


 Cite this: *RSC Adv.*, 2018, 8, 12635

 Received 8th February 2018
Accepted 26th March 2018

DOI: 10.1039/c8ra01236a

rsc.li/rsc-advances

Divergent synthesis of dual 1,4-dihydropyridines with different substituted patterns from enaminones and aldehydes through domino reactions†

 Fu-Jun Liu,^a Tian-Tian Sun,^a Yun-Gang Yang,^a Chao Huang^{*b}
and Xue-Bing Chen ^{*a}

A concise and efficient protocol for the regioselective synthesis of dual 1,4-dihydropyridines with several substituted patterns has been developed from a cascade cyclization of enaminones and aldehydes in different media (EtOH/CH₃CN). The one-pot cascade reaction involves at least five reactive sites and generates multiple C–C and C–N bonds. The established protocol explores the chemistry of enaminones by employing their three reactive sites. The method has several advantages including mild conditions, operational simplicity, and high bond-forming efficiency. It may offer promise in a variety of biochemical applications.

Introduction

Molecularly diverse and complex heterocycles play an important role in both organic synthesis and discovery of new pharmaceutical reagents.¹ 1,4-Dihydropyridines (1,4-DHPs) derivatives represent one of the most important classes of heterocycles due to their application in biological activities and molecular functions. For example, 1,4-DHPs are contained in marketed drugs such as the calcium channel blockers nifedipine, felodipine, nicardipine, and nimodipine. During the last several decades, it has been demonstrated that 1,4-DHPs are involved in various biological applications, *i.e.* antibacterial,² anticonvulsant,³ anti-HIV,⁴ anti-tumour,⁵ radioprotective,⁶ and neuroprotection⁷ activities; they could also act as adenosine-A3 receptor antagonism⁸ and sirtuin inhibitor.⁹ In view of their high significance, numerous methodologies for 1,4-DHPs have been introduced.¹⁰ However, few strategies have been successfully developed for efficient and concise access to highly functionalized and molecularly diverse target products. Therefore, it is of great importance to build libraries of target compounds in a parallel manner.

Multicomponent domino reactions (MCDRs) are powerful tools in modern organic synthesis because they enable more than

two building blocks to combine in a single-step operation to generate complex structures through the simultaneous formation of multiple bonds.¹¹ With their inherent characteristics, *i.e.*, step efficiency, atom economy, target molecules diversity, operational simplicity. MCDRs have become an essential tool for generating complex molecular libraries in the screening of biologically and pharmacologically active candidates.

As a group of versatile and powerful synthons, enaminones have been used for construction of diverse heterocyclic systems.¹² These compounds include acridines,¹³ indoles,¹⁴ naphthyridines,¹⁵ quinolones,¹⁶ pyrroles,¹⁷ thiazines,¹⁸ pyridines,¹⁹ and thiazoles.²⁰ Some of these heterocycles which are synthesized from enaminones also demonstrate promising biological activity.²¹ So far, a number of natural product-like heterocycles have been successfully synthesized based on enaminones. Their synthetic methodology and associated medicinal activity should be engaged in the chemistry community.

In pursuit of our research interests regarding the development of MCRs based on enaminones, we report a convenient and efficient protocol for the regioselective synthesis of two libraries of 1,4-DHPs **3** and **4** *via* a tandem annulation of enaminones **1** and aldehydes **2** in EtOH and CH₃CN, respectively (Scheme 1). At least five distinct reactive sites participate in this process.

Results and discussion

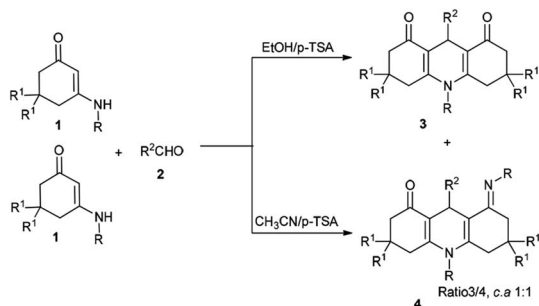
On the basis of our recent work, we examined the domino reaction which employed *N*-*p*-F-Ph substituted enaminone **1a** and 4-chlorobenzaldehyde **2a** as the substrates (Table 1).

^aKey Laboratory of Natural Pharmaceutical and Chemical Biology of Yunnan Province, School of Science, Honghe University, Mengzi, Yunnan 661100, China. E-mail: orangekaka@126.com

^bSchool of Chemistry and Environment, Engineering Research Center of Biopolymer Functional Materials of Yunnan, Yunnan Minzu University, Kunming, Yunnan 650503, China

† Electronic supplementary information (ESI) available: Detailed experimental procedures. CCDC 1819954. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c8ra01236a





Scheme 1 Proposed mechanism for the construction of 1,4-DHPs **3** and **4**.

First, the reaction was executed without any catalyst in anhydrous ethanol at reflux; no reaction occurred even within 3 hours (Table 1, entry 1). Next, different types of organic bases, such as piperidine, Et₃N, DBU, and DABCO, were employed as catalysts, but no transformation was observed (Table 1, entries 2–5). Nevertheless, when *p*-TSA (0.2 equiv.) was added, compound **3a** was obtained in a yield of 66% (Table 1, entry 6). Other acids, such as TFA, HOAc and L-proline were also investigated, but could not generate the reaction efficiently (Table 1, entries 7–9). The reaction conditions were then optimized by screening several solvents. When *p*-TSA was added to a solution of **1a** and **2a** in CH₃CN (Table 1, entry 10), a new compound **4a**

Table 1 Optimization of the reaction conditions for the model reaction^a

Entry	Solvent	Catalyst ^b	Time (h)	Yield ^c (%)	
				3a	4a
1	EtOH	—	4	n.r	n.r
2	EtOH	Piperidine	3	n.r	n.r
3	EtOH	Et ₃ N	3	n.r	n.r
4	EtOH	DBU	3	n.r	n.r
5	EtOH	DABCO	3	n.r	n.r
6	EtOH	<i>p</i> -TSA	3	66	n.r
7	EtOH	TFA	2	64	n.r
8	EtOH	HOAc	2	n.r	n.r
9	EtOH	L-proline	2	n.r	n.r
10	CH ₃ CN	<i>p</i> -TSA	2	43	36
11	CH ₃ CN	TFA	2	50	34
12	CH ₃ CN	TfOH	2	n.r	Trace
13	1,4-Dioxane	<i>p</i> -TSA	2	30	25
14	DMF	<i>p</i> -TSA	2	45	28
15	CH ₃ OH	<i>p</i> -TSA	2	n.r	n.r

^a The reaction was performed with **1a** (1.0 mmol), **2a** (0.6 mmol), and the solvent (15 mL) was under reflux temperature. ^b Catalyst (0.3 mmol) was added to the reaction. ^c Isolated yields were based on enaminone **1a**.

was generated in 36% yield. In order to efficiently obtain a single final product, additional attempts were made. For example, three types of solvents, *i.e.*, 1,4-dioxane, DMF, and CH₃OH, and acidic catalysts TFA, and TfOH were used in the reaction. However, the yields of **3a** and **4a** were decreased, and likewise, the vying preference for the formation of **4a** was unsatisfied (Table 1, entries 11–15). Thus, ethanol was the best medium for selectively obtaining product **3a**. It was discovered that the optimum reaction conditions for the synthesis of **3a** include *p*-TSA as the catalyst and EtOH as the medium at reflux for 3 h. Conversely, the best conditions for the preparation of **4a** are conducted in CH₃CN.

With the optimal reaction conditions, the synthesis of 1,4-DHPs **4** was tested by using a range of readily available enaminones and different substituted aldehydes. As shown in Table 2, for precursors **1** and **2** bearing either electron-withdrawing or electron-donating substituents on the aromatic ring, or the aromatic groups (for **2**) with diverse substitution patterns (*para* or *meta*), all reactions proceeded smoothly to provide the corresponding 1,4-DHPs derivatives. The reaction was also investigated by using alkyl enaminone **1h**, which yielded the corresponding target molecule **3m**.

After completing the synthesis of compounds **3**, the domino reaction was studied for preparing other target molecules **4** (Scheme 2). First, the scope of substrates **1** was tested by using 3-amino-5,5-dimethylcyclohex-2-enones. The reaction results of various 3-aminocyclohex-2-enonephenyls with aldehydes

Table 2 Substrate scope of **1** and synthesis of target molecules **3**^a

Entry	1 (R/R ¹)	2 (R ²)	3	Yield ^b (%)
1	1a (4-FC ₆ H ₅ /CH ₃)	2a (4-ClC ₆ H ₅)	3a	66
2	1a (4-FC ₆ H ₅ /CH ₃)	2b (C ₆ H ₅)	3b	58
3	1b (3-FC ₆ H ₅ /CH ₃)	2b (C ₆ H ₅)	3c	62
4	1c (3-ClC ₆ H ₅ /CH ₃)	2a (4-ClC ₆ H ₅)	3d	63
5	1c (3-ClC ₆ H ₅ /CH ₃)	2b (C ₆ H ₅)	3e	68
6	1d (4-BrC ₆ H ₅ /CH ₃)	2a (4-ClC ₆ H ₅)	3f	65
7	1d (4-BrC ₆ H ₅ /CH ₃)	2b (C ₆ H ₅)	3g	62
8	1e (3-BrC ₆ H ₅ /CH ₃)	2b (C ₆ H ₅)	3h	60
9	1f (C ₆ H ₅ /CH ₃)	2a (4-ClC ₆ H ₅)	3i	65
10	1f (C ₆ H ₅ /CH ₃)	2b (C ₆ H ₅)	3j	63
11	1f (C ₆ H ₅ /CH ₃)	2c (4-OCH ₃ C ₆ H ₅)	3k	64
12	1g (3-CH ₃ C ₆ H ₅ /CH ₃)	2b (C ₆ H ₅)	3l	62
13	1h (<i>n</i> -butyl/CH ₃)	2a (4-ClC ₆ H ₅)	3m	70
14	1i (4-ClC ₆ H ₅ /H)	2a (4-ClC ₆ H ₅)	3n	71
15	1j (3-ClC ₆ H ₅ /H)	2a (4-ClC ₆ H ₅)	3o	72
16	1k (3-BrC ₆ H ₅ /H)	2c (4-OCH ₃ C ₆ H ₅)	3p	68
17	1l (4-CH ₃ C ₆ H ₅ /H)	2a (4-ClC ₆ H ₅)	3q	60
18	1a (4-FC ₆ H ₅ /CH ₃)	2d (<i>n</i> -propyl)	3r	62

^a The reaction was performed with **1** (1.0 mmol), **2** (0.6 mmol), and *p*-TSA (0.3 mmol) in EtOH (15 mL) at reflux for 3 hours. ^b Isolated yields based on enaminones **1**.



demonstrate that the process tolerates both 3-amino-5,5-dimethylcyclohex-2-enones **1** and aromatic aldehydes **2** bearing either electron-donating or electron-withdrawing substituents on the aryl group. However, as both compounds **3** and **4** are generated from this reaction, the yields of **4** would be relatively low (yields **3** : **4**, *c.a.* 1 : 1).

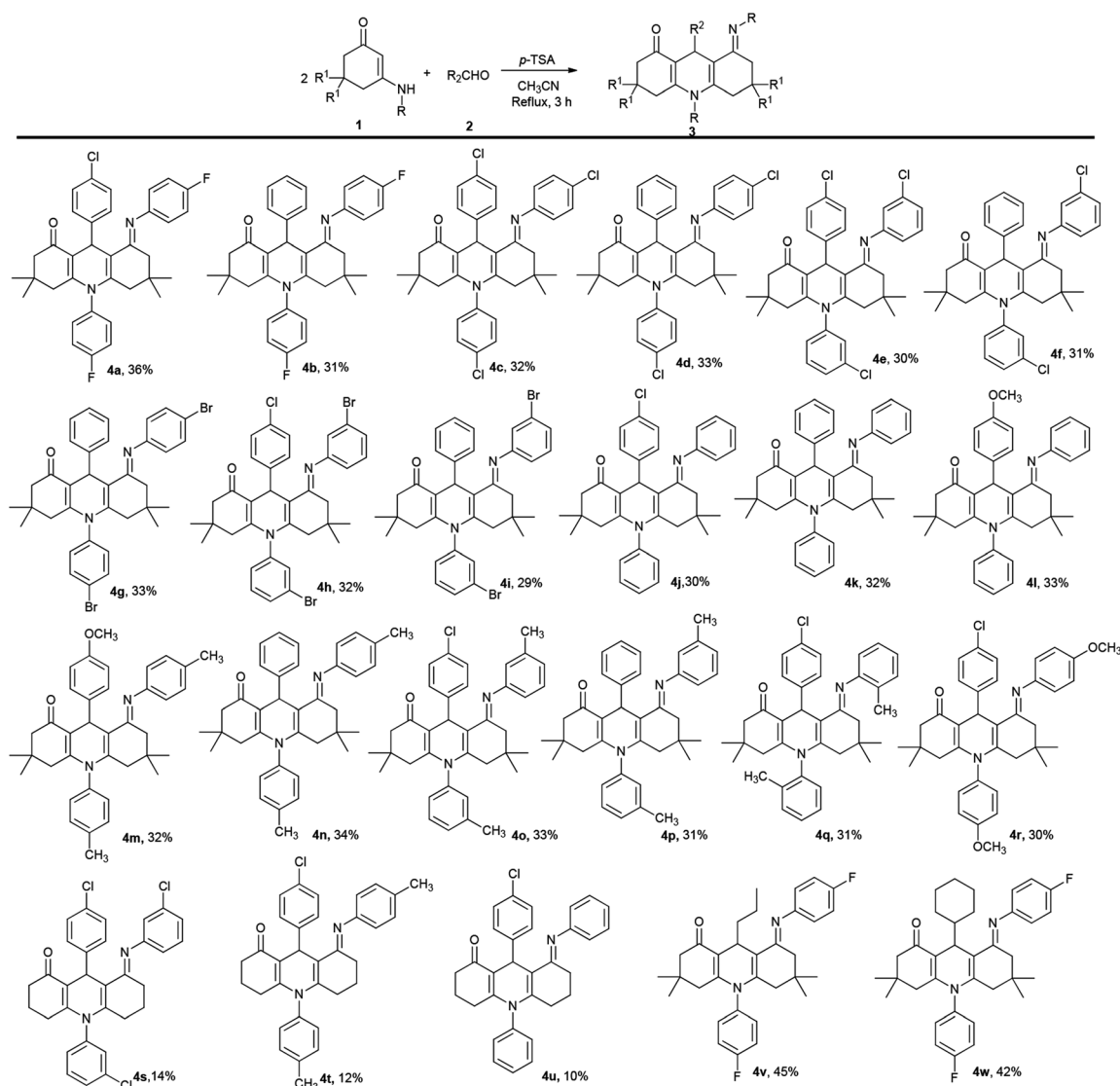
Next, the reaction was examined using *N*-substituted 3-aminocyclohex-2-enonephenyls. Unfortunately, the results did not yield much success. Most of the *N*-substituted 3-aminocyclohex-2-enonephenyls generated a low yield of **4** but a high yield of **3** (Scheme 2, **4s–4u**). It is worthwhile noting that compounds **4** are difficult to separate by conventional methods, like column chromatography and recrystallization. Hitherto, only three compounds were readily obtained by using *N*-substituted 3-aminocyclohex-2-enonephenyls.

Finally, aliphatic aldehydes butyraldehyde and cyclohexanecarboxaldehyde were also employed in this process, and both reactions proceeded well giving the corresponding 1,4-DHPs

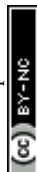
4v and **4w**. And it was observed that the aliphatic aldehydes gave the major compounds **4** while products **3** were scarcely generated.

The chemical structures of 1,4-DHPs **3** and **4** were characterized by IR, ¹H NMR, ¹³C NMR, and HRMS, and unequivocally confirmed by X-ray diffraction analysis of a monocrystal of **3n** (Fig. 1, CCDC 1819954).

The possible mechanism for the formation of products **3/4** is shown in Scheme 3. Take aromatic aldehyde as the example. First, the benzaldehyde **2** accepts a proton to form **5**. Enaminone **1** serves as a heteroene component to react with **5** accompanying the loss of one molecule of H₂O to generate intermediate **6** via an aza-ene reaction. Following this, compound **6** undergoes imine-enamine tautomerization to produce **7**. Intermediate **7** accepts a proton to form **8**, and the elimination of water from intermediate **7** gives iminium ion **9**. Enaminone **1** then participates in a Michael addition with compound **9** to form intermediate **10**. Two potential reactions then occur in intermediate **10**. In pathway 1, the –NH group



Scheme 2 Substrate scope of the reaction for 1,4-DHPs **4**. The reaction was performed with **1** (1.0 mmol), **2** (0.6 mmol), and *p*-TSA (0.3 mmol) in CH₃CN (10 mL) at reflux for 2 h. The yields were isolated based on enaminones **1**.



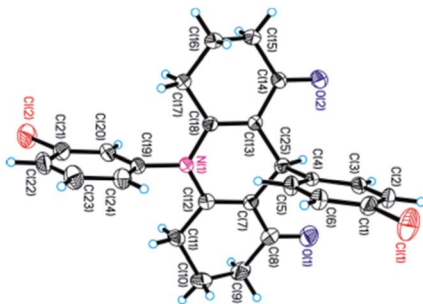
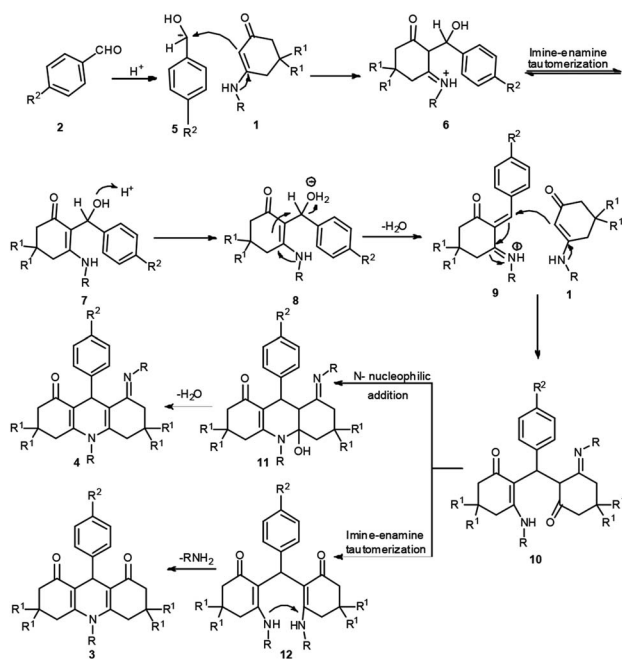


Fig. 1 X-ray crystal structures of **3n**; ellipsoids are drawn at 30% probability level.



Scheme 3 Proposed mechanism for the construction of 1,4-DHPs **3** and **4**.

undergoes an intramolecular attack of the carbonyl group, resulting in a cyclization reaction that forces it to lose a molecule of water, affording **4**. In pathway 2, intermediate **10** undergoes imine-enamine tautomerization to give intermediate **12** and elimination of aniline gives 1,4-DHPs **3**.

Conclusions

In conclusion, we have successfully developed an operationally simple, one-pot three component reaction for the selective synthesis of two libraries of highly functionalized 1,4-DHPs derivatives by using of EtOH or CH₃CN as media *via* a tandem cyclization of enaminones **1** with aldehydes **2**. The reaction displays many attractive features, including excellent regioselectivity, mild and environmentally friendly conditions, and molecular diversities. Moreover, these series of 1,4-DHPs may provide potential biological activities for medical treatment.

Further studies will be conducted in our laboratories in due course.

Experimental

General

All compounds were fully characterized by spectroscopic data. The NMR spectra were recorded on Bruker AVIII-400 (¹H: 400 MHz, ¹³C: 100 MHz) or Bruker AVIII-500 (¹H: 500 MHz, ¹³C: 125 MHz) and chemical shifts (δ) are expressed in ppm, and *J* values are given in Hz, CDCl₃ was used as solvent. IR spectra were recorded on a FT-IR Thermo Nicolet Avatar 360 using a KBr pellet. The reactions were monitored by thin-layer chromatography (TLC) using silica gel GF₂₅₄. The melting points were determined on XT-4A melting point apparatus and are uncorrected. HRMS were performed on a Agilent LC/Msd TOF and monoisotopic mass instrument.

General procedure for the synthesis of compounds **3**

A mixture of enaminones **1** (1.0 mmol), aldehydes **2** (0.6 mmol), *p*-TSA (0.3 mmol), and EtOH (15 mL) was stirred at reflux for 3 h. After the desired product was formed as indicated by TLC, the reaction mixture was quenched with saturated NH₄Cl solution (2 mL) and extracted with ethyl acetate (40 mL). The organic phase was dried over Mg₂SO₄, and concentrated under vacuum. The residue was purified by flash chromatography (petroleum ether/ethyl acetate = 2 : 3) giving a white solid **3**.

9-(4-chlorophenyl)-10-(4-fluorophenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione (3a). White solid; mp 296–298 °C; IR (KBr): 2959, 1649, 1618, 1500, 1371, 1226 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ = 7.35 (d, *J* = 8.4 Hz, 2H, ArH), 7.20–7.29 (m, 6H, ArH), 5.24 (s, 1H, CH), 2.03–2.22 (m, 6H, CH₂), 1.78–1.83 (m, 2H, CH₂), 0.96 (s, 6H, 2 × CH₃), 0.81 (s, 6H, 2 × CH₃); ¹³C NMR (100 MHz, CDCl₃): δ = 195.7, 163.6 (d, ¹*J*_{C-F} = 249.8 Hz), 149.7, 144.6, 134.9, 131.6, 130.9, 129.5, 129.3, 128.2, 117.3, 114.5, 50.1, 41.9, 32.4, 32.4, 29.7, 26.8; HRMS (ESI-TOF): *m/z* calcd for C₂₉H₃₀ClFNO₂⁺ [(*M* + *H*)⁺], 478.1944; found, 478.1943.

10-(4-fluorophenyl)-3,3,6,6-tetramethyl-9-phenyl-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione (3b). White solid; mp 298–299 °C; IR (KBr): 2959, 1641, 1510, 1402, 1220, 700 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ = 7.43 (d, *J* = 8.0 Hz, 2H, ArH), 7.24–7.30 (m, 6H, ArH), 7.10–7.13 (m, 1H, ArH), 5.29 (s, 1H, CH), 2.21 (AB, *J* = 16.0 Hz, 2H, CH₂), 2.14 (AB, *J* = 16.0 Hz, 2H, CH₂), 2.08 (AB, *J* = 16.0 Hz, 2H, CH₂), 1.83 (AB, *J* = 16.0 Hz, 2H, CH₂), 0.97 (s, 6H, 2 × CH₃), 0.82 (s, 6H, 3 × CH₃); ¹³C NMR (100 MHz, CDCl₃): δ = 195.7, 162.5 (d, ¹*J*_{C-F} = 249.0 Hz), 149.5, 146.0, 135.1, 135.0, 131.8, 128.1, 127.8, 126.0, 117.2, 114.8, 50.2, 41.9, 32.6, 32.4, 29.8, 26.8; HRMS (ESI-TOF): *m/z* calcd for C₂₉H₃₁FNO₂⁺ [(*M* + *H*)⁺], 444.2333; found, 444.2332.

General procedure for the synthesis of compounds **4**

A mixture of enaminones **1** (1.0 mmol), aldehydes **2** (0.6 mmol), *p*-TSA (0.3 mmol), and CH₃CN (10 mL) was stirred at reflux for 2 h. After the desired product was formed as indicated by TLC, the reaction mixture was quenched with saturated NH₄Cl



solution (2 mL) and extracted with ethyl acetate (40 mL). The organic phase were dried over Mg_2SO_4 , and concentrated under vacuum. The residue was purified by flash chromatography (petroleum ether/ethyl acetate = 1 : 1) giving a yellow solid **4**.

(E)-9-(4-chlorophenyl)-10-(4-fluorophenyl)-8-((4-fluorophenyl)imino)-3,3,6,6-tetramethyl-3,4,5,6,7,8,9,10-octahydroacridin-1(2H)-one (4a). Yellow solid; mp 260–262 °C; IR (KBr): 2959, 1649, 1500, 1371, 1226, 846 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ = 7.41 (t, J = 8.0 Hz, 2H, ArH), 7.17–7.27 (m, 6H, ArH), 6.87–6.93 (m, 2H, ArH), 6.41–6.47 (m, 2H, ArH), 5.54 (s, 1H, CH), 5.25 (d, J = 32.4 Hz, 1H, CH), 1.92–2.24 (m, 6H, 3 $\times$ CH_2), 1.67–1.83 (m, 2H, CH_2), 0.95 (s, 3H, CH_3), 0.85 (s, 3H, CH_3), 0.83 (s, 3H, CH_3), 0.78 (s, 3H, CH_3); ^{13}C NMR (100 MHz, CDCl_3): δ = 195.8, 162.4 (d, $^1J_{\text{C-F}}$ = 245.0 Hz), 158.8 (d, $^1J_{\text{C-F}}$ = 238.5 Hz), 150.3, 148.0, 145.4, 142.0, 145.4, 142.0, 135.4, 131.4, 131.1, 129.6, 127.8, 120.7 (d, $^3J_{\text{C-F}}$ = 7.5 Hz), 120.6 (d, $^3J_{\text{C-F}}$ = 7.5 Hz), 117.0 (d, $^2J_{\text{C-F}}$ = 21.5 Hz), 115.4 (d, $^2J_{\text{C-F}}$ = 21.9 Hz), 115.1 (d, $^2J_{\text{C-F}}$ = 21.9 Hz), 114.6, 113.1, 50.2, 41.9, 40.8, 33.2, 32.4, 31.4, 29.9, 29.6, 26.7; HRMS (ESI-TOF): m/z calcd for $\text{C}_{35}\text{H}_{34}\text{ClF}_2\text{N}_2\text{O}^+[(\text{M} + \text{H})^+]$, 571.2322; found, 571.2323.

(E)-10-(4-fluorophenyl)-8-((4-fluorophenyl)imino)-3,3,6,6-tetramethyl-9-phenyl-3,4,5,6,7,8,9,10-octahydroacridin-1(2H)-one (4b). Yellow solid; mp 233–234 °C; IR (KBr): 2957, 1644, 1579, 1367, 1267, 853 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ = 7.51 (d, J = 8.0 Hz, 2H, ArH), 7.24–7.28 (m, 6H, ArH), 7.15–7.11 (m, 1H, ArH), 6.91–6.95 (m, 2H, ArH), 6.48 (d, J = 8.0 Hz, 2H, ArH), 5.63 (s, 1H, CH), 2.01–2.27 (m, 6H, 3 $\times$ CH_2), 1.81–1.87 (m, 2H, CH_2), 0.99 (s, 3H, CH_3), 0.88 (s, 3H, CH_3), 0.83 (s, 3H, CH_3), 0.74 (s, 3H, CH_3); ^{13}C NMR (100 MHz, CDCl_3): δ = 195.9, 162.3 (d, $^1J_{\text{C-F}}$ = 249.0 Hz), 158.8 (d, $^1J_{\text{C-F}}$ = 238.0 Hz), 150.19, 148.21, 146.69, 141.85, 135.57, 135.53, 131.59, 128.18, 127.69, 125.57, 120.72 (d, $^3J_{\text{C-F}}$ = 8.0 Hz), 116.9 (d, $^2J_{\text{C-F}}$ = 21.3 Hz), 115.3 (d, $^2J_{\text{C-F}}$ = 22.0 Hz), 115.1 (d, $^2J_{\text{C-F}}$ = 22.0 Hz), 114.9, 113.4, 50.3, 41.9, 41.8, 40.8, 33.5, 32.4, 31.5, 30.0, 29.6, 26.8, 26.69; HRMS (ESI-TOF): m/z calcd for $\text{C}_{35}\text{H}_{35}\text{F}_2\text{N}_2\text{O}^+[(\text{M} + \text{H})^+]$, 537.2712; found, 537.2713.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (No. 61361002, 21662046), Applied Basic Research Project of Yunnan (2017FD156), and Yunnan Province Department of Education Fund (2016ZZX217).

Notes and references

- (a) J. D. Sunderhaus, C. Dockendorff and S. F. Martin, *Org. Lett.*, 2007, **9**, 4223; (b) F. Liéby-Muller, T. Constantieux and J. Rodriguez, *J. Am. Chem. Soc.*, 2005, **127**, 17176; (c) C. Lamberth and J. Dinges, in *Bioactive Heterocyclic Compound Classes: Pharmaceuticals*, ed. C. Lamberth and J. Dinges, Wiley-VCH, Weinheim, 2012, ch. 1, pp. 3–5; (d) C. Hulme and V. Gore, *Curr. Med. Chem.*, 2003, **10**, 51.
- H. M. Refat and A. A. Fadda, *Eur. J. Med. Chem.*, 2013, **70**, 419.
- (a) R. Surendra Kumar, A. Idhayadhulla, A. Jamal Abdul Nasser, S. Kavimani and S. Indumathy, *Indian J. Pharm. Sci.*, 2010, **72**, 719; (b) B. B. Subudhi, P. K. Panda, S. P. Swain and P. Sarangi, *Acta Pol. Pharm.*, 2009, **66**, 147.
- (a) A. Hilgeroth, *Mini-Rev. Med. Chem.*, 2002, **2**, 235; (b) C. K. Chu, V. S. Bhadti, K. J. Doshi, J. T. Etse, J. M. Gallo, F. D. Boudinot and R. F. Schinazi, *J. Med. Chem.*, 1990, **33**, 2188; (c) A. Hilgeroth and H. Lilie, *Eur. J. Med. Chem.*, 2003, **38**, 495.
- (a) H. A. Abbas, W. A. El Sayed and N. M. Fathy, *Eur. J. Med. Chem.*, 2010, **45**, 973; (b) S. R. Morshed, K. Hashimoto, Y. Murotani, M. Kawase, A. Shah, K. Satoh, H. Kikuchi, H. Nishikawa, J. Maki and H. Sakagami, *Anticancer Res.*, 2005, **25**, 2033; (c) J. Robert and C. Jarry, *J. Med. Chem.*, 2003, **46**, 4805.
- I. O. Donkor, X. Zhou, J. Schmidt, K. C. Agrawal and V. Kishore, *Bioorg. Med. Chem.*, 1998, **6**, 563.
- V. Klusa, *Drugs Future*, 1995, **20**, 135.
- A. H. Li, S. Moro, N. Forsyth, N. Melman, X.-D. Ji and K. A. Jacobson, *J. Med. Chem.*, 1999, **42**, 706.
- A. Mai, S. Valente, S. Meade, V. Carafa, M. Tardugno, A. Nebbioso, A. Galmozzi, N. Mitro, E. D. Fabiani, L. Altucci and A. Kazantsev, *J. Med. Chem.*, 2009, **52**, 5496.
- (a) J.-P. Wan and Y.-Y. Liu, *RSC Adv.*, 2012, **2**, 9763; (b) G. Li and J. C. Antilla, *Org. Lett.*, 2009, **11**, 1075; (c) D. Zhang, L.-Z. Wu, L. Zhou, X. Han, Q.-Z. Yang, L.-P. Zhang and C.-H. Tung, *J. Am. Chem. Soc.*, 2004, **126**, 3440; (d) P. R. Girling, A. S. Batsanov, H. C. Shen and A. Whiting, *Chem. Commun.*, 2012, 4893; (e) Y. Nakaike, N. Nishiwaki, M. Ariga and Y. Tobe, *J. Org. Chem.*, 2014, **79**, 2163; (f) J.-P. Wan, R.-H. Zhou, Y.-Y. Liu and M.-Z. Cai, *RSC Adv.*, 2013, **3**, 2477.
- (a) V. Estevez, M. Villacampa and J. C. Menendez, *Chem. Soc. Rev.*, 2010, **39**, 4402; (b) E. Ruijter, R. Scheffelaar and R. V. A. Orru, *Angew. Chem., Int. Ed.*, 2011, **50**, 6234; (c) N. Isambert, M. d. M. S. Duque, J. C. Plaquevent, Y. Genisson, J. Rodriguez and T. Constantieux, *Chem. Soc. Rev.*, 2011, **40**, 1347; (d) J. Yu, F. Shi and L.-Z. Gong, *Acc. Chem. Res.*, 2011, **44**, 1156; (e) B. Ganem, *Acc. Chem. Res.*, 2009, **42**, 463; (f) A. Dömling, *Chem. Rev.*, 2006, **106**, 17; (g) J.-P. Wan, L. Gan and Y.-Y. Liu, *Org. Biomol. Chem.*, 2017, **15**, 9031.
- (a) B. Stanovnik and J. Svete, *Chem. Rev.*, 2004, **104**, 2433; (b) J.-P. Wan and Y. Gao, *Chem. Rec.*, 2016, **16**, 1164.
- (a) B. Jiang, X. Wang, H.-W. Xu, M.-S. Tu, S.-J. Tu and G.-G. Li, *Org. Lett.*, 2013, **15**, 1540; (b) W.-J. Hao, J.-Q. Wang, X.-P. Xu, S.-L. Zhang, S.-Y. Wang and S.-J. Ji, *J. Org. Chem.*, 2013, **78**, 12362; (c) X.-B. Chen, X.-Q. Wang, Y. Hong and W. Liu, *Asian J. Org. Chem.*, 2016, **5**, 907; (d) H.-Y. Wang, L.-L. Li, W. Lin, P. Xu, Z.-B. Huang and D.-Q. Shi, *Org. Lett.*, 2012, **14**, 4598.
- (a) H. Xu, B. Zhou, P. Zhou, J. Zhou, Y.-H. Shen, F.-C. Yu and L.-L. Li, *Chem. Commun.*, 2016, **52**, 8002; (b) X.-B. Chen, T.-B. Luo, G.-Z. Gou, J. Wang and W. Liu, *Asian J. Org. Chem.*, 2015, **4**, 921; (c) B. Jiang, M.-S. Yi, F. Shi, S.-J. Tu, S. Pindi, P. McDowell and G.-G. Li, *Chem. Commun.*, 2012, **48**, 808; (d) J.-D. Hu, C.-P. Cao, W. Lin, M.-H. Hu,



- Z.-B. Huang and D.-Q. Shi, *J. Org. Chem.*, 2014, **79**, 7935; (e) L. Wang, L.-X. Shi, L. Liu, Z.-X. Li, T. Xu, W.-J. Hao, G.-G. Li, S.-J. Tu and B. Jiang, *J. Org. Chem.*, 2017, **82**, 3605.
- 15 (a) J.-Y. Li, Q.-Y. Li, B. Jiang and S.-J. Tu, *RSC Adv.*, 2013, **3**, 5056; (b) B. Jiang, Y. Li, M.-S. Tu, S.-L. Wang, S.-J. Tu and G.-G. Li, *J. Org. Chem.*, 2012, **77**, 7497.
- 16 (a) M.-Y. Li, H.-W. Xu, W. Fan, Q. Ye, X. Wang, B. Jiang, S.-L. Wang and S.-J. Tu, *Tetrahedron*, 2014, **70**, 1004; (b) F.-C. Yu, B. Zhou, H. Xu, Y.-M. Li, J. Lin, S.-J. Yan and Y.-H. Shen, *Tetrahedron*, 2015, **71**, 1036; (c) X.-B. Chen, H.-R. Bai and C. Huang, *Chin. J. Org. Chem.*, 2017, **31**, 881; (d) X.-B. Chen, J.-W. Gong, X.-D. Zhang, X.-L. Liu, W. Liu and Y.-C. Wang, *Tetrahedron*, 2018, **74**, 401.
- 17 (a) B. Jiang, X. Wang, M.-Y. Li, Q. Wu, Q. Ye, H.-W. Xu and S.-J. Tu, *Org. Biomol. Chem.*, 2012, **10**, 8533; (b) C.-P. Cao, W. Lin, M.-H. Hu, Z.-B. Huang and D.-Q. Shi, *Chem. Commun.*, 2013, **49**, 6983.
- 18 Z.-Y. Gu, J.-J. Gao, Y.-S. Wang and S.-J. Ji, *Chem. Sci.*, 2016, **7**, 4067.
- 19 (a) N. Ma, B. Jiang, G. Zhang, S.-J. Tu, W. Waver and G.-G. Li, *Green Chem.*, 2010, **12**, 1357; (b) S. Rana, M. Brownb and C. Mukhopadhyay, *RSC Adv.*, 2013, **3**, 3291; (c) F.-C. Yu, B. Zhou, H. Xu, K.-J. Chang and Y.-H. Shen, *Tetrahedron Lett.*, 2015, **56**, 837; (d) P. Zhou, B. Hu, J. Yang, L.-D. Li, K.-R. Rao, D.-F. Zhu and F.-C. Yu, *Eur. J. Org. Chem.*, 2017, **29**, 7256; (e) X.-J. Tu, W.-J. Hao, Q. Ye, S.-S. Wang, B. Jiang, G.-G. Li and S.-J. Tu, *J. Org. Chem.*, 2014, **79**, 11110; (f) J.-P. Wan, Y.-F. Lin, Y.-F. Jin, M.-L. Xu and Y.-Y. Liu, *Tetrahedron*, 2014, **70**, 7874; (g) S. Cao, S.-S. Zhong, C.-F. Hu, J.-P. Wan and C.-P. Wen, *Chin. J. Chem.*, 2015, **33**, 568.
- 20 X.-B. Chen, X.-Q. Wang, J.-N. Song, Q.-L. Yang, W. Liu and C. Huang, *Org. Biomol. Chem.*, 2017, **15**, 3611.
- 21 (a) J. A. Makawana, M. P. Patel and R. G. Patel, *Chin. Chem. Lett.*, 2012, **23**, 427; (b) C. Hundsdörfer, H. J. Hemmerling, C. Götz, F. Totzke, P. Bednarski, M. L. Borgne and J. Jose, *Bioorg. Med. Chem.*, 2012, **20**, 2282.

