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Pseudo three-component approach to coumarin-annulated azepines: synthesis of coumarin[3,4-*b*] azepines†

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A series of coumarin-annulated azepines were synthesized *via* acid-catalyzed condensation of 3-amino-4-hydroxycoumarin with two equivalents of substituted acetophenones in toluene with moderate to good yields. A plausible mechanism for this pseudo three-component reaction was proposed.

Introduction

Azepines, unsaturated seven-membered heterocycles with a nitrogen replacing a carbon at one position, are one of the most well-known molecules that exhibit a wide range of therapeutic activities.[1] Their activities are generally imparted when the azepines are fused with other molecular scaffolds such as benzene. Apart from this, the annulated 1,4- and 1,5-diazepine derivatives are also found to be the privileged heterocycles with various potent biological properties. These molecular skeletons are frequently seen in many pharmaceuticals[2] currently available on the markets. For instance, benzene-annulated azepines (benzazepines) such as benazepril are ACE inhibitors used primarily in the treatment of hypertension;[3] fenoldopam is used as an antihypertensive agent;[4] lorcaserinis is a weight-loss drug;[5] and varenicline is a prescription medication used to treat nicotine addiction.[6] Fig. 1 shows structures of some biologically important annulated azepine/diazine derivatives which are the active components of the existing drugs. On the other hand, coumarins represent another important class of heterocycles that have wide applications in the areas of medicinal chemistry[7] and functional materials.[8] Similar to that of azepines, when coumarins are fused with other molecular scaffolds, the resulting compounds may also exhibit unique or even unprecedented properties. For example, phenanthridine-annulated coumarins have been found to possess negative thermochromic properties;[9] pyran-annulated coumarins have been reported to exhibit molecular switching properties;[10] pyrrole-annulated coumarins have been demonstrated to possess redox-switching properties.[11]

While various efforts have been focused on the preparation of benzazepines and coumarin-fused heterocycles, the synthesis of coumarin-annulated azepines have not been well-explored in the literature.[12] Scheme 1 outlines the previous preparation of benzazepines **1** and **2** *via* acid-catalyzed condensation of acetophenone with 2-fluoroaniline in toluene under reflux conditions and with 2-aminophenol under microwave irradiation conditions, respectively. The fluorine atom of 2-fluoroaniline serves as a leaving group in the synthesis of 2,4-diphenyl-3*H*-1-benzazepine **1**,[13] whereas the hydroxyl group of 2-aminophenol functions as a nucleophile in the pseudo three-component synthesis of diphenyloxazepine **2**.[14] Recently graphene nanosheets have also been used to prepare dibenzo[1,4]diazepine **3** in water.[15] Nevertheless, none of the reported methods has focused on the preparation of coumarin[3,4-*b*]azepines. In our continuing efforts to develop new methodology for the preparation of coumarin-fused heterocycles[16] and to subsequently investigate their potential biological or functional properties, we made an attempt to synthesize the coumarin-fused azepine

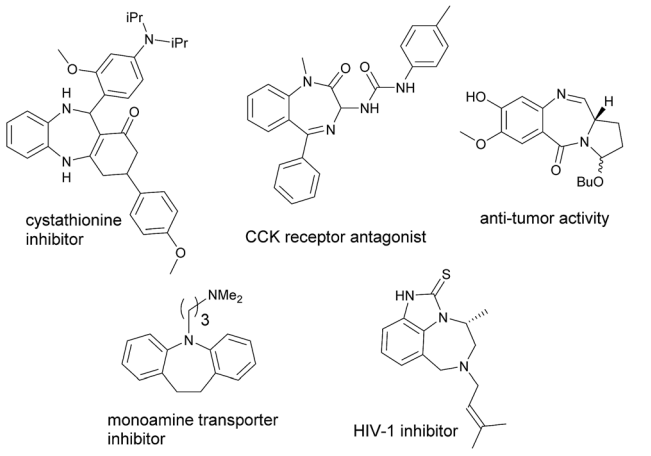

Fig. 1 Structures of some biologically active azepine/diazine derivatives.

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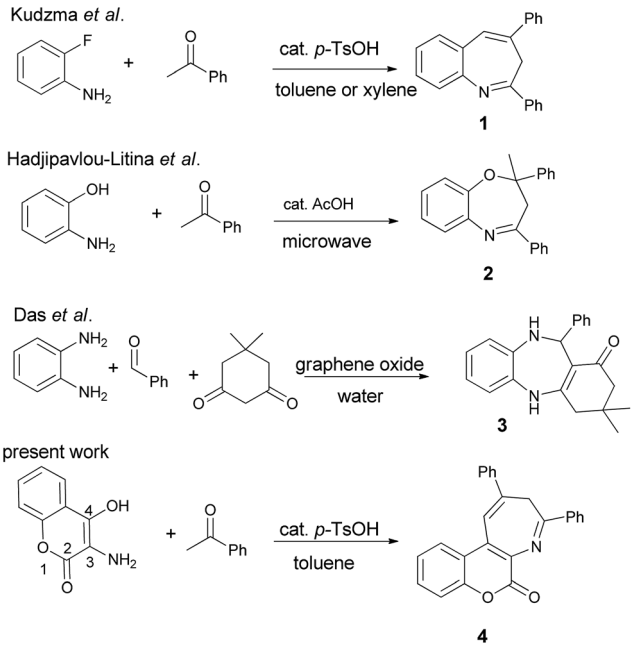
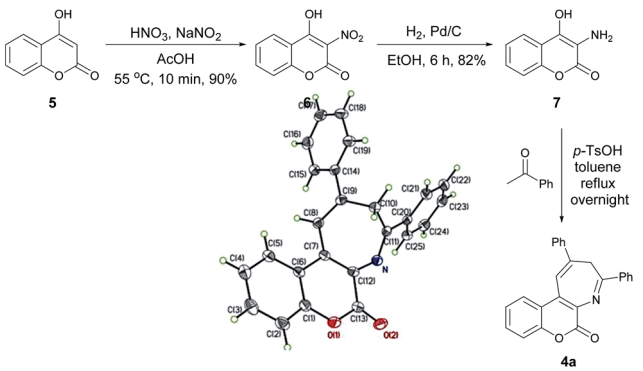


Scheme 1 Synthetic methods for benzazepines and their derivatives.

derivatives in a multi-component manner. Herein we report the acid-catalyzed pseudo three-component synthesis of coumarin [3,4-*b*]azepines by sequential condensations of 3-amino-4-hydroxycoumarin with two equiv. of substituted acetophenones. For present methodology, the substrate scope is investigated and a possible reaction mechanism is deduced.

Results and discussion

The proposed synthesis of coumarin[3,4-*b*]azepine **4a** is shown in Scheme 2. It started with nitration of commercially available 4-hydroxycoumarin (**5**) with sodium nitrite and nitric acid in acetic acid to give 3-hydroxy-4-nitrocoumarin[17] (**6**) and followed by the Pd/C reduction under hydrogen atmosphere to yield the 3-amino-4-hydroxycoumarin (**7**).[18] Final refluxing of aminocoumarin **7** with two equivalent of acetophenone in the presence of one equivalent of *p*-TsOH in toluene for 12 h afforded

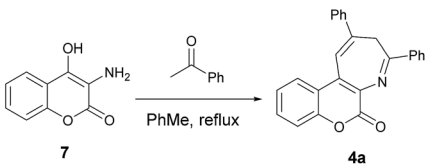


Scheme 2 Preparation of compound **4a** and its ORTEP crystal structure.[19]

the coumarin[3,4-*b*]azepine **4a**. To our delight, the pseudo three-component approach proved to be successful. The molecular structure of **4a** was elucidated by spectroscopic data as well as by the ORTEP crystal analysis.[19] In the ^{1}H NMR spectra of **4a**, two characteristic broad singlet absorption peaks at the chemical shift of 2.19 and 4.99 ppm were observed, which were assigned to the methylene protons flanked by the two phenyl rings in the azepine moiety. A similar observation has been previously reported in the literature for 2,4-diaryl-3*H*-1-benzazepines.[20] Since the yield of the target compound **4a** was found to be mere 32%, the optimizations of reaction conditions were then under taken. Table 1 lists the results of optimization of reaction parameters for **4a**. The combination of *p*-TsOH and molecular sieves (4 Å) was found to be the best reaction conditions. As the loading of *p*-TsOH decreased from 1.0 to 0.5 equiv. (entries 1 and 2), the yield of **4a** increased from 32 to 57%. The highest yield (80%) was recorded when 0.2 equiv. of *p*-TsOH was employed (entry 3). Among the Lewis acids screened, only $Yb(OTf)_3$ showed considerable activity (entry 6, 64%) and the rest of them were found be below average (entries 4 and 8). These results prompted us to employ the conditions of 0.2 equiv. of *p*-TsOH (entry 3) in the subsequent reactions reported in the present study.

After successfully realizing the preparation of coumarin-annulated azepine **4a**, we then turned our attention to investigate the scope and limitation of this pseudo three-component reaction. A series of acetophenones bearing different substituents at either *ortho* or *para* position of the aromatic ring were examined. Fig. 2 lists the structures and yields of the prepared coumarin[3,4-*b*]azepines **4a–o**. The results suggested that substrates with either an electron-donating group such as OMe and phenyl or an electron-withdrawing group such as Br, NO_2, and CN substituted at the *para* position of acetophenone all gave the corresponding products **4b–f** with yields between 60–70%, indicating that the inductive effect of the *para*-substituents has little influence on the reaction yield. Nevertheless, both *para*-amino substituted acetophenones such as 1-

Table 1 Optimization of reaction parameters for **4a**[a]



Entry	Acid	Equiv.	Time (h)	Yield[b] (%)
1	*p*-TsOH	1.0	12	32
2	*p*-TsOH	0.5	12	57
3	*p*-TsOH	0.2	6	80
4	$FeCl_3$	0.2	12	nr[c]
5	$AlCl_3$	0.2	12	16
6	$Yb(OTf)_3$	0.2	10	64
7	$SnCl_4$	0.2	12	nr[c]
8	$ZnCl_2$	0.2	12	42

[a] In entries 3 to 8, 4 Å MS was added. [b] Isolated yield. [c] No reaction.

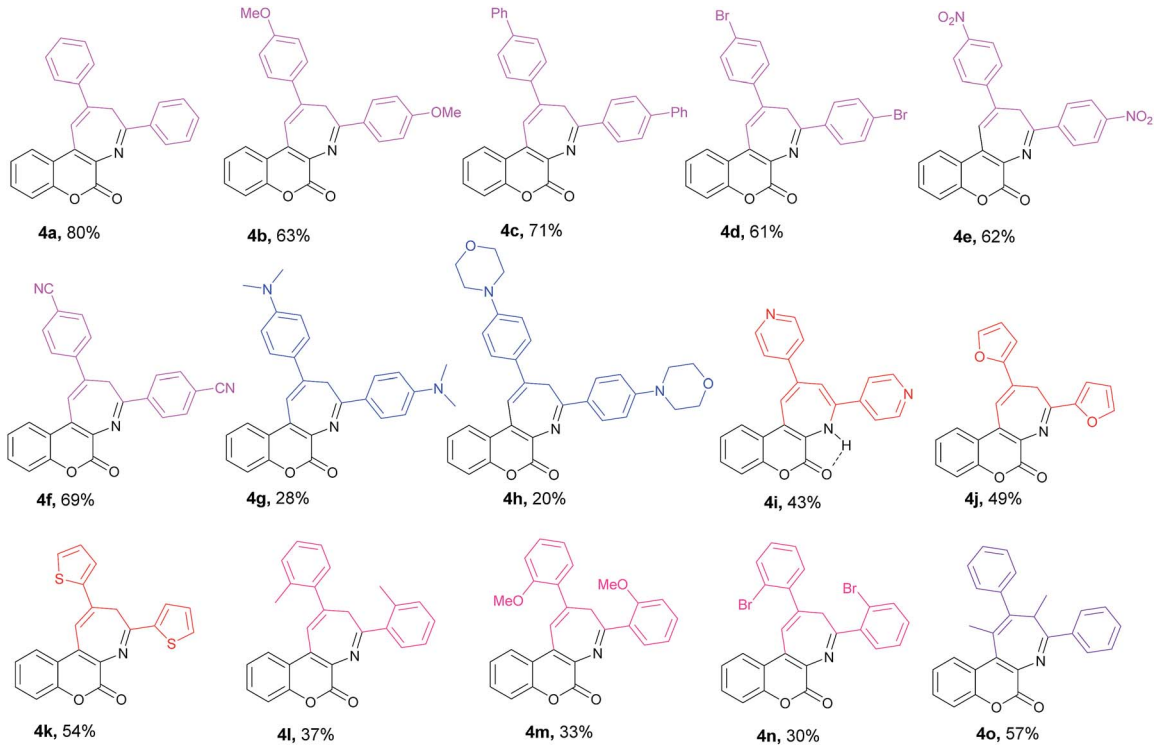


Fig. 2 Structures of the prepared coumarin[3,4-*b*]azepines **4a–o**.

(4-(dimethylamino)phenyl)ethan-1-one and 1-(4-morpholinophenyl)ethan-1-one gave the respective products **4g** and **6h** with low yields. This observation may be attributed to the strong resonance effect of *p*-amino group rendering 3-acetophenone less susceptible to nucleophilic attack by aminocoumarin. For compounds containing hetero aryl groups like 4-acetylpyridine, 2-acetylfuran, and 2-acetylthiophene, they can all serve as substrates for this reaction to afford the corresponding azepines **4i–k** in moderate yields. The substrates bearing methyl, methoxy, or bromo at the *ortho* position at the phenyl ring of acetophenone generally suffered for low yields, presumably due to the steric hindrance caused by the *ortho* substituent. Consequently, the even bulkier substrates such as *o*-nitroacetophenone and 1-(naphthalen-2-yl)ethan-1-one failed to give any of the expected azepines. When propiophenone was employed as the aromatic ketone substrate, the azepine **4o** was obtained in 57% yield. This observation suggests that the substrate scope of this reaction is not limited to methyl ketones only. Nevertheless, when the ketone substrate was further extended from propiophenone to isopropyl phenyl ketone, no expected product was observed. Fig. 3 shows the X-ray crystal structures of **4j** and **4n**.[19] It is noteworthy that the prepared azepines all exist in the imine forms on the azepine ring, except for compound **4i**. In proton NMR spectra of **4i**, the observation of an intramolecular hydrogen bonding absorption peak at 12.14 ppm along with two small doublets ($J = 1.6$ Hz) olefinic hydrogen absorptions at 8.24 and 8.22 ppm clearly indicates that **4i** exists in the enamine form. The reason why only **4i** exists in the enamine form in solution is currently under investigation.

In order to gain more insights into the mechanism of this pseudo three-component reaction, we performed an experiment by introducing just one equiv. of acetophenone to react with aminocoumarin **7**. In this control reaction, compound **4a** was obtained as the major product, along with a trace amount of a minor product. This minor product was isolated and further characterized by spectroscopic analysis to be the imine **8** (Scheme 3). In the proton NMR spectrum, a singlet peak at 2.75 ppm was clearly observed and assigned to be the methyl absorption of **8**. The detection of formation of the intermediate imine **8** in this pseudo three-component reaction provides solid evidence that the mechanism involves the first condensation of aminocoumarin with acetophenone to give the imine **8**.

Scheme 4 depicts the proposed mechanism for this pseudo three-component synthesis of coumarin-annulated azepines in details. It presumably starts with dehydration of 3-amino-4-hydroxycoumarin (**7**) with acetophenone to give the imine **8** which is in equilibrium with the enamine **9**. The enamine **9**

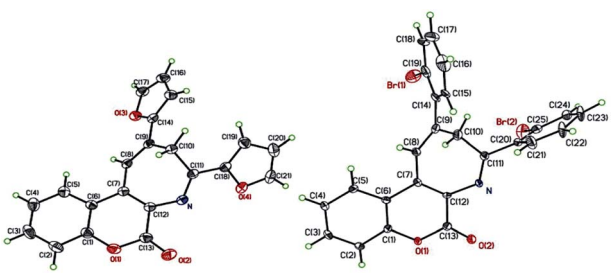
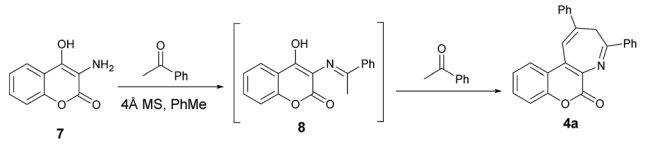
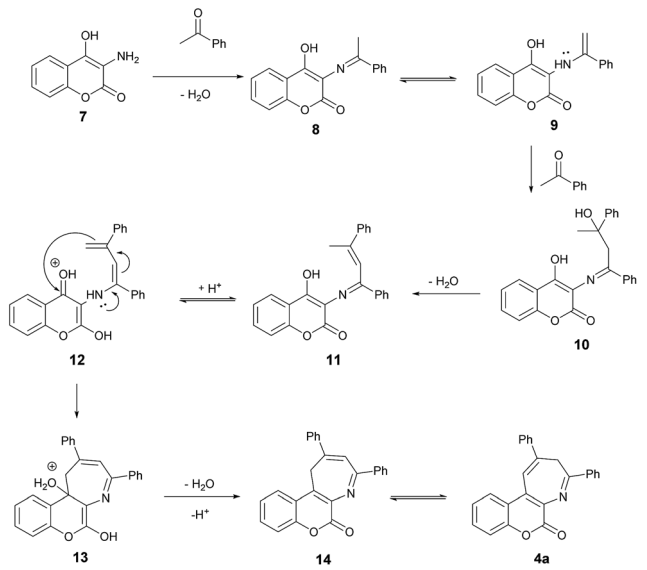


Fig. 3 ORTEP crystal structures of **4j** (left) and **4n** (right).



Scheme 3 Formation of the intermediate **8** and its conversion to the product **4a**.



Scheme 4 Proposed mechanism for the formation of **4a**.

further reacts with the second molecule of acetophenone to form the tertiary alcohol **10**. The subsequent dehydration to remove the second water molecule affords the imine **11** which again is in equilibrium with the enamine **12**. The intramolecular addition of enamine to the 4-position of the coumarin ring of **12** yields the cyclized **13**. The elimination of the third water molecule along with deprotonation of **13** furnishes the **16**. Final acid-catalyzed isomerization of **14** affords the product azepine **4a**. This methodology provides an easy and quick access to the coumarin[3,4-*b*]azepines.

Conclusions

In summary, we have demonstrated that coumarin-annulated azepines can be efficiently constructed *via* *p*-TsOH-catalyzed pseudo three-component coupling of 3-amino-4-hydroxycoumarin with two equiv. of acetophenone. The scope of the reaction is illustrated by preparation of 15 coumarin[3,4-*b*]azepine analogs with moderate to good yields. The biological evaluation of the prepared coumarin-annulated azepines is currently underway.

Experimental

Instrumentation

Melting points were determined on a Mel-Temp melting point apparatus in open capillaries and are uncorrected. Infrared (IR) spectra were recorded using 1725XFT-IR spectrophotometer. High resolution mass spectra (HRMS) were obtained on a Thermo Fisher Scientific Finnigan MAT95XL spectrometer using magnetic sector analyzer[1] H NMR (400 MHz) and ^{13}C NMR (100, or 150 MHz) spectra were recorded on a Varian VXR300 or Bruker 400/600 spectrometer. Chemical shifts were reported in parts per million on the δscale relative to an internal standard (tetramethylsilane, or appropriate solvent peaks) with coupling constants given in hertz. ^{1}H NMR multiplicity data are denoted by s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). Analytical thin-layer chromatography (TLC) was carried out on Merck silica gel 60G-254 plates (25 mm) and developed with the solvents mentioned. Visualization was accomplished by using portable UV light, ninhydrin spray and iodine chamber. Flash chromatography was performed in columns of various diameters with Merck silica gel (230–400 mesh ASTM 9385 kieselgel 60H) by elution with the solvent systems. Solvents, unless otherwise specified, were reagent grade and distilled once prior to use. All new compounds exhibited satisfactory spectroscopic and analytical data.

Synthesis of 4-hydroxy-3-nitrocoumarin (6)

To a stirred suspension of 4-hydroxycoumarin (**5**, 4.0 g, 24.67 mmol, 1.0 equiv.) in AcOH (50 mL) was added sodium nitrite (17 mg, 0.25 mmol, 0.01 equiv.) in one portion and HNO_3 (3.5 mL) drop wise. The resulting mixture was stirred at room temperature for 5 min and followed by heating at 70 °C for 30 min in an oil bath. As the brown solution attained to room temperature, the pure compound crystallized out from the solution. These crystals were filtered, washed with hexanes (6 × 50 mL), and dried *in vacuo* to afford 3-nitro-4-hydroxycoumarin (**6**) as off-yellow shiny crystals. 4.6 g; yield 90%; $R_f = 0.15$ (10% MeOH/DCM); mp 176–177 °C (lit.[16] 177 °C); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.41 (bs, 1H), 7.88 (dd, $J = 7.8$, 1.5 Hz, 1H), 7.52 (td, $J = 8.1$, 1.8 Hz, 1H), 7.24–7.16 (m, 2H).

Synthesis of 3-amino-4-hydroxycoumarin (7)

To a suspension of 4-hydroxy-3-nitrocoumarin (**6**, 4.0 g, 22.58 mmol) in ethanol (200 mL) was added 10% Pd/C (50 mg) at room temperature. The resulting solution was stirred under H_2 atmosphere for 6 h at that temperature. After the completion of the reaction, the suspension was filtered through the celite pad, washed extensively with MeOH (3 × 30 mL), acetone (3 × 30 mL), and concentrated to afford an off-white solid. 2.82 g; yield 82%; $R_f = 0.16$ (10% MeOH/DCM); mp 216 °C (lit.[17] 222–224 °C); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.19 (bs, 2H), 7.84 (dd, $J = 8.0$, 1.6 Hz, 1H), 7.47 (td, $J = 7.6$, 1.6 Hz, 1H), 7.25–7.21 (m, 2H).

General procedure for the preparation of coumarin-fused azepines (4)

To a 100 mL round bottom flask was charged with 3-amino-4-hydroxycoumarin (1.0 equiv.), acetophenone derivative (2.1 equiv.), *p*-TsOH (0.2 equiv.), and 4 Å molecular sieves in anhydrous toluene (25 mL). The resulting mixture was refluxed for about 8–10 h. The dark solution was allowed to attain to the room temperature and the solvent was evaporated *in vacuo*. The

residue was redissolved in DCM (50 mL), filtered, and washed with copious amounts of DCM. The resulting solvent was concentrated *in vacuo* and the product was subjected to flash column chromatography to afford the coumarin-fused azepine derivative.

4a. Off-yellow solid; yield 80%; R_f = 0.42 (30% EtOAc/hexanes); mp 220–221 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.89 (dd, J = 8.0, 1.6 Hz, 2H), 7.83 (dd, J = 7.8, 1.2 Hz, 1H), 7.62–7.60 (m, 2H), 7.50–7.40 (m, 5H), 7.38 (s, 1H), 7.39–7.35 (m, 1H), 7.33–7.29 (m, 3H), 5.01 (bs, 1H), 2.18 (bs, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 159.9, 152.0, 150.2, 138.4, 137.7, 136.0, 132.4, 131.1, 131.0, 129.8, 129.4, 129.1, 128.7, 128.5, 127.9, 124.4, 124.2, 119.7, 119.2, 117.2, 36.9; IR ν_{max} (ATR) 3427, 3062, 1721, 1602, 1446, 1280, 1186, 1067, 765, 690 cm^{-1}; HRMS (EI) calcd for $C_{25}H_{17}NO_2$ [M$^+$] 363.1259 found 363.1252.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

1 N. A. Nedolya and B. A. Trofimov, *Chem. Heterocycl. Compd.*, 2013, **49**, 152.
2 I. Khan, Anupama and B. Singh, *Sci. Rev. Chem. Commun.*, 2015, **5**, 13.
3 J. A. Balfour and K. L. Goa, *Drugs*, 1991, **42**, 511.
4 J. Weinstock, D. L. Ladd, J. W. Wilson, C. K. Brush, N. C. F. Yim, G. Gallagher Jr, M. E. McCarthy, J. Silvestri and H. M. Sarau, *J. Med. Chem.*, 1986, **29**, 2315.
5 B. M. Smith, J. M. Smith, J. H. Tsai, J. A. Schultz, C. A. Gilson, S. A. Estrada, R. R. Chen, D. M. Park, E. B. Prieto, C. S. Gallardo, D. Sengupta, P. I. Dosa, J. A. Covel, A. Ren, R. R. Webb, N. R. A. Beeley, M. Martin, M. Morgan, S. Espitia, H. R. Saldana, C. Bjenning, K. T. Whelan, A. J. Grottick, F. Menzaghi and W. J. Thomsen, *J. Med. Chem.*, 2008, **51**, 305.
6 J. W. Coe, P. R. Brooks, M. G. Vetelino, M. C. Wirtz, E. P. Arnold, J. Huang, S. B. Sands, T. I. Davis, L. Lebel, C. B. Fox, A. Shrikhande, J. H. Heym, E. Schaeffer, H. Rollema, Y. Lu, R. S. Mansbach, L. K. Chambers, C. C. Rovetti, D. W. Schulz, F. D. Tingley and B. T. O'Neill, *J. Med. Chem.*, 2005, **48**, 3474.
7 (*a*) C. A. James, A. L. Coelho, M. Gevaert, P. Forgione and V. Snieckus, *J. Org. Chem.*, 2009, **74**, 4094; (*b*) N. Thasana, R. Worayuthakarn, P. Kradanrat, E. Hohn, L. R. Young and S. Ruchirawat, *J. Org. Chem.*, 2007, **72**, 9379; (*c*) I. Kostova, *Curr. HIV Res.*, 2006, **4**, 347; (*d*) T. L. Yao, D. W. Yue and R. C. Larock, *J. Org. Chem.*, 2005, **70**, 9985; (*e*) F. Borges, F. Roleira, N. Milhazes and L. Santana, *Curr. Med. Chem.*, 2005, **12**, 887; (*f*) D. L. Yu, M. Suzuki and L. Xie, *Med. Res. Rev.*, 2003, **23**, 322.
8 (*a*) B. N. Goguen, A. Aemissegger and B. Imperiali, *J. Am. Chem. Soc.*, 2011, **133**, 11038; (*b*) Y. Hori, H. Ueno, S. Mizukami and K. Kikuchi, *J. Am. Chem. Soc.*, 2009, **131**, 16610; (*c*) L. Chen, T. S. Hu and Z. Yao, *Eur. J. Org. Chem.*, 2008, 6175; (*d*) K. Komatsu, Y. Urano, H. Kojima and T. Nagano, *J. Am. Chem. Soc.*, 2007, **129**, 13447; (*e*) M. T. Lee, C. K. Yen, W. P. Yang, H. H. Chen, C. H. Liao, C. H. Tsai and C. H. Chen, *Org. Lett.*, 2004, **6**, 1241; (*f*) K. Hara, M. Kurashige, Y. Dan-oh, C. Kasada, A. Shinpo, S. Suga, K. Sayama and H. Arakawa, *New J. Chem.*, 2003, **27**, 783; (*g*) E. Quanten, P. Adriaens, F. C. Deschryver, R. Roelandts and H. Degreef, *Photochem. Photobiol.*, 1986, **43**, 485.
9 J. J. Chen, K. T. Li and D. Y. Yang, *Org. Lett.*, 2011, **13**, 1658.
10 K. T. Li, Y. B. Lin and D. Y. Yang, *Org. Lett.*, 2012, **14**, 1190.
11 C. H. Lin and D. Y. Yang, *Org. Lett.*, 2013, **15**, 2802.
12 (*a*) S. Ranatunga, C.-H. A. Tang, C. W. Kang, C. L. Kriss, B. J. Kloppenburg, C.-C. A. Hu and J. R. Del Valle, *J. Med. Chem.*, 2014, **57**, 4289; (*b*) Y. Kuroki, R. Akao, T. Inazumi and M. Noguehi, *Tetrahedron*, 1994, **50**, 1063; (*c*) M. A. Waly, M. M. Mashaly, M. N. Khodeir and A. Omar, *Boll. Chim. Farm.*, 1994, **113**, 698; (*d*) K. R. Prasad and M. Darbarwar, *Synth. Commun.*, 1990, **20**, 1379.
13 K. Ramig, S. Alli, M. Cheng, R. Leung, R. Razi, M. Washington and L. V. Kudzma, *Synlett*, 2007, **18**, 2868.
14 C. G. Neochoritis, C. A. Tsoleridis, J. Stephanidou-Stephanatou, C. A. Kontogiorgis and D. J. Hadjipavlou-Litina, *J. Med. Chem.*, 2010, **53**, 8409.
15 N. Kausar, P. Mukherjee and A. R. Das, *RSC Adv.*, 2016, **6**, 88904.
16 (*a*) K. B. Manjappa, W. F. Jhang, S. Y. Huang and D. Y. Yang, *Org. Lett.*, 2014, **16**, 5690; (*b*) K. B. Manjappa, J. R. Syu and D. Y. Yang, *Org. Lett.*, 2016, **18**, 332; (*c*) K. B. Manjappa, Y. T. Peng, W. F. Jhang and D. Y. Yang, *Tetrahedron*, 2016, **72**, 853.
17 N. C. Ganguly, M. Datta, P. De and R. Chakravarty, *Synth. Commun.*, 2003, **33**, 647.
18 I. Brady, D. Leane, H. P. Hughes, R. J. Forster and T. E. Keyes, *Dalton Trans.*, 2004, **21**, 334.
19 Crystallographic data (excluding structure factors) for **4a**, **4j**, and **4n** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC-1568069, 1568070, and 1568068, respectively.†
20 (*a*) K. Ramig, E. M. Greer, D. J. Szalda, S. Karimi, A. Ko, L. Boulos, J. Gu, N. Dvorkin, H. Bhramdat and G. Subramaniam, *J. Org. Chem.*, 2013, **78**, 8028; (*b*) K. Ramig, *Tetrahedron*, 2013, **69**, 10783.