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Efficient synthesis of novel *N*-substituted 2-carboxy-4-quinolones *via* lithium bis(trimethylsilyl) amide (LiHMDS)-induced *in situ* cyclocondensation reaction†

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A different approach for the synthesis of *N*-substituted 2-carboxy-4-quinolones using direct reductive amination followed by LiHMDS-induced cyclocondensation has been developed. A range of analogues of the title compounds with broad substrate scope were obtained in moderate yields and good regioselectivity.

Introduction

4-Quinolone, a nitrogen containing heterocycle, constitutes the core structure in a wide line up of natural products, synthetic materials and pharmacologically active molecules.[1] Besides constituting a vital class of marketed antibiotics (*e.g.* ciprofloxacin, moxifloxacin, levofloxacin, gemifloxacin, norfloxacin, ofloxacin *etc.*)[2] quinolone derivatives also been used in various therapeutic areas as they exhibit antimitotic,[3] anticancer,[3b,4] antimalarial,[5] antimicrobial,[6] antidiabetic,[7] antiviral,[8] anti-HIV[9] and anti-inflammatory activities.[10] Moreover, this scaffold exhibits the potential to act as an inhibitor of various vital enzymes such as topoisomerase I,[11] topoisomerase II and IV gyrase,[12] farnesyltransferase,[13] tubulin,[14] P-glycoprotein[15] and casein kinase 2 (CK2).[16] Such interesting biological applications have fascinated medicinal chemists worldwide, thus this scaffold is the foremost synthetic target, and chemists are seeking to develop new synthetic protocols to access quinolone bearing pharmacophores (Fig. 1).

Most commonly adopted methods for the construction of 4-quinolones such as Conard–Limach, Gould–Jacobs, Niementowski, Grohe–Heitzer and Camp cyclizations require the condensation of aniline and carboxylate derivatives followed by cyclisation.[17] Some other methodologies were further developed with certain modifications including cycloacylation of aza-Michael adducts in the presence of Eaton's reagent,[18] diphenyl ether,[19] PPA,[20] dowtherm,[21] Pd-catalysed *N*-arylation of *Z*-enamines,[22] and alkoxide promoted rearrangement of isatinacetamides[23] (Scheme 1). Although these reactions were efficient in introducing ester functionality at the 2-position of 4-quinolones, most of them require harsh conditions such as the use of metal catalysts,[22] strong acids and high temperatures.[18–21] These extremely harsh conditions make them complicated in terms of synthesis and purification of end products and thus result in unsatisfactory yields, narrow substrate scope and poor regioselectivities. Moreover, *N*-aryl substitution requires a multi-step procedure which further added to its disadvantages.[24] So it is necessary to design simple and cost effective procedures for the synthesis of *N*-aryl-2-carboxy substituted 4-quinolone compounds.

Earlier Haesslein *et al.* synthesised 1,3-disubstituted-2-carboxy quinolones *via* reductive amination followed by condensation in the presence of a mild base. Although this

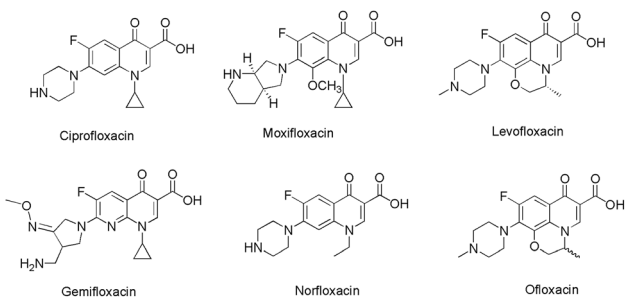

Fig. 1 Few examples of antibiotics bearing quinolone core.

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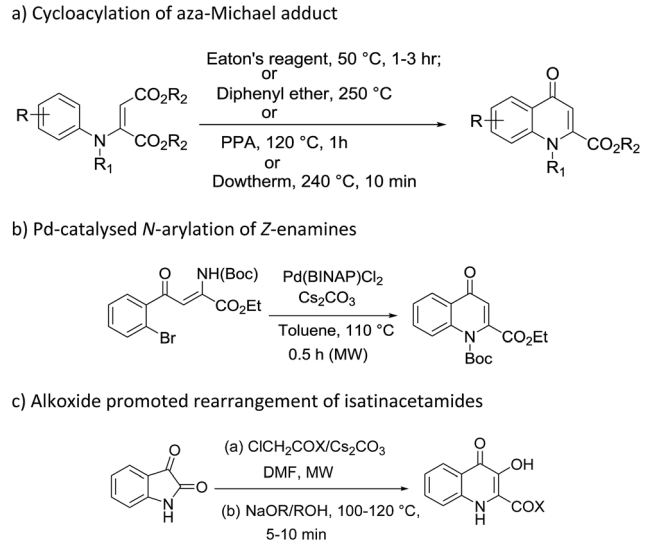
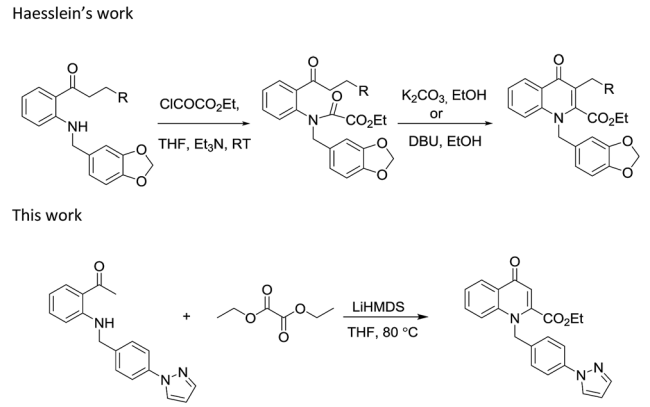


Scheme 1 Methods for the construction of 4-quinolones.



Scheme 2 Theme of this work.

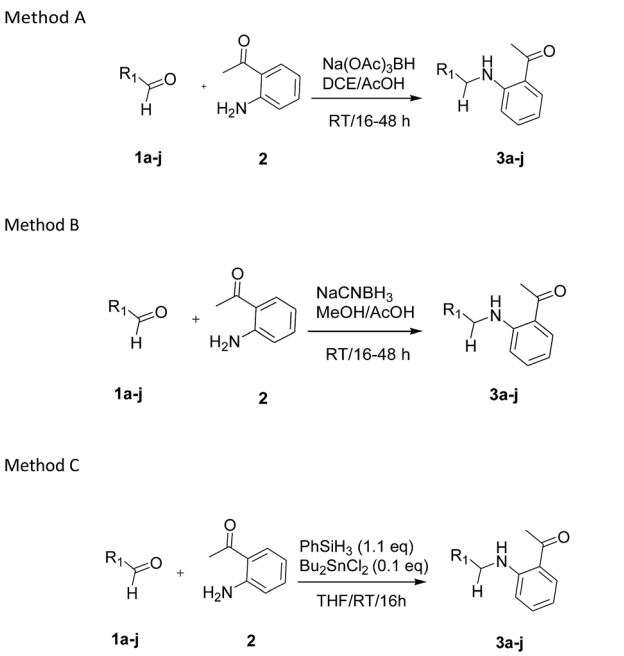
effective and practical methodology provides an easy route for the synthesis of *N*-aryl-2-carboxy substituted 4-quinolone compounds, its two-step procedure and incompatibility of reaction conditions to introduce different heterocyclic scaffolds at the 1-position add to its disadvantages.[25] So in order to overcome these drawbacks, we have devised a LiHMDS induced *in situ* cyclocondensation reaction to give *N*-aryl-2-carboxy substituted 4-quinolones from readily available aldehydes and 2′-amino acetophenone. To the best of our knowledge, this method is the first example of LiHMDS catalyzed direct C–N bond formation in one step *via in situ* cyclocondensation to furnish *N*-aryl-2-carboxy substituted 4-quinolone compounds (Scheme 2).

Results and discussion

Our preliminary studies focused on the reductive amination approach between commercially available aldehydes and 2′-aminoacetophenone in the presence of hydride reducing agents such as sodium triacetoxyborohydride ($NaBH(OAc)_3$),[26] sodium cyanoborohydride ($NaBH_3CN$),[27] phenylsilane ($PhSiH_3$)/dibutyltin dichloride (Bu_2SnCl_2)[28] (Scheme 3). Among all three methods, reductive amination with $PhSiH_3/Bu_2SnCl_2$ gave excellent yields of all the products in the range of 84–95% while the other two methods gave low to moderate yields (Table 1). The structures of compounds **3c** and **3e** were also confirmed by single crystal X-ray diffraction. ORTEP diagrams of these compounds with ellipsoids drawn at the 30% probability level along with their atomic numbering schemes are shown in Fig. 2.

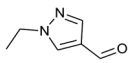
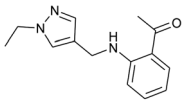
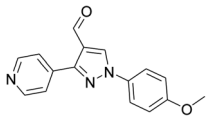
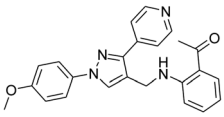
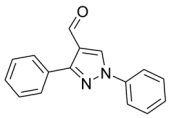
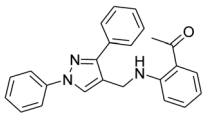
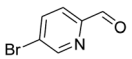
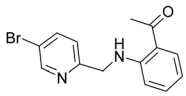
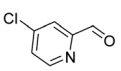
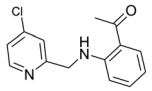
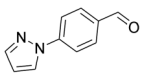
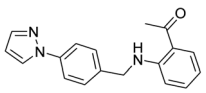
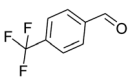
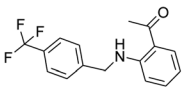
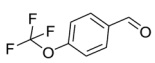
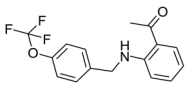
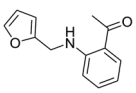
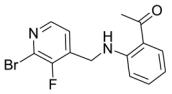
Further, we examined the reaction between **3g** and diethyl oxalate to investigate the experimental conditions which include the optimization of base, solvent and temperature. As shown in Table 2, four different bases (entries 1–15) were examined in the presence of 2.5 eq. of diethyl oxalate where LiHMDS (entry 15) showed the highest reaction rate as compared to only 10% yield of target product (entry 12) observed in the presence of NaH. Other bases such as NaOMe and Na^{t}OBt were ineffective in producing any product. We also tested solvents in combination with different bases out of which, LiHMDS/THF combination gave the best results. The effect of temperature was also investigated in the presence of different combinations of bases and solvent and it was concluded that when temperature was raised from 0 °C to reflux temperature using LiHMDS/THF, the reaction gave the product in 56% yield.

Using the optimized conditions, we next explored the scope of LiHMDS induced *in situ* cyclisation to yield *N*-substituted 4-quinolones. As shown in Table 3, the corresponding *N*-aryl-2-carboxy substituted 4-quinolones were obtained in moderate yield at reflux temperature with all the reductive amination products. The substrates bearing



Scheme 3 Methods used for reductive amination in this study.

Table 1 Comparative yield of reductive amination product using different methods

S. no.	Aldehyde	Product	Yield (method A)	Yield (method B)	Yield (method C)
1		 **3a**	45%	43%	91%
2		 **3b**	48%	45%	95%
3		 **3c**	54%	51%	95%
4		 **3d**	40%	43%	84%
5		 **3e**	50%	47%	92%
6		 **3f**	53%	60%	88%
7		 **3g**	40%	45%	91%
8		 **3h**	42%	37%	91%
9		 **3i**	34%	41%	85%
10		 **3j**	30%	40%	90%

electron-withdrawing or electron-donating substituents on aryl as well as heteroaryl rings showed no marked difference in the transformation. However, introduction of furan ring resulted in the reduced yield of target compound, **4i** which might be due to presence of lone pair of electron on oxygen which is making NH proton partially available for abstraction with base. Under the optimized conditions, substrate containing *p*-chloro pyridinyl, **3e** was not tolerated as it might be

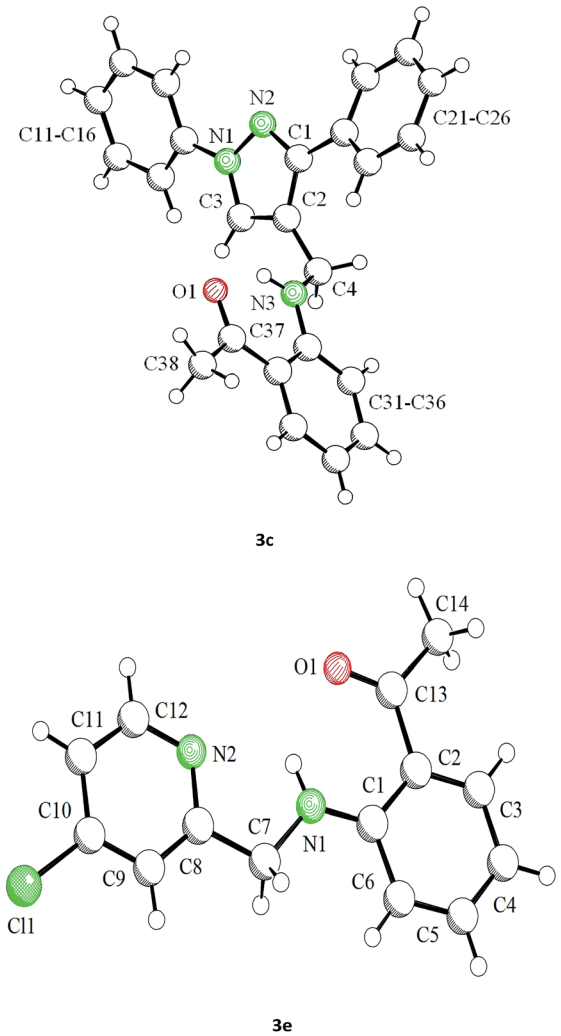
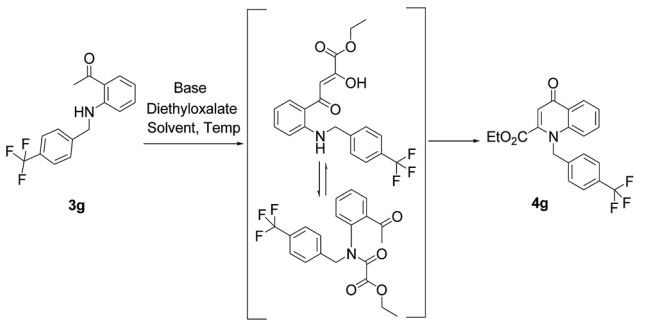


Fig. 2 Molecular structures of **3c** and **3e** in the solid state (SCHAKAL plot).

due to the presence of chlorine at para position which is enhancing the electron density on the pyridine ring thus attracting the NH proton towards the nitrogen of pyridine through hydrogen bonding, therefore making it unavailable for abstraction even by the strong base. While, various other functionalities such as ethyl, methoxy, fluoro, bromo, trifluoromethoxy, trifluoromethyl were well tolerated under the standard conditions. Further hydrolysis of the ester substituted *N*-aryl-4-quinolones in the presence of LiOH/H_2O/THF gave corresponding acid in moderate to good yield for **5b–d**, **5f–j** (Table 4). However, the low yield (22%) of **5a** might be due to the quaternization of pyrazole ring during work up.

A plausible mechanism for *in situ* cyclocondensation step has been elucidated in Scheme 4. Initially, anion generated from the secondary amine in the presence of base attacks the carbonyl group of diethyloxalate to generate the *N*-acetylated product. Then the abstraction of α-proton from methylketone resulted in the generation of anion which in turn attack the amidic carbonyl carbon of the *N*-acetylated intermediate. Then

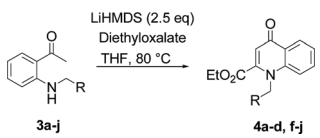
Table 2 Optimization of cyclocondensation reaction to form 4-quinolones[a]



Entry	Base	Solvent	Temp (°C)	Yield[b] (%)
1	NaOMe	MeOH	0	NR[c]
2	NaOMe	MeOH	RT	NR[c]
3	NaOMe	MeOH	80	NR[c]
4	NaOMe	THF	0	NR[c]
5	NaOMe	THF	RT	NR[c]
6	NaOMe	THF	80	NR[c]
7	Na^{t}OBut	THF	0	NR[c]
8	Na^{t}OBut	THF	RT	NR[c]
9	Na^{t}OBut	THF	80	NR[c]
10	NaH	THF	0	NR[c]
11	NaH	THF	RT	NR[c]
12	NaH	THF	80	10
13	LiHMDS	THF	0	NR[c]
14	LiHMDS	THF	RT	NR[c]
15	LiHMDS	THF	80	56

[a] Reaction conditions: **3g** (2.04 mmol), diethyloxalate (5.1 mmol), base (2.5 eq.), solvent (20 mL), 16 h. [b] The yields of isolated products. [c] No reaction.

Table 3 *N*-aryl-2-carboxylate 4-quinolone scope



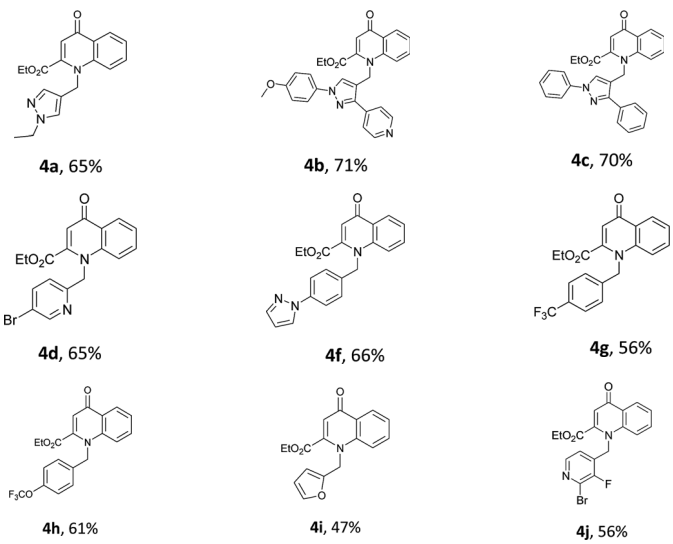
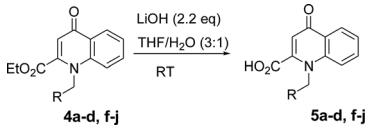
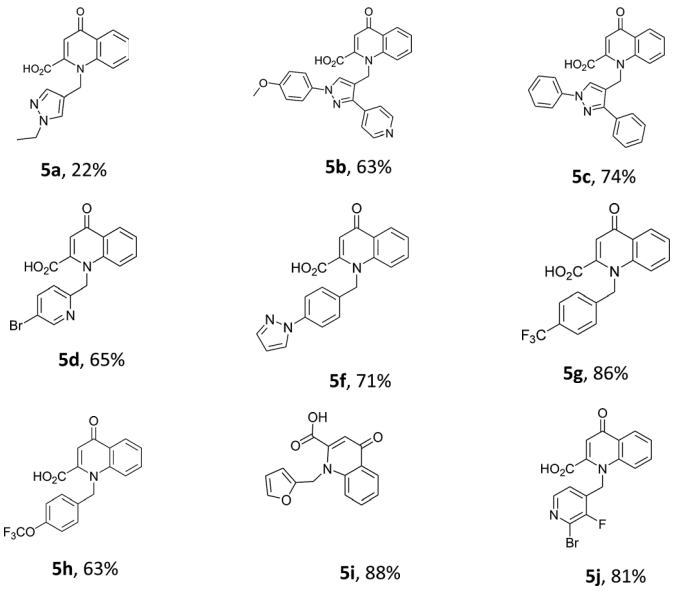
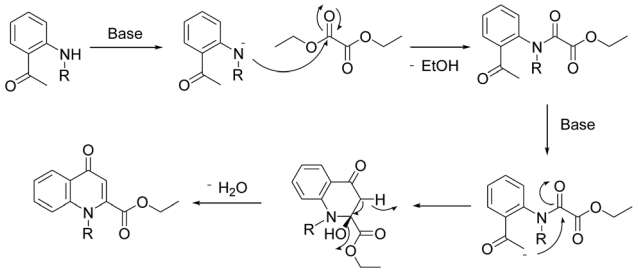


Table 4 Basic hydrolysis of *N*-aryl-2-carboxylate 4-quinolone







Scheme 4 Possible mechanism for *in situ* cyclocondensation.

under the basic conditions, cyclocondensation reaction takes place to form quinolone ring with the elimination of water molecule.

Conclusions

In summary, we successfully developed a LiHMDS catalyzed protocol for C–N bond formation in one step *via in situ* cyclocondensation to give the title compounds. The secondary amines utilized for the formation of quinolones tolerated a wide variety of functional groups. The biological studies of these quinolones are under process and further applications of this protocol for broader substrate scope to explore the synthesis of other biologically active molecules is underway in our laboratory. We are also working on alternative methods to improve the yield as well as avoiding such harsh conditions.

Conflict of interest

The authors declare no competing financial interest.

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Notes and references

1 J. Huang, Y. Chen, A. O. King, M. Dilmeghani, R. D. Larsen and M. M. Faul, *Org. Lett.*, 2008, **10**, 2609–2612.
2 S. Gupta, P. Ghosh, S. Dwivedi and S. Das, *RSC Adv.*, 2014, **4**, 6254–6260.
3 (*a*) S. C. Kuo, H. Z. Lee, J. P. Juang, Y. T. Lin, T. S. Wu, J. J. Chang, D. Lednicer, K. D. Paull and C. M. Lin, *J. Med. Chem.*, 1993, **36**, 1146–1156; (*b*) M. Hadjeri, E. L. Peiller, C. Beney, N. Deka, M. A. Lawson, C. Dumontet and A. Boumendjel, *J. Med. Chem.*, 2004, **47**, 4964–4970.
4 S. Nakamura, M. Kozuka, K. F. Bastow, H. Tokuda, H. Nishino, M. Suzuki, J. Tatsuzaki, S. L. M. Natschke, S. C. Kuo and K. H. Lee, *Bioorg. Med. Chem.*, 2005, **13**, 4396–4401.
5 (*a*) N. Mahmoudi, L. Ciceron, J. F. Franetich, K. Farhati, O. Silvie, W. Eling, R. Sauerwein, M. Danis, D. Mazier and F. Derouin, *Antimicrob. Agents Chemother.*, 2003, **47**, 2636–2639; (*b*) R. M. Cross, A. Monastyrskyi, T. S. Mutka, J. N. Burrows, D. E. Kyle and R. Manetsch, *J. Med. Chem.*, 2010, **53**, 7076–7094.
6 (*a*) D. T. Chung, C. Y. Tsai, S. J. Chen, L. W. Chang, C. H. R. King, C. H. Hsu, K. M. Chiu, H. C. Tan, Y. T. Chang and M. C. Hsu, *Antimicrob. Agents Chemother.*, 2010, **54**, 411–417; (*b*) E. Meyer, F. Schwab, P. Gastmeier, H. Ruden and A. Heininger, *J. Antimicrob. Chemother.*, 2007, **60**, 619–624.
7 D. Edmont, R. Rocher, C. Plisson and J. Chenault, *Bioorg. Med. Chem. Lett.*, 2000, **10**, 1831–1834.
8 (*a*) B. A. Lucero, C. R. B. Gomes, I. C. P. P. Frugulhetti, L. V. Faro, L. Alvarenga, M. C. B. V. de-Souza, T. M. L. de-Souza and V. F. Ferreiraa, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 1010–1013; (*b*) M. Llinas-Brunet, M. D. Bailey, E. Ghiro, V. Gorys, T. Halmos, M. Poirier, J. Rancourt and N. Goudreau, *J. Med. Chem.*, 2004, **47**, 6584–6594.
9 (*a*) F. Santos, P. Abreu, H. Castro, I. Paixão, C. Cirne-Santos, V. Giongo, J. Barbosa, B. Simonetti, V. Garrido, D. Bou-Habib, D. Silva, P. Batalha, J. Temerozo, T. Souza, C. Nogueira, A. Cunha, C. Rodrigues, V. Ferreira and M. de Souza, *Bioorg. Med. Chem.*, 2009, **17**, 5476–5481; (*b*) M. Sato, T. Motomura, H. Aramaki, T. Matsuda, M. Yamashita, Y. Ito, H. Kawakami, Y. Matsuzaki, W. Watanabe, K. Yamataka, S. Ikeda, E. Kodama,

M. Matsuoka and H. Shinkai, *J. Med. Chem.*, 2006, **49**, 1506–1508.

10 J. Regan, T. W. Lee, R. M. Zindell, Y. Bekkali, J. Bentzien, T. Gilmore, A. Hammach, T. M. Kirrane, A. J. Kukulka, D. Kuzmich, R. M. Nelson, J. R. Proudfoot, M. Ralph, J. Pelletier, D. Souza, L. Zuvela-Jelaska, G. Nabozny and D. S. Thomson, *J. Med. Chem.*, 2006, **49**, 7887–7896.

11 Q. D. You, Z. Y. Li, C. H. Huang, Q. Yang, X. J. Wang, Q. L. Guo, X. G. Chen, X. G. He, T. K. Li and J. W. Chern, *J. Med. Chem.*, 2009, **52**, 5649–5661.

12 K. Drlica and X. Zhao, *Microbiol. Mol. Biol. Rev.*, 1997, **3**, 377–392.

13 Q. Li, A. Claiborne, T. Li, L. Hasvold, V. S. Stoll, S. Muchmore, C. G. Jakob, W. Gu, J. Cohen, C. Hutchins and D. Frost, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 5367–5370.

14 Y. H. Chang, M. H. Hsu, S. H. Wang, L. J. Huang, K. Qian, S. L. Morris-Natschke, E. Hamel, S. C. Kuo and K. H. Lee, *J. Med. Chem.*, 2009, **52**, 4883–4891.

15 B. Medeiros, H. Landau, M. Morrow, R. Lockerbie, T. Pitts and S. Eckhardt, *Leukemia*, 2007, **21**, 739–746.

16 A. Golub, O. Yakovenko, V. Bdzhola, V. Sapelkin, P. Zien and S. Yarmoluk, *J. Med. Chem.*, 2006, **49**, 6443–6450.

17 (*a*) R. M. Cross and R. Manetsch, *J. Org. Chem.*, 2010, **75**, 8654–8657; (*b*) C. P. Jones, K. W. Anderson and S. L. Buchwald, *J. Org. Chem.*, 2007, **72**, 7968–7973.

18 D. Zewge, C. Y. Chen, C. Deer, P. G. Dormer and D. L. Hughes, *J. Org. Chem.*, 2007, **72**, 4276–4279.

19 A. K. Pandey, R. Sharma, R. Shivahare, A. Arora, N. Rastogi, S. Gupta and P. M. S. Chauhan, *J. Org. Chem.*, 2013, **78**, 1534–1546.

20 F. Salvaggio, J. T. Hodgkinson, L. Carro, S. M. Geddis, W. R. J. D. Galloway, M. Welch and D. R. Spring, *Eur. J. Org. Chem.*, 2016, 434–437.

21 I. Borza, S. Kolok, K. Galgóczy, A. Gere, C. Horváth, S. Farkas, I. Greiner and G. Domány, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 406–409.

22 K. Y. Park, J. Lee, S. J. Park, J. N. Heo and H. J. Lim, *Adv. Synth. Catal.*, 2015, **357**, 3917–3926.

23 M. S. Shmidt, I. A. Perillo, A. Camelli, M. A. Fernández and M. M. Blanco, *Tetrahedron Lett.*, 2016, **57**, 1022–1026.

24 X. Chen, J. Klöckner, J. Holze, C. Zimmermann, W. K. Seemann, R. Schrage, A. Bock, K. Mohr, C. Tränkle, U. Holzgrabe and M. Decker, *J. Med. Chem.*, 2014, **58**, 560–576.

25 J. L. Haesslein, I. Baholet, M. Fortin, A. Iltis, J. Khider, A. M. Periers, C. Pierre and J. P. Vevert, *Bioorg. Med. Chem. Lett.*, 2000, **10**, 1487–1490.

26 A. F. Abdel-Magid, K. G. Carson, B. D. Harris, C. A. Maryanoff and R. D. Shah, *J. Org. Chem.*, 1996, **61**, 3849–3862.

27 R. F. Borch, M. D. Bernstein and H. D. Durst, *J. Am. Chem. Soc.*, 1971, **93**, 2897–2904.

28 R. Apodaca and W. Xiao, *Org. Lett.*, 2001, **3**, 1745–1748.