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LiCl-promoted amination of β -methoxy amides (γ -lactones)[†]

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An efficient and mild method has been developed for the amination of β -methoxy amides (γ -lactones) including natural products michelolide, costunolide and parthenolide derivatives by using lithium chloride in good yields. This reaction is applicable to a wide range of substrates with good functional group tolerance. Mechanism studies show that the reactions undergo a LiCl promoted MeOH elimination from the substrates to form the corresponding α,β -unsaturated intermediates followed by the Michael addition of amines.

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The formation of carbon–nitrogen bonds remains one of the most fundamental and widely practiced reactions in organic synthesis, due to the prevalence of this functionality in the preparations of functional molecules in pharmaceutical chemistry, biochemistry and material sciences.¹ Various synthetic methodologies have been developed to form C(sp³)-N bonds, including the Goldberg reaction,² Buchwald–Hartwig reaction,³ imine reduction⁴ and the nucleophilic addition of carbon–nucleophiles to imine derivatives.⁵ Meanwhile, the formations of C(sp³)-N bonds can be achieved by reductive amination, which involves the conversion of a carbonyl group to an amine *via* an imine intermediate, such as Eschweiler–Clarke reaction⁶ and Borch reductive amination.⁷ Nucleophilic substitution of alkyl(pseudo)halides with amines (amine alkylation) serves as one direct strategy for the preparation of alkylamines, while the necessity of pre-installation of the halogen atoms and the production of stoichiometric inorganic salt wastes are considered as two main drawbacks for its application in large scale industrial synthesis.⁸

Methoxy as the leaving group in the amination reactions has recently attracted the attention of organic chemists. For instance, Chiba and coworkers reported a method for the nucleophilic amination of methoxy arenes,⁹ which was achieved by using sodium hydride (NaH) in the presence of lithium iodide (LiI) through a concerted nucleophilic aromatic substitution pathway (Fig. 1a).¹⁰ Kondo and coworkers demonstrated that the organic superbases *t*-Bu-P4 efficiently catalyzes the

amination of methoxy(hetero)arenes with the amine nucleophiles (Fig. 1b).¹¹ The *t*-Bu-P4 is also suitable to catalyze the amination of β -(hetero)arylethyl ethers with amines to synthesize β -(hetero)arylethylamines (Fig. 1c).¹² Sun and coworkers reported that C–S bond cleavage to access *N*-substituted acrylamide and β -aminopropanamide (Fig. 1d).¹³

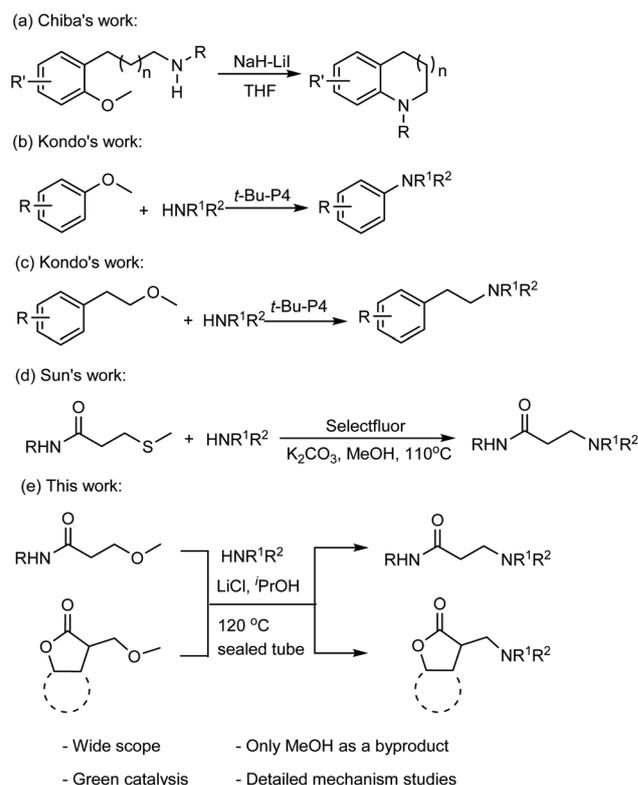


Fig. 1 Amination reactions of methyl ethers.

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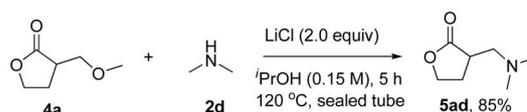
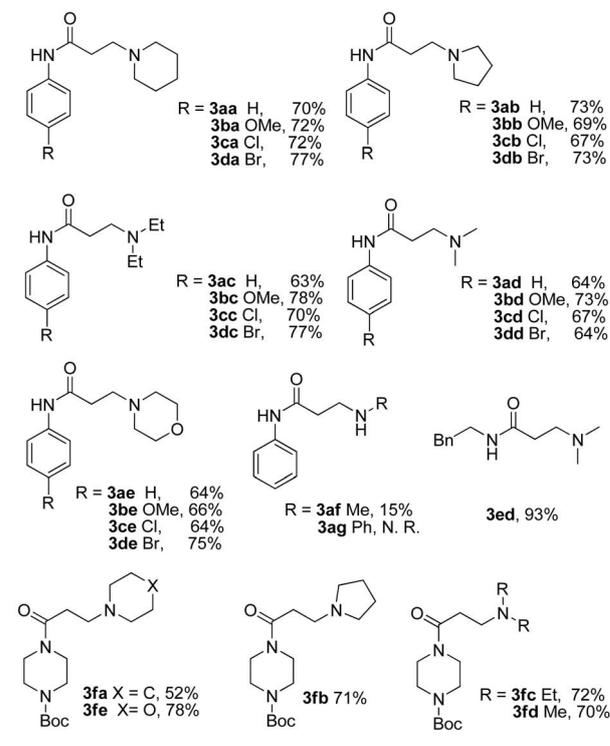
[†] Electronic supplementary information (ESI) available: Experimental details, including procedures, syntheses and characterization of new compounds; and ¹H and ¹³C NMR spectra. CCDC 1999852. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d0ra07170f



Recently, we described the application of a CuBr–LiCl composite for the short-chain alkoxylation of aryl bromides.¹⁴ During that course of study, the single-shell lithium ion was found to embrace a unique affinity for oxygen and can be used as an additive to activate C–O bond and facilitate the nucleophilic reaction. On the basis of this study, we herein present the synthesis of β -amino amides (γ -lactones) *via* the elimination of methoxy group followed by Michael addition of an amine, that was promoted by LiCl in good yields under conventional conditions.

We initiated our study with the reaction of 3-methoxy-*N*-phenylpropanamide **1a** and piperidine **2a** in the presence of lithium salts (Table 1). It was found that the reaction performed in ⁱPrOH at 120 °C in a sealed tube proceeded smoothly in the presence of 2.0 equiv. of LiCl, giving the desired product **3aa** in 70% yield (entry 1), while using other additives, including LiBr, LiI, LiOTf, Li₂CO₃ and NaCl instead, dramatically decreased the yields (entries 2–6). ⁱPrOH was proved to be a better solvent, whereas using other solvents, such as DMF or toluene, gave poor results (entries 7 and 8). Lowering the equivalent of LiCl to 1.0 equiv. reduced the yield of **3aa** to 38% (entry 9). No conversion was observed when the reaction was performed in the absence of LiCl (entry 10). Moreover, reducing the reaction temperature or reaction time resulted in diminished yields (entries 11 and 12). Therefore, 1.0 equiv. of 3-methoxy propanamide, 2.0 equiv. of alkyl amine and 2.0 equiv. of LiCl in ⁱPrOH was chosen as the standard condition for the amination of 3-methoxy propanamides.

With the optimized condition in hand, the substrate scope and functional group tolerance of the transformation was then examined (Scheme 1). It was found that the 3-methoxy-*N*-arylpropanamides without substitution or substituted with



Scheme 1 Evaluation of the substrate scope of β -methoxy amides and amines. ^aReactions were carried out with **1a** (1.0 equiv.), **2a** (2.0 equiv.) and LiCl (2.0 equiv.) in ⁱPrOH (0.15 M) at 120 °C for 12 h in sealed tube. Yields of isolated products are given.

Table 1 Examination of the reaction conditions^a

Entry	Additive (equiv.)	Solvent	<i>T</i> (°C)	Time (h)	Yield ^b (%)
1	LiCl (2.0)	ⁱ PrOH	120	12	70
2	LiBr (2.0)	ⁱ PrOH	120	12	30
3	LiI (2.0)	ⁱ PrOH	120	12	43
4	LiOTf (2.0)	ⁱ PrOH	120	12	38
5	Li ₂ CO ₃ (2.0)	ⁱ PrOH	120	12	6
6	NaCl (2.0)	ⁱ PrOH	120	12	N. R.
7	LiCl (2.0)	DMF	120	12	46
8	LiCl (2.0)	Toluene	120	12	21
9	LiCl (1.0)	ⁱ PrOH	120	12	38
10 ^c	—	ⁱ PrOH	120	12	N. R.
11	LiCl (2.0)	ⁱ PrOH	80	12	23
12	LiCl (2.0)	ⁱ PrOH	120	6	49

^a Reaction conditions: **1a** (0.45 mmol), **2a** (0.90 mmol) and additive (2.0 equiv.) in solvent (3.0 mL) at 120 °C in sealed tube. ^b Yield of isolated product. ^c No LiCl was used.

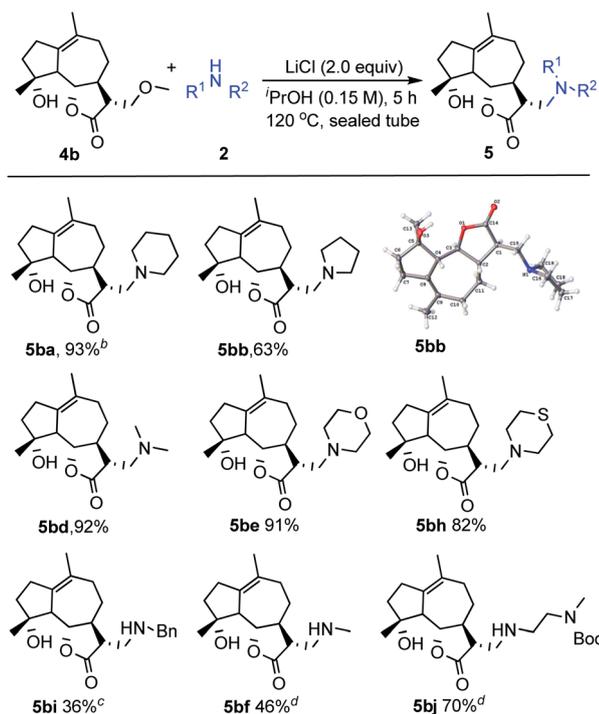
electron-donating (–OMe) or electron-withdrawing (–Cl, –Br) groups at the *para*-position of the *N*-aryl ring exhibit good tolerance under the present conditions, giving good yields of 70–77% (**3aa–3da**). Moreover, the diversity of amines was studied, including pyrrolidine, diethyl amine, dimethyl amine, morpholine and methyl amine solution, and the amination products were formed in moderate to good yields in all cases (**3ab–3db**, **3ac–3dc**, **3ad–3dd**, **3ae–3de**, **3af**). However, when using anilin (**2g**) as the starting material, no reaction took place. Replacement of the *N*-phenyl substituent with a benzyl group (**1e**) led to an increased yield of 83% (**3ed**). Remarkably, challenging 3-methoxypropanoyl piperazine derivatives also worked well under the optimized conditions, producing the desired products in good yields (**3fa–3fe**). Promoted by the successful amination of the amide, we then extended this transformation to β -methoxy γ -lactones. It was noteworthy to find that 3-methoxymethyl γ -lactones **4a** also worked for this reaction with the high yield of 85% **5ad**.



Encouraged by the above results, our research was then extended to perform this transformation between the natural product michelolide derivatives **4b** with β -methoxy γ -lactone subunit and various amines **2** (Scheme 2).¹⁵ Due to a high tolerance and compatibility of function groups, this strategy can be applied to **4b** possessing both hydroxy group and carbon-carbon double bond. Both cyclic amines (**2a**, **2b**, **2e**, **2h**) and linear amines (**2d**, **2i**, **2f**, **2j**) gave the corresponding products in moderate to excellent yields. Additionally, the structure of product **5bb** was unambiguously identified by X-ray crystallography.

Meanwhile, it is well demonstrated that amine substituted natural products is an efficient hydrophilic modification strategy used in medicinal chemistry.¹⁶ Therefore, this system was then extended to the amination of other natural product derivatives (**4c–4g**) containing β -methoxy γ -lactone subunit (Table 2).¹⁷ Argabin derivative **4c** underwent the amination to give the product (**5cd**) in 99% yield, which is equivalent to the commercially available antitumor agent Argabin-DMA.^{16a,18} Michelolide derivative (**4d** and **4e**) gave similarly good yields, in which the epoxy subunit does not affect the yield under the optimized conditions.¹⁹ The costunolide derivative **4f** was converted to the corresponding product **5fd** in 60% yield, while the reaction based on the parthenolide derivative **4g** gave the desired product **5gd** in 48% yield.

The investigation on the mechanism of reaction was conducted by detailed control experiments as follows (Scheme 3):



Scheme 2 Evaluation of the substrate scope of amines with michelolide derivatives. ^aReactions were carried out with **4b** (1.0 equiv.), **2** (2.0 equiv.) and LiCl (2.0 equiv.) in ⁱPrOH (0.15 M) at 120 °C for 5 h in sealed tube. Yields of isolated products are given. ^bReaction was conducted for 10 h. ^cReaction was conducted for 20 h. ^dReaction was conducted for 15 h.

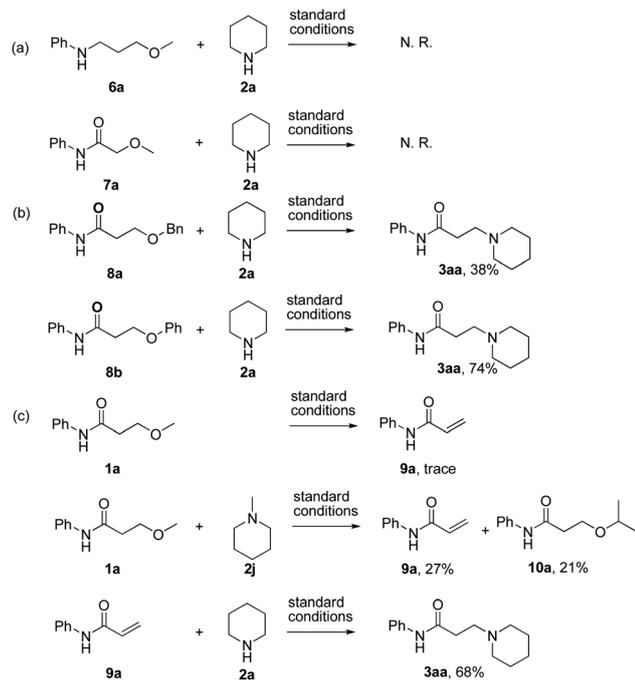
Table 2 Evaluation of the substrate scope of β -methoxy γ -lactones of natural products^a

Entry	Substrate	Product	Yield ^b (%)
1			99
2			70
3			61 ^c
4			60
5			48

^a Reactions were carried out with **4** (1.0 equiv.), **2d** (2.0 equiv.) and LiCl (2.0 equiv.) in ⁱPrOH (0.15 M) at 120 °C for 5 h in sealed tube. ^b Yields of isolated products are given. ^c Reaction was conducted for 18 h.

first, *N*-(3-methoxypropyl)aniline (**6a**) and 2-methoxy-*N*-phenylacetamide (**7a**) were prepared and subjected to the previously described standard condition respectively (Scheme 3a). In these reactions, no reaction took place, suggesting that the subunit of carbonyl β -ethers was essential for this reaction. Second, the desired product **3aa** was obtained under the standard reaction conditions when the substrates bearing either 3-benzyloxy or 3-phenoxy groups were used as the starting materials (Scheme 3b). Thus, these results supported a mechanism that there would undergo an intermediate in common. Moreover, the expected product **3aa** was not observed when the reaction of **1a** without LiCl was examined (Table 1, entry 7), verifying that LiCl also essential in this elimination process. Finally, the reaction of 3-methoxy-*N*-phenylacetamide (**1a**) under the standard reaction condition was examined in absence of amine, only trace of eliminate product (**9a**) was observed (Scheme 3c). Subsequently, when 2 equiv. of 1-methylpiperidine (**2j**) was added to the reaction above, both α,β -unsaturated amide **9a** and the 3-isopropyl substituted product **10a** were isolated in 27% and 21% yield respectively. Then the reaction of eliminate product **9a** and piperidine **2a** was examined, and the desired product **3aa** was afforded in 68% yield, which indicated that elimination and addition process would be involved in this procedure. These experiments provided evidence that the amine **2** not only



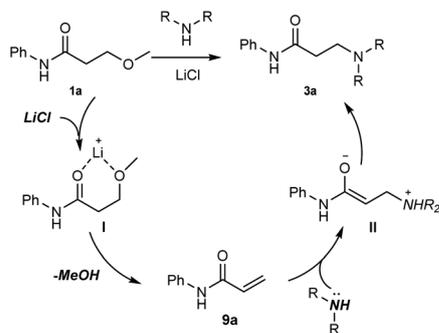


Scheme 3 Control experiments. ^aReactions were carried out with **6a**, **7a**, **8a**, **8b** and **1a** (1.0 equiv.), **2a** and **2j** (2.0 equiv.) and LiCl (2.0 equiv.) in ¹PrOH (0.15 M) at 120 °C for 12 h in sealed tube. Yields of isolated products are given.

reacted as the substrate, but also exhibited the basicity in favor of the formation of the α,β -unsaturated product.

On the basis of the aforementioned mechanistic studies, a tentative pathways was proposed in Scheme 4: (1) the chelation between Li cation and oxygen atoms gives the intermediate **I**, which would accelerate the following elimination reaction step; (2) the elimination of MeOH leads to the α,β -unsaturated amide **9a**; (3) the Michael addition of an amine to **9a** affords the corresponding enolate **II**; (4) the tautomerization of **II** generates the product **3a**.

In conclusion, we reported a novel strategy for the synthesis of the β -amino amides (γ -lactones). The reaction shows a broad substrate scope for β -methoxy amides (γ -lactones) and a wide range of natural product derivatives including michelolide, costunolide and parthenolide derivatives. Moreover, this amination reaction provides an alternative β -position hydrophilic



Scheme 4 Tentative pathways of the reaction.

modification route of γ -lactones in medicinal chemistry, which would proceed through two steps, which includes the initial formation of the α,β -unsaturated amide by the elimination of MeOH followed by the Michael addition with amines. Further investigation on detailed applications is currently underway.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Notes and references

- (a) G. Evano, N. Blanchard and M. Toumi, *Chem. Rev.*, 2008, **108**, 3054–3131; (b) J. F. Hartwig, *Nature*, 2008, **455**, 314–322; (c) P. Ruiz-Castillo and S. L. Buchwald, *Chem. Rev.*, 2016, **116**, 12564–12649.
- (a) E. R. Strieter, D. G. Blackmond and S. L. Buchwald, *J. Am. Chem. Soc.*, 2005, **127**, 4120–4121; (b) W. Deng, Y.-F. Wang, Y. Zou, L. Liu and Q.-X. Guo, *Tetrahedron Lett.*, 2004, **45**, 2311–2315.
- (a) M. M. Heravi, Z. Kheilkordi, V. Zadsirjan, M. Heydari and M. Malmir, *J. Organomet. Chem.*, 2018, **861**, 17–104; (b) S. Sá, M. B. Gawande, A. Velinho, J. P. Veiga, N. Bundaleski, J. Trigueiro, A. Tolstogousov, O. M. N. D. Teodoro, R. Zboril, R. S. Varma and P. S. Branco, *Green Chem.*, 2014, **16**, 3494–3500.
- C. P. Casey, G. A. Bikzhanova and I. A. Guzei, *J. Am. Chem. Soc.*, 2006, **128**, 2286–2293.
- T. Iwai, T. Ito, T. Mizuno and Y. Ishino, *Tetrahedron Lett.*, 2004, **45**, 1083–1086.
- (a) G. Xu, B. Chen, B. Guo, D. He and S. Yao, *Analyst*, 2011, **136**, 2385–2390; (b) J. R. Jones, P. B. Langham, S.-Y. Lu and R. Wood, *Green Chem.*, 2002, **4**, 464–466.
- (a) N. Uday Kumar, B. Sudhakar Reddy, V. Prabhakar Reddy and R. Bandichhor, *Tetrahedron Lett.*, 2012, **53**, 4354–4356; (b) R. S. Varma and R. Dahiya, *Tetrahedron*, 1998, **54**, 6293–6298.
- (a) D. S. Surry and S. L. Buchwald, *Chem. Sci.*, 2011, **2**, 27–50; (b) S. Bhunia, G. G. Pawar, S. V. Kumar, Y. Jiang and D. Ma, *Angew. Chem., Int. Ed.*, 2017, **56**, 16136–16179.
- A. Kaga, H. Hayashi, H. Hakamata, M. Oi, M. Uchiyama, R. Takita and S. Chiba, *Angew. Chem., Int. Ed.*, 2017, **56**, 11807–11811.
- (a) J. H. Pang, A. Kaga and S. Chiba, *Chem. Commun.*, 2018, **54**, 10324–10327; (b) Y. Huang, G. H. Chan and S. Chiba, *Angew. Chem., Int. Ed.*, 2017, **56**, 6544–6547; (c) P. C. Too, G. H. Chan, Y. L. Tnay, H. Hirao and S. Chiba, *Angew. Chem., Int. Ed.*, 2016, **55**, 3719–3723.



- 11 (a) M. Shigeno, K. Hayashi, K. Nozawa-Kumada and Y. Kondo, *Org. Lett.*, 2019, **21**, 5505–5508; (b) M. Shigeno, K. Hayashi, K. Nozawa-Kumada and Y. Kondo, *Chem.–Eur. J.*, 2019, **25**, 6077–6081.
- 12 (a) M. Shigeno, R. Nakamura, K. Hayashi, K. Nozawa-Kumada and Y. Kondo, *Org. Lett.*, 2019, **21**, 6695–6699; (b) S. Luo, D. G. Yu, R. Y. Zhu, X. Wang, L. Wang and Z. Shi, *Chem. Commun.*, 2013, **49**, 7794–7796.
- 13 K. Yang, Y. Li, Z. Y. Ma, L. Tang, Y. Yin, H. Zhang, Z. Y. Li and X. Q. Sun, *Eur. J. Org. Chem.*, 2019, **33**, 5812–5814.
- 14 Y. Guo, X.-M. Fan, M. Nie, H.-W. Liu, D.-H. Liao, X.-D. Pan and Y.-F. Ji, *Eur. J. Org. Chem.*, 2015, **21**, 4744–4755.
- 15 J. Li, S. Li, J. Guo, Q. Li, J. Long, C. Ma, Y. Ding, C. Yan, L. Li, Z. Wu, H. Zhu, K. K. Li, L. Wen, Q. Zhang, Q. Xue, C. Zhao, N. Liu, I. Ivanov, M. Luo, R. Xi, H. Long, P. G. Wang and Y. Chen, *J. Med. Chem.*, 2018, **61**, 4155–4164.
- 16 (a) J. D. Zhai, D. Li, J. Long, H. L. Zhang, J. P. Lin, C. J. Qiu, Q. Zhang and Y. Chen, *J. Org. Chem.*, 2012, **77**, 7103–7107; (b) J. R. Woods, H. Mo, A. A. Bieberich, T. Alavanja and D. A. Colby, *J. Med. Chem.*, 2011, **54**, 7934–7941.
- 17 Y. H. Ding, H. X. Fan, J. Long, Q. Zhang and Y. Chen, *Bioorg. Med. Chem. Lett.*, 2013, **23**, 6087–6092.
- 18 R. Csuk, A. Heinold, B. Siewert, S. Schwarz, A. Barthel, R. Kluge and D. Strohl, *Arch. Pharm.*, 2012, **345**, 215–222.
- 19 Q. Zhang, Y. Lu, Y. Ding, J. Zhai, Q. Ji, W. Ma, M. Yang, H. Fan, J. Long, Z. Tong, Y. Shi, Y. Jia, B. Han, W. Zhang, C. Qiu, X. Ma, Q. Li, Q. Shi, H. Zhang, D. Li, J. Zhang, J. Lin, L. Y. Li, Y. Gao and Y. Chen, *J. Med. Chem.*, 2012, **55**, 8757–8769.

