated yields.

The experiments clearly showed an increased reaction rate when the synthesis of tetrahydrochromene reaction was catalyzed by the PPL as compared to other enzymes. Based on the mechanism of lipase-catalyzed[16,19,23] carbon–carbon formation which has been widely accepted, we propose a mechanism for the synthesis of tetrahydrochromene derivative as shown in Scheme 1. Firstly, **1a** and **2a** form **5** quickly by Knoevenagel condensation, while the 1,3-dicarbonyl compound is pre-activated by the lipase. After the transfer of a proton, intermediate **7** is converted to **8**. Secondly, intermediate **6**, which is also pre-activated by the lipase, is attacked by **8**, which leads to a new C–C bond formation via Michael addition, and then **10** is obtained. Thirdly, after enolization and addition to the cyano group, the intermediate **12** is formed, and the desired product **4a** is obtained via isomerization. We will study this proposed mechanism further in detail.

3. Conclusion

In summary, we herein report an unprecedented lipase (PPL)-catalyzed one-pot synthesis of tetrahydrochromene derivatives reaction in the presence of water. This reaction can be carried out under mild conditions and covers a great range of substrates. This novel protocol provides an efficient, environmental friendly synthetic route for tetrahydrochromene derivatives, and extends the application of enzymes in pharmaceutical industry.

4. Experimental

4.1. General

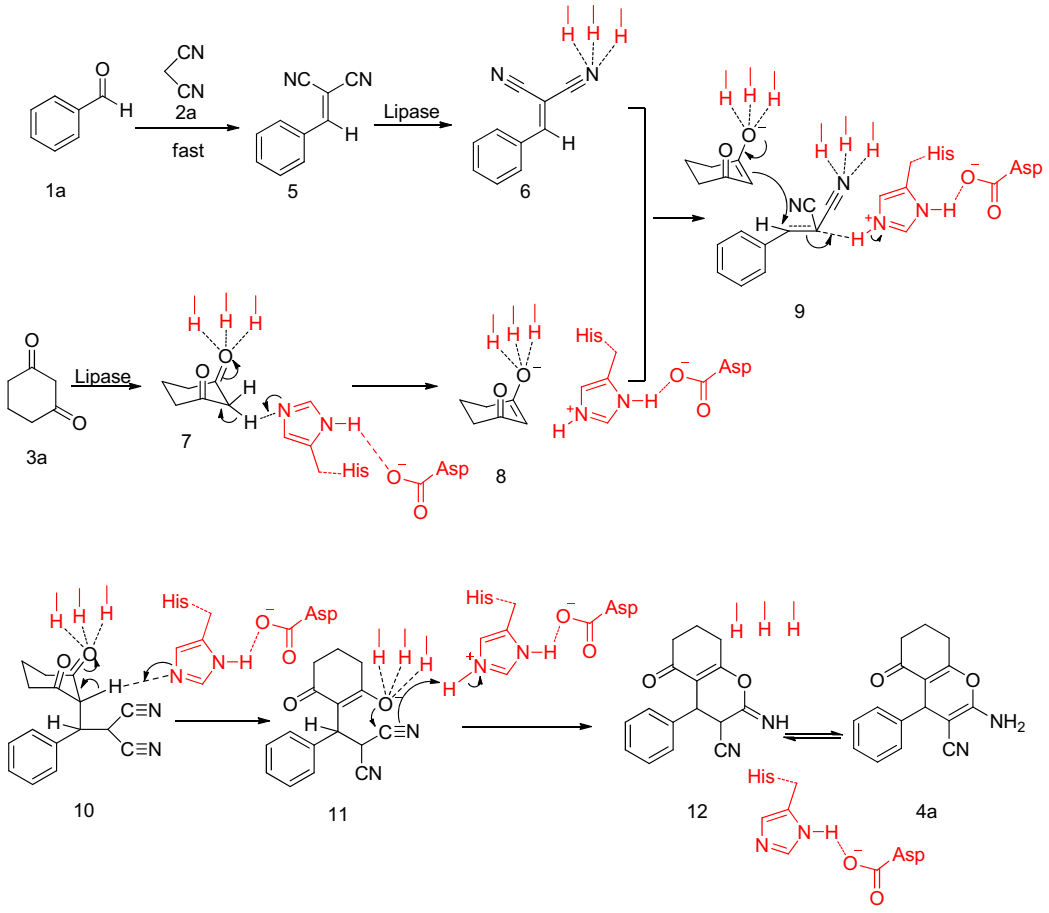
Commercial reagents were used without further purification, unless otherwise indicated. All solvents were distilled prior to use. Reactions were performed in oven-dried glassware. Analytical TLC was performed on *Merck* precoated TLC (silica gel 60 F_{254}) plates. Melting points were recorded on an *X4-Data* microscopic melting point apparatus and are uncorrected. EIMS were acquired on a *Bruker Esquire 3000* plus spectrometer. ESI-MS: *Thermo Finnigan LCQ Advantage* instrument in *m/z*. HRMS: *Agilent 6210 TOF* instrument. ^1H and ^{13}C NMR were recorded on a *Bruker Avance 400* spectrometer at 400 MHz in DMSO-d_6 using TMS as internal standard. C^{18} column was used in the HPLC experiments with MeOH/water=50:50 (v/v), 1.0 mL/min and UV detection at 254 nm. All the known products were characterized by comparing the ^1H NMR data with those reported in the literature. The structures of new compounds were confirmed by ^1H, ^{13}C NMR, MS, and HRMS-ESI. All enzymes were purchased from Acros, Aldrich, and TCI and used directly: Amano lipase AK from *Pseudomonas fluorescens* (EC, 3.1.1.3), Amano lipase M from *M. javanicus* (EC, 3.1.1.3), Amano lipase A from *A. niger* (EC, 3.1.1.3), Lipase AY30 (EC, 3.1.1.3), lipase acrylic resin from *Candida antarctica* (EC, 3.1.1.3), lipase from *Porcine pancreas* (EC, 3.1.1.3).

4.2. General procedure for the synthesis of tetrahydrochromene derivatives

A suspension of aromatic aldehydes (1 mmol), malononitrile or cyanoacetic ester (1 mmol), 1,3-dicarbonyl compounds (1 mmol), and 30 mg PPL in 4 mL EtOH in the presence of water (1 mL) was shaken at 35 °C and 160 rpm for 1 h to complete the reaction (monitored by TLC), and the reaction was terminated by filtering off the enzyme. Then the filtered liquor was kept at −8 °C overnight. The precipitated product was filtered and washed with water and cooled EtOH to afford the pure **4**[**a**–**e′**].

*4.2.1. 2-Amino-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (**4a**).* White crystalline solid: mp 213–215 °C (lit.[26a] 212–214 °C); ^1H NMR (DMSO-d_6, δ, ppm): 7.29–7.26 (m, 2H), 7.19–7.14 (m, 3H), 7.00 (s, 2H), 4.18 (s, 1H), 2.67–2.54 (m, 2H), 2.35–2.20 (m, 2H), 1.99–1.83 (m, 2H); ^{13}C NMR (DMSO-d_6, δ, ppm): 195.6, 165.0, 158.5, 141.7, 132.0, 129.7, 129.3, 128.0, 127.4, 119.2, 112.8, 56.8, 36.2, 32.6, 26.4, 19.8; MS (EI): *m/z*=266.

*4.2.2. 2-Amino-7,7-dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (**4b**).* White crystalline solid: mp 224–225 °C (lit.[8] 224 °C); ^1H NMR (DMSO-d_6, δ, ppm): 7.30–7.26 (m, 2H), 7.19–7.13 (m, 3H), 7.01 (s, 2H), 4.17 (s, 1H), 2.56–2.46 (m, 2H), 2.27–2.07 (dd, J_1=16.0 Hz, J_2=60.4 Hz, 2H), 1.03 (s, 3H), 0.94 (s, 3H); ^{13}C NMR (DMSO-d_6, δ, ppm): 195.3, 162.2, 158.2, 144.5, 128.1 (CH×2), 126.9 (CH×2),



Scheme 1. Proposed mechanism.

126.3, 119.5, 112.5, 58.2, 49.9, 35.6, 31.8 (CH×2), 28.4, 26.8; MS (EI): *m*/*z*=294.

*4.2.3. 2-Amino-4-(2-nitrophenyl)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (**4c**).* Yellow crystalline solid: mp 196–198 °C (lit.[26b] 196–198 °C); ^{1}H NMR (DMSO-d_6, δ, ppm): 7.81–7.79 (dd, J_1=1.2 Hz, J_2=8.0 Hz, 1H), 7.66–7.62 (m, 1H), 7.43–7.37 (m, 2H), 7.19 (s, 2H), 4.94 (s, 1H), 2.60–2.57 (m, 2H), 2.29–2.11 (m, 2H), 1.96–1.77 (m, 2H); MS (EI): *m*/*z*=311.

*4.2.4. 2-Amino-7,7-dimethyl-4-(2-nitrophenyl)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (**4d**).* Yellow crystalline solid: mp 224–226 °C (lit.[26b] 223–224 °C); ^{1}H NMR (DMSO-d_6, δ, ppm): 7.83–7.80 (dd, J_1=1.2 Hz, J_2=8.4 Hz, 1H), 7.67–7.63 (m, 1H), 7.43–7.35 (m, 2H), 7.21 (s, 2H), 4.95 (s, 1H), 2.56–2.43 (q, 2H, J=17.6 Hz), 2.22–1.99 (dd, J_1=8.0 Hz, J_2=35.6 Hz, 2H), 1.01 (s, 3H), 0.88 (s, 3H); MS (EI): *m*/*z*=339.

*4.2.5. 2-Amino-4-(3-nitrophenyl)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (**4e**).* Yellow crystalline solid: mp 201–202 °C (lit.[26c] 198–200 °C); ^{1}H NMR (DMSO-d_6, δ, ppm): 8.09–8.02 (m, 2H), 7.71–7.69 (d, J=8.0 Hz, 1H), 7.63–7.59 (t, J=8.0 Hz, 1H), 7.21 (s, 2H), 4.44 (s, 1H), 2.70–2.58 (m, 2H), 2.37–2.22 (m, 2H), 2.01–1.90 (m, 2H); ^{13}C NMR (DMSO-d_6, δ, ppm): 195.6, 164.8, 158.3, 147.5, 146.7, 134.0, 129.7, 121.5 (CH×2), 119.2, 112.6, 56.9, 36.2, 35.3, 26.5, 19.7; MS (EI): *m*/*z*=311.

*4.2.6. 2-Amino-7,7-dimethyl-4-(3-nitrophenyl)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (**4f**).* Yellow crystalline solid: mp 211–212 °C (lit.[8] 210 °C); ^{1}H NMR (DMSO-d_6, δ, ppm): 8.10–8.08 (d, 1H, J=7.6), 7.99 (s, 1H), 7.69–7.61 (m, 2H), 7.20 (s, 2H), 4.42 (s, 1H), 2.56 (s, 2H), 2.30–2.10 (m, 2H), 1.05 (s, 3H), 0.96 (s, 3H); ^{13}C NMR (DMSO-d_6, δ, ppm): 195.7, 163.1, 158.6, 147.7, 146.9, 134.1, 129.9, 121.7, 121.6, 119.3, 111.7, 57.1, 56.0, 49.8, 35.3, 31.7, 28.2, 26.7; MS (EI): *m*/*z*=339.

*4.2.7. 2-Amino-4-(4-nitrophenyl)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (**4g**).* Yellow crystalline solid: mp 234–236 °C (lit.[26b] 235–236 °C); ^{1}H NMR (DMSO-d_6, δ, ppm): 8.18–8.16 (d, J=8.4 Hz, 2H), 7.49–7.46 (d, J=8.8 Hz, 2H), 7.20 (s, 2H), 4.38 (s, 1H), 2.70–2.58 (m, 2H), 2.37–2.22 (m, 2H), 2.01–1.88 (m, 2H); MS (EI): *m*/*z*=311.

*4.2.8. 2-Amino-7,7-dimethyl-4-(4-nitrophenyl)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (**4h**).* Yellow crystalline solid: mp 178–180 °C (lit.[8] 179 °C); ^{1}H NMR (DMSO-d_6, δ, ppm): 8.19–8.17 (d, J=8.4 Hz, 2H), 7.48–7.46 (d, J=8.4 Hz, 2H), 7.21 (s, 2H), 4.39 (s, 1H), 2.60–2.55 (m, 2H), 2.29–2.10 (dd, J_1=16.4 Hz, J_2=60.0 Hz, 2H), 1.05 (s, 3H), 0.97 (s, 3H); MS (EI): *m*/*z*=339.

*4.2.9. 2-Amino-5-oxo-4-(2-(trifluoromethyl)phenyl)-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (**4i**).* Yellow crystalline solid: mp 210–211 °C; ^{1}H NMR (DMSO-d_6, δ, ppm): 7.64–7.57 (m, 2H), 7.40–7.31 (m, 2H), 7.04 (s, 2H), 4.55 (s, 1H), 2.72–2.57 (m, 2H), 2.32–2.14 (m, 2H), 2.00–1.88 (m, 2H); ^{13}C NMR (DMSO-d_6, δ, ppm): 195.5, 160.1, 156.1, 132.9, 128.9, 127.8, 126.0 (CH×2), 119.1, 114.2, 113.9, 58.1, 35.2, 30.6, 27.8, 19.8; MS (EI): *m*/*z*=334;

HRMS-ESI: calcd for $C_{17}H_{13}F_3N_2O_2$ $(M+H)^+$: 335.0929; found: 335.0925.

*4.2.10. 2-Amino-7,7-dimethyl-5-oxo-4-(2-(trifluoromethyl)phenyl)-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (**4j**).* Yellow crystalline solid: mp 216–218 °C (lit.[26c] 218–220 °C); ^{1}H NMR (DMSO-d_6, δ, ppm): 7.64–7.57 (m, 2H), 7.39–7.36 (t, J=7.6 Hz, 1H), 7.29–7.27 (d, J=8.0 Hz, 1H), 7.07 (s, 2H), 4.56 (s, 1H), 2.60–2.55 (m, 2H), 2.25–2.03 (dd, J_1=15.6 Hz, J_2=73.6 Hz, 2H), 1.04 (s, 3H), 0.97 (s, 3H); MS (EI): m/z=362.

*4.2.11. 2-Amino-4-(4-hydroxyphenyl)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (**4k**).* Yellow crystalline solid: mp 234–236 °C (lit.[26b] 234–236 °C); ^{1}H NMR (DMSO-d_6, δ, ppm): 9.25 (s, 1H), 6.94–6.92 (m, 4H), 6.66–6.64 (d, J=8.8 Hz, 2H), 4.07 (s, 1H), 2.59–2.56 (m, 2H), 2.29–2.19 (m, 2H), 1.97–1.85 (m, 2H); ^{13}C NMR (DMSO-d_6, δ, ppm): 195.5, 163.7, 158.0, 155.7, 135.0 (CH×2), 127.9, 119.8, 114.8 (CH×2), 114.0, 58.5, 36.4, 34.5, 26.5, 19.9; MS (EI): m/z=282.

*4.2.12. 2-Amino-4-(4-hydroxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (**4l**).* Yellow crystalline solid: mp 205–206 °C (lit.[9] 204–205 °C); ^{1}H NMR (DMSO-d_6, δ, ppm): 9.26 (s, 1H), 6.93–6.91 (m, 4H), 6.66–6.64 (d, J=8.4 Hz, 2H), 4.05 (s, 1H), 2.49–2.43 (m, 2H), 2.25–2.06 (dd, J_1=16.0 Hz, J_2=60.4 Hz, 2H), 1.02 (s, 3H), 0.94 (s, 3H); MS (EI): m/z=310.

*4.2.13. 2-Amino-4-(3,4-dimethoxyphenyl)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (**4m**).* White crystalline solid: mp 227–229 °C (lit.[26d] 228–231 °C); ^{1}H NMR (DMSO-d_6, δ, ppm): 6.96 (s, 2H), 6.86–6.84 (d, J=8.4 Hz, 1H), 6.72 (s, 1H), 6.65–6.63 (dd, J_1=2.0 Hz, J_2=8.0 Hz, 1H), 4.14 (s, 1H), 3.71 (s, 3H), 3.70 (s, 3H), 2.65–2.58 (m, 2H), 2.31–2.26 (m, 2H), 1.98–1.87 (m, 2H); MS (EI): m/z=326.

*4.2.14. 2-Amino-4-(3,4-dimethoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (**4n**).* White crystalline solid: mp 191–193 °C (lit.[26e] 178–180 °C); ^{1}H NMR (DMSO-d_6, δ, ppm): 6.96 (s, 2H), 6.87–6.85 (d, 1H, J=8.4 Hz), 6.69–6.68 (d, J=2.0 Hz, 1H), 6.66–6.64 (dd, J_1=2.0 Hz, J_2=8.0 Hz, 1H), 4.12 (s, 1H), 3.71 (s, 3H), 3.70 (s, 3H), 2.52–2.49 (m, 2H), 2.28–2.08 (m, 2H), 1.03 (s, 3H), 0.97 (s, 3H); MS (EI): m/z=354.

*4.2.15. 2-Amino-4-(2-methoxyphenyl)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (**4o**).* Yellow crystalline solid: mp 200–201 °C (lit.[26f] 200–202 °C); ^{1}H NMR (DMSO-d_6, δ, ppm): 7.17 (s, 2H), 6.98–6.94 (m, 2H), 6.86–6.82 (m, 2H), 4.53 (s, 1H,), 3.76 (s, 3H), 2.65–2.55 (m, 2H), 2.33–2.19 (m, 2H), 1.99–1.84 (m, 2H); MS (EI): m/z=296.

*4.2.16. 2-Amino-4-(2-methoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (**4p**).* Yellow crystalline solid: mp 203–205 °C; ^{1}H NMR (DMSO-d_6, δ, ppm): 7.17–7.13 (t, J=8.0 Hz, 1H), 6.99–6.97 (d, J=7.2 Hz, 1H), 6.95–6.93 (d, J=8.0 Hz, 1H), 6.86–6,83 (m, 3H), 4.47 (s, 1H), 3.74 (s, 3H), 2.52–2.46 (m, 2H), 2.26–2.03 (m, 2H), 1.03 (s, 3H), 0.96 (s, 3H); MS (EI): m/z=324.

*4.2.17. 2-Amino-5-oxo-4-(m-tolyl)-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (**4q**).* White crystalline solid: mp 248–249 °C; ^{1}H NMR (DMSO-d_6, δ, ppm): 7.17–7.14 (m, 1H), 6.98 (s, 1H), 6.95–6.92 (d, J=8.4 Hz, 2H), 4.14 (s, 1H), 2.67–2.57 (m, 2H), 2.34–2.20 (m, 2H), 2.26 (s, 3H), 1.98–1.82 (m, 2H); ^{13}C NMR (DMSO-d_6, δ, ppm): 195.7, 164.3, 158.4, 144.7, 137.2, 128.2, 127.6, 127.2, 124.2, 119.7, 113.8, 58.2, 36.3, 35.3, 26.4, 21.0; MS (EI): m/z=280; HRMS-ESI: calcd for $C_{17}H_{16}N_2O_2$ $(M+H)^+$: 281.1212; found: 281.1210.

*4.2.18. 2-Amino-7,7-dimethyl-5-oxo-4-(m-tolyl)-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (**4r**).* White crystalline solid: mp 223–225 °C; ^{1}H NMR (DMSO-d_6, δ, ppm): 7.18–7.14 (m, 1H), 6.98 (s, 1H, Ph-H), 6.93–6.94 (d, J=8.4 Hz, 2H), 4.12 (s, 1H), 2.06 (s, 2H), 2.26 (s, 3H), 2.26–2.08 (m, 2H), 1.03 (s, 3H), 0.96 (s, 3H); ^{13}C NMR (DMSO-d_6, δ, ppm): 195.2, 162.1, 158.1, 144.4, 137.0, 128.0, 127.5, 124.1, 119.5, 112.5, 58.3, 49.9, 35.5, 31.8, 28.4, 26.7, 21.1; MS (EI): m/z=308; HRMS-ESI: calcd for $C_{19}H_{20}N_2O_2$ $(M+H)^+$: 309.1525; found: 309.1528.

*4.2.19. 3-Amino-4-(4-methoxyphenyl)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-2-carbonitrile (**4s**).* Yellow crystalline solid: mp 190–192 °C; ^{1}H NMR (DMSO-d_6, δ, ppm): 7.07–7.05 (d, J=8.4 Hz, 2H), 6.97 (s, 2H), 6.84–6.82 (d, J=8.8 Hz, 2H), 4.13 (s, 1H), 3.70 (s, 3H), 2.63–2.54 (m, 2H), 2.33–2.19 (m, 2H), 1.97–1.79 (m, 2H); ^{13}C NMR (DMSO-d_6, δ, ppm): 195.7, 164.0, 158.3, 157.9, 136.8, 128.1 (CH×2), 119.7, 114.0, 113.6 (CH×2), 58.4, 54.9, 36.3, 34.6, 26.4, 19.7; MS (EI): m/z=296.

*4.2.20. 2-Amino-4-(4-methoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (**4t**).* Yellow crystalline solid: mp 199–201 °C (lit.[26a] 201 °C); ^{1}H NMR (DMSO-d_6, δ, ppm): 7.05–7.03 (d, J=8.8 Hz, 2H), 6.97 (s, 2H), 6.84–6.82 (d, J=8.4 Hz, 2H), 4.11 (s, 1H), 3.70 (s, 3H), 2.55–2.44 (m, 2H), 2.26–2.06 (dd, J_1=16.0 Hz, J_2=22.4 Hz, 2H), 1.03 (s, 3H), 0.94 (s, 3H); ^{13}C NMR (DMSO-d_6, δ, ppm): 195.3, 161.8, 158.1, 157.6, 136.6, 128.0 (CH×2), 119.6, 113.4 (CH×2), 58.4, 54.9, 49.9, 34.7, 31.8, 28.4, 26.8; MS (EI): m/z=324.

*4.2.21. 2-Amino-4-(2-chlorophenyl)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (**4u**).* Yellow crystalline solid: mp 212–214 °C (lit.[26c] 210–212 °C); ^{1}H NMR (DMSO-d_6, δ, ppm): 7.36–7.33 (m, 1H), 7.28–7.24 (m, 1H), 7.21–7.17 (m, 2H), 7.03 (s, 2H), 4.70 (s, 1H), 2.66–2.56 (m, 2H), 2.33–2.17 (m, 2H), 2.00–1.83 (m, 2H); MS (EI): m/z=300.

*4.2.22. 2-Amino-4-(2-chlorophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (**4v**).* Yellow crystalline solid: mp 209–210 °C (lit.[26c] 214–215 °C); ^{1}H NMR (DMSO-d_6, δ, ppm): 7.37–7.35 (m, 1H), 7.28–7.25 (m, 1H), 7.21–7.16 (m, 2H), 7.05 (s, 2H), 4.70 (s, 1H), 2.57–2.46 (m, 2H), 2.27–2.05 (dd, J_1=16.0 Hz, J_2=69.6 Hz, 2H), 1.04 (s, 3H), 0.98 (s, 3H); MS (EI): m/z=328.

*4.2.23. 2-Amino-4-(furan-2-yl)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (**4w**).* Black crystalline solid: mp 199–200 °C; ^{1}H NMR (DMSO-d_6, δ, ppm): 7.48 (d, J=0.8 Hz, 1H), 7.09 (s, 2H), 6.32–6.31 (q, J=1.6 Hz, 1H), 6.06–6.05 (d, J=2.8 Hz, 1H), 4.33 (s, 1H), 2.60–2.57 (t, J=2.0 Hz, 2H), 2.34–2.31 (t, J=6.8 Hz, 2H), 2.00–1.85 (m, 2H); ^{13}C NMR (DMSO-d_6, δ, ppm): 195.5, 165.1, 159.2, 155.7, 141.7, 119.5, 111.4, 110.3, 105.0, 55.2, 36.1, 28.9, 26.4, 19.7; MS (EI): m/z=256; HRMS-ESI: calcd for $C_{14}H_{12}N_2O_3$ $(M+H)^+$: 257.0848; found: 257.0845.

*4.2.24. 2-Amino-4-(furan-2-yl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (**4x**).* Black crystalline solid: mp 201–203 °C; ^{1}H NMR (DMSO-d_6, δ, ppm): 7.48–7.47 (d, J=0.8 Hz, 1H), 7.08 (s, 2H), 6.32–6.31 (q, J=1.6 Hz, 1H), 6.058–6.051 (d, J=2.8 Hz, 1H), 4.32 (s, 1H), 2.55–2.42 (dd, J_1=18.0 Hz, J_2=34.0 Hz, 2H), 2.30–2.14 (dd, J_1=16.0 Hz, J_2=48.0 Hz, 2H), 1.04 (s, 3H), 0.98 (s, 3H); ^{13}C NMR (DMSO-d_6, δ, ppm): 195.3, 163.2, 159.2, 155.7, 141.7, 119.5, 110.4, 110.3, 105.0, 55.3, 49.8, 31.7, 28.9, 28.3, 26.5; MS (EI): m/z=284; HRMS-ESI: calcd for $C_{16}H_{16}N_2O_3$ $(M+H)^+$: 285.1161; found: 285.1157.

*4.2.25. 2-Amino-5-oxo-4-propyl-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (**4y**).* White crystalline solid: mp 188–190 °C; ^{1}H NMR (DMSO-d_6, δ, ppm): 6.87 (s, 2H), 3.16–3.14 (t, J=4.8 Hz, 1H), 2.49–2.47 (m, 2H), 2.37–2.30 (m, 2H), 1.99–1.83 (m, 2H), 1.46–1.27

(m, 2H), 1.22–1.12 (m, 2H), 0.85–0.82 (t, J=7.2 Hz, 3H); ^{13}C NMR (DMSO-d_6, δ, ppm): 196.0, 164.6, 159.5, 120.1, 113.7, 55.3, 37.4, 36.4, 29.1, 26.4, 20.0, 17.6, 14.0; MS (EI): m/z=232; HRMS-ESI: calcd for $C_{13}H_{16}N_2O_2$ $(M+H)^+$: 233.1212; found: 233.1208.

*4.2.26. 2-Amino-7,7-dimethyl-5-oxo-4-propyl-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (**4z**).* White crystalline solid: mp 181–183 °C; ^{1}H NMR (DMSO-d_6, δ, ppm): 6.88 (s, 2H), 3.14–3.12 (t, J=4.4 Hz, 1H), 2.45–2.31 (dd, J_1=18.0 Hz, J_2=38.4 Hz, 2H), 2.29–2.15 (dd, J_1=16.0 Hz, J_2=36.8 Hz, 2H), 1.49–1.28 (m, 2H), 1.21–1.10 (m, 2H), 1.01 (s, 3H), 0.99 (s, 3H), 0.84–0.81 (t, J=7.2 Hz, 3H); ^{13}C NMR (DMSO-d_6, δ, ppm): 196.0, 162.9, 159.6, 120.0, 112.5, 55.3, 50.0, 37.1, 31.7, 29.1, 28.5, 26.6, 17.7, 14.0; MS (EI): m/z=260. HRMS-ESI: calcd for $C_{15}H_{20}N_2O_2$ $(M+H)^+$: 261.1525; found: 261.1521.

*4.2.27. Ethyl 2-amino-4-(4-nitrophenyl)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carboxylate (**4a′**).* Yellow crystalline solid: mp 181–182 °C; ^{1}H NMR (DMSO-d_6, δ, ppm): 8.56 (s, 2H), 8.42–8.39 (d, J=8.8 Hz, 1H), 8.25–8.23 (d, J=8.8 Hz, 2H), 4.38–4.32 (q, J=7.2 Hz, 2H), 3.99 (s, 1H), 2.43–2.35 (m, 2H), 2.21–2.10 (m, 2H), 1.98–1.82 (m, 2H), 1.34–1.31 (t, J=7.2 Hz, 3H); ^{13}C NMR (DMSO-d_6, δ, ppm): 195.4, 161.1, 152.6, 149.2, 145.2, 137.2 (CH×2), 131.6, 129.7, 124.1 (CH×2), 122.4, 114.8, 106.6, 99.9, 62.7, 58.8, 13.9; MS (EI): m/z=358.

*4.2.28. Ethyl 2-amino-4-(4-methoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carboxylate (**4b′**).* Yellow crystalline solid: mp 185–186 °C (lit.[26g] 185–187 °C); ^{1}H NMR (DMSO-d_6, δ, ppm): 8.12–8.10 (d, J=8.4 Hz, 2H), 7.72 (s, 2H), 7.42–7.41 (d, J=8.4 Hz, 2H), 4.61 (s, 1H), 3.97–3.91 (m, 2H), 2.61–2.47 (m, 2H), 2.31–2.05 (dd, J_1=16.0 Hz, J_2=86.8 Hz, 2H), 1.10–1.05 (m, 6H), 0.89 (s, 3H); MS (EI): m/z=386.

*4.2.29. Ethyl 2-amino-5-oxo-4-(2-(trifluoromethyl)phenyl)-5,6,7,8-tetrahydro-4H-chromene-3-carboxylate (**4c′**).* White crystalline solid: mp 178–180 °C; ^{1}H NMR (DMSO-d_6, δ, ppm): 7.71 (s, 2H), 7.49–7.46 (m, 2H), 7.30–7.21 (m, 2H), 5.14 (s, 1H), 3.93–3.87 (m, 2H), 2.62–2.59 (m, 2H), 2.31–2.21 (m, 2H), 1.96–1.74 (m, 2H), 0.96–0.92 (t, J=7.2 Hz, 3H); MS (EI): m/z=381.

*4.2.30. Ethyl 2-amino-4-(4-hydroxyphenyl)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carboxylate (**4d′**).* White crystalline solid: mp 226–227 °C; ^{1}H NMR (DMSO-d_6, δ, ppm): 9.09 (s, 1H), 7.47 (s, 2H), 6.93–6.90 (d, J=8.8 Hz, 2H), 6.58–6.56 (d, J=8.4 Hz, 2H), 4.42 (s, 1H), 3.97–3.92 (q, J=6.8 Hz, 2H), 2.63–2.59 (m, 2H), 2.33–2.19 (m, 2H), 1.97–1.78 (m, 2H), 1.11–1.08 (t, J=7.2, 3H); MS (EI): m/z=329.

*4.2.31. Ethyl 2-amino-5-oxo-4-(m-tolyl)-5,6,7,8-tetrahydro-4H-chromene-3-carboxylate (**4e′**).* Yellow crystalline solid: mp 196–198 °C (lit.[26h]); ^{1}H NMR (DMSO-d_6, δ, ppm): 8.361 (s, 2H), 7.09–7.05 (m, 1H), 6.95 (s, 1H), 6.93–6.88 (m, 2H), 4.95 (s, 1H), 3.97–3.92 (q, J=7.2 Hz, 2H), 2.66–2.58 (m, 2H), 2.41–2.33 (m, 2H), 2.23 (s, 3H), 1.87–1.81 (m, 2H), 1.11–1.08 (t, J=6.8 Hz, 3H); MS (EI): m/z=327.

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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.2011.09.137.

References and notes

1. (a) Lu, D.; Li, Y.; Gong, Y. *J. Org. Chem.* **2010**, *75*, 6900; (b) Stachulski, A. V.; Berry, N. G.; Low, A. C. L.; Moores, S. L.; Row, E.; Warhurst, D. C.; Adagu, I. S.; Rossignol, J. F. *J. Med. Chem.* **2006**, *49*, 1450; (c) Elinson, M. N.; Dorofeev, A. S.; Miloserdov, F. M.; Ilovaisky, A. I.; Feducovich, S. K.; Belyakov, P. A.; Nikishina, G. I. *Adv. Synth. Catal.* **2008**, *350*, 591; (d) Sun, W.; Cama, L. J.; Birzin, E. T.; Warrier, S.; Locco, L.; Mosley, R.; Hammond, M. L.; Rohrer, S. P. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1468; (e) Nicolaou, K. C.; Pfefferkorn, J. A.; Roecker, A. J.; Cao, G. Q.; Barluenga, S.; Mitchell, H. J. *J. Am. Chem. Soc.* **2000**, *122*, 9939.
2. (a) Bonsignore, L.; Loy, G.; Secci, D.; Calignano, A. *Eur. J. Med. Chem.* **1993**, *28*, 517; (b) Terao, K.; Niki, E. J. *Free Radical Biol. Med.* **1986**, *2*, 193; (c) Deng, J. Z.; Sun, D. A.; Starck, S. R.; Hecht, S. M.; Cerny, R. L.; Engen, J. R. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1147; (d) Maloney, D. J.; Hecht, S. M. *Org. Lett.* **2005**, *7*, 4297; (e) Kashiwada, Y.; Yamazaki, K.; Ikeshiro, Y.; Yamagishi, T.; Fujioka, T.; Mihashi, K.; Mizuki, K.; Cosentino, L. M.; Fowke, K.; Morris-Natschke, S. L.; Lee, K. H. *Tetrahedron* **2001**, *57*, 1559; (f) Triggle, D. J. *Cell. Mol. Neurobiol.* **2003**, *23*, 293.
3. (a) Gourdeau, H.; Leblond, L.; Hamelin, B.; Desputeau, C.; Dong, K.; Kianicka, I.; Custeau, D.; Bourdeau, C.; Geerts, L.; Cai, S. X.; Drewe, J.; Labrecque, D.; Kasibhatla, S.; Tseng, B. *Mol. Cancer Ther.* **2004**, *3*, 1375; (b) Kemnitzer, W.; Drewe, J.; Jiang, S.; Zhang, H.; Wang, Y.; Zhao, J.; Jia, S.; Herich, J.; Labreque, D.; Storer, R.; Meerovitch, K.; Bouffard, D.; Rej, R.; Denis, R.; Blais, C.; Lamothe, S.; Attardo, G.; Gourdeau, H.; Tseng, B.; Kasibhatla, S.; Cai, S. X. *J. Med. Chem.* **2004**, *47*, 6299; (c) Wang, J. L.; Liu, D.; Zhang, Z.; Shan, S.; Han, X.; Srinvasula, S. M.; Croce, C. M.; Alnemeri, E. S.; Huang, Z. *Proc. Natl. Acad. Sci. U.S.A.* **2000**, *97*, 7124.
4. Shaabani, A.; Ghadari, R.; Sarvary, A.; Rezayan, A. H. *J. Org. Chem.* **2009**, *74*, 4372.
5. (a) Skommer, J.; Wlodkowic, D.; MVttç, M.; Eray, M.; Pelkonen, J. *Leukemia Res.* **2006**, *30*, 322; (b) Anderson, D. R.; Hegde, S.; Reinhard, E.; Gomez, L.; Vernier, W. F.; Lee, L.; Liu, S.; Sambandam, A.; Snider, P. A.; Masih, L. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1587; (c) Kemnitzer, W.; Kasibhatla, S.; Jiang, S.; Zhang, H.; Zhao, J.; Jia, S.; Xu, L.; Crogan-Grundy, C.; Denis, R.; Barriault, N.; Vaillancourt, L.; Charron, S.; Dodd, J.; Attardo, G.; Labrecque, D.; Lamothe, S.; Gourdeau, H.; Tseng, B.; Drewe, J.; Cai, S. X. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4745; (d) Kasibhatla, S.; Gourdeau, H.; Meerovitch, K.; Drewe, J.; Reddy, S.; Qiu, L.; Zhang, H.; Bergeron, F.; Bouffard, D.; Yang, Q.; Herich, J.; Lamothe, S.; Cai, S. X.; Tseng, B. *Mol. Cancer Ther.* **2004**, *3*, 1365.
6. Curini, M.; Rosati, O.; Marcotullio, M. C.; Montanari, F.; Campagna, V.; Pace, V.; Cravotto, G. *Eur. J. Org. Chem.* **2006**, 746.
7. Rostamizadeh, S.; Amani, A. M.; Mahdavinia, G. H.; Amiri, G.; Sepehrian, H. *Ultason. sonochem.* **2010**, *17*, 306.
8. Fotouhi, L.; Heravi, M. M.; Fatehi, A.; Bakhtiari, K. *Tetrahedron Lett.* **2007**, *48*, 5379.
9. Banerjee, S.; Horn, A.; Khatri, H.; Sereda, G. *Tetrahedron Lett.* **2011**, *52*, 1878.
10. Devi, I.; Bhuyan, P. J. *Tetrahedron Lett.* **2004**, *45*, 8625.
11. Marti, C.; Carreira, E. M. *Eur. J. Org. Chem.* **2003**, *12*, 2209.
12. (a) De Souza, R. O. M. A.; Antunes, O. A. C.; Kroutil, W. *J. Org. Chem.* **2009**, *74*, 6157; (b) Hessenauer-Ilicheva, N.; Franke, A.; Meyer, D.; Woggon, W.-D.; van Eldik, R. *Chem.—Eur. J.* **2009**, *15*, 2941; (c) Champion, E.; Andre, I.; Mouli, C.; Boutet, J.; Descroix, K.; Morel, S.; Monsan, P.; Mulard, L. A.; Remaud-Siméon, M. *J. Am. Chem. Soc.* **2009**, *131*, 7379; (d) Burton, S. G.; Cowan, D. A.; Woodley, J. M. *Nat. Biotechnol.* **2002**, *20*, 37.
13. Khersonsky, O.; Roodveldt, C.; Tawfik, D. S. *Curr. Opin. Chem. Biol.* **2006**, *10*, 498.
14. (a) Li, C.; Feng, X. W.; Wang, N.; Zhou, Y. J.; Yu, X. Q. *Green Chem.* **2008**, *10*, 616; (b) Branneby, C.; Carlqvist, P.; Magnusson, A.; Hult, K.; Brinck, T.; Berglund, P. *J. Am. Chem. Soc.* **2003**, *125*, 874.
15. (a) Lou, F. W.; Liu, B. K.; Wu, Q.; Lu, D. S.; Lin, X. F. *Adv. Synth. Catal.* **2008**, *350*, 1959; (b) Torre, O.; Alfonso, I.; Gotor, V. *Chem. Commun.* **2004**, 1724; (c) Svedendahl, M.; Hult, K.; Berglund, P. *J. Am. Chem. Soc.* **2005**, *127*, 17988.
16. Akai, S.; Tanimoto, K.; Kita, Y. *Angew. Chem.* **2004**, *116*, 1431.
17. Feng, X. W.; Li, C.; Wang, N.; Li, K.; Zhang, W. W.; Wang, Z.; Yu, X. Q. *Green Chem.* **2009**, *11*, 1933.
18. Li, K.; He, T.; Li, C.; Feng, X. W.; Wang, N.; Yu, X. Q. *Green Chem.* **2009**, *11*, 777.
19. Wang, J. L.; Liu, B. K.; Yin, C.; Wu, Q.; Lin, X. F. *Tetrahedron* **2011**, *67*, 2689.
20. Lai, Y. F.; Zheng, H.; Chai, S. J.; Zhang, P. F.; Chen, X. Z. *Green Chem.* **2010**, *12*, 1917.
21. Chai, S. J.; Lai, Y. F.; Zheng, H.; Zhang, P. F. *Helv. Chim. Acta* **2010**, *93*, 2231.
22. Chai, S. J.; Lai, Y. F.; Xu, J. C.; Zheng, H.; Zhu, Q.; Zhang, P. F. *Adv. Synth. Catal.* **2011**, *353*, 371.
23. (a) Gernot, A. S.; Harald, P.; Oliver, M.; Mandana, G.-K. *Chem. Rev.* **2011**, *111*, 4141; (b) Akai, S.; Naka, T.; Omura, S.; Tanimoto, K.; Imanishi, M.; Takebe, Y.; Matsugi, M.; Kita, Y. *Chem.—Eur. J.* **2002**, *8*, 4255.
24. (a) Chanda, A.; Valery, V. F. *Chem. Rev.* **2009**, *109*, 725; (b) Firouzabadi, H.; Iranpoor, N.; Abbasi, M. *Adv. Synth. Catal.* **2009**, *351*, 755.
25. (a) Duwensee, J.; Wenda, S.; Ruth, W.; Kragl, U. *Org. Process Res. Dev.* **2010**, *14*, 48; (b) Lozano, P.; Piamtongkam, R.; Kohns, K.; Diego, T. D.; Vaultier, M.; Iborra, J. L. *Green Chem.* **2007**, *9*, 780.
26. (a) Elinson, M. N.; Dorofeev, A. S.; Feducovich, S. K.; Gorbunov, S. V.; Nasybullin, R. F.; Miloserdov, F. M.; Nikishin, G. I. *Eur. J. Org. Chem.* **2006**, 4335; (b) Gong, K.; Wang, H. L.; Luo, J.; Liu, Z. L. *J. Heterocycl. Chem.* **2009**, *46*, 1145; (c) Fang, D.; Zhang, H. B.; Liu, Z. L. *J. Heterocycl. Chem.* **2010**, *47*, 63; (d) Shi, D. Q.; Mou, J.; Zhuang, Q. Y.; Wang, X. S. *J. Chem. Res.* **2004**, *12*, 821; (e) Li, Y. l.; Du, B. X.; Wang, X. S.; Shi, D. Q.; Tu, S. J. *J. Heterocycl. Chem.* **2006**, *43*, 685; (f) Song, S. J.; Shan, Z. X.; Jin, Y. *Lett. Org. Chem.* **2010**, *7*, 64; (g) Tahmassebi, D.; Bryson, J. A.; Binz, S. I. *Synth. Commun.* **2011**, *41*, 2701; (h) Dong, Z. H.; Liu, X. H.; Feng, J. H.; Wang, M.; Lin, L. L.; Feng, X. M. *Eur. J. Org. Chem.* **2011**, 137.