Easy Access to Crystalline Indolines through hydrogen bond Transfer

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Abstract:

Several indoline derivatives with specific geometries are biologically active and have inhibitor properties. Many indolines are a key part of natural products. Much attention has been focused on the development of synthetic routes for their easy access. Current synthesis depends largely on metal catalysis, iodine reagents and Oxone. To date, no synthetic route has been established which is metal-, reagent-free and environmentally friendly and provides a base for green chemistry. Here we report the first facile metal- and reagent-free synthesis of indoline derivatives, which could potentially be influential in the design of new biologically active compounds. The synthesis proceeds through intramolecular amination between a urea nucleophile and unactivated alkene. The ring closure occurs in a few hours in the presence of pre-dried silica gel and gives good yields of indolines products but in the absence of silica gel, the ring closure occurred overnight with stirring in dry solvent. An electron withdrawing group (EWG) at the substituted aryl moiety of ureas increases the hydrogen bond donor ability of substrates that mediate the internal proton transfer at the terminal alkene and results in facile amination to give the indoline product with an "in plane" orientation of the carbonyl group and aromatic part of indoline framework. Such orientation in indolines is important for potent biological activities.

Introduction

The indoline moiety is an important component of many natural products[1] pharmaceuticals[2] (Fig. 1) and in addition, optically active indoline derivatives serve as either organocatalysts or chiral auxiliaries for asymmetric transformations.[3] Indoline derivatives have been proven to exhibit anticancer properties[4], tried as sensitizers of bacteria against β-lactam antibacterial agents,[5] worked as promising human protein kinase inhibitors[6], apoptosis protein inhibitors[7], and monoacylglycerol acyltransferase-2 inhibitors.[8] Due to the promising role of indoline derivatives in biological activities, much attention has been focused on the development of synthetic routes for their easy access. The routine routes to synthesise this kind of nitrogen heterocycles follows the transformation through oxidative difunctionalization of unactivated alkenes. The famous and advance transformations are alkenes vicinal

difunctionalization.[9] A problem with the synthesis of most indoline derivatives is the involvement of toxic and expensive metals.[10] Although metal-free synthesis has been reported, these protocols depend on iodine reagents and Oxone.[11] Organic methodologies involving metal-free and one-pot synthesis of target compounds are desirable because they tend to display perfect atom economy. Toward this goal, we also focus our attention on the one-pot synthesis of indoline derivatives. Herein, we report a facile metal-free and reagent-free in situ synthesis of indolines (**4a, b**) in the presence and absence of silica gel. Silica gel has a uniform and 3D network containing silicon oxide units. In hydrated form, silica gel behaves akin to silicic acid and has been used in chemical synthesis under mild conditions and gave high chemo-, regio- and stereoselective products without complex isolation procedures in comparison with homogeneous reactions. It is also a simple reaction catalysing agent in cyclisation reactions.[12]

The mainframe of the structure of the indoline derivatives (**4**) under investigation is similar to those in anticancer agents and natural products (see Fig.1), and thus the synthesis could be influential in designing complex indoline- based structures with good biologically activities. In 1990, King et al.[4a] reported 5-hydroxytryptamine (5-HT_3) receptor antagonists that showed that aromaticity in the 5-membered ring of the bicyclic aromatic nucleus is not necessary for potency. Instead, an "in plane" orientation of the carbonyl group is important. They argued that the 5-membered indoline ring acts as a spacer to maintain orientation of the carbonyl linkage and the monocyclic aromatic system. Taking into consideration the points highlighted by King et al. we introduced an additional substituted aromatic ring on opposite side of the indoline framework which could help to enhance biological activity. Indapamide (see Fig.1) has the same mainframe as **4a, b** and is use as drug for the treatment of hypertension and decompensate heart failure.[13] Takayanagi group reported similar indoline derivatives which interact with muscarinic receptors. These derivative contracted guinea-pig ileum and behaved as antagonists.[4b]

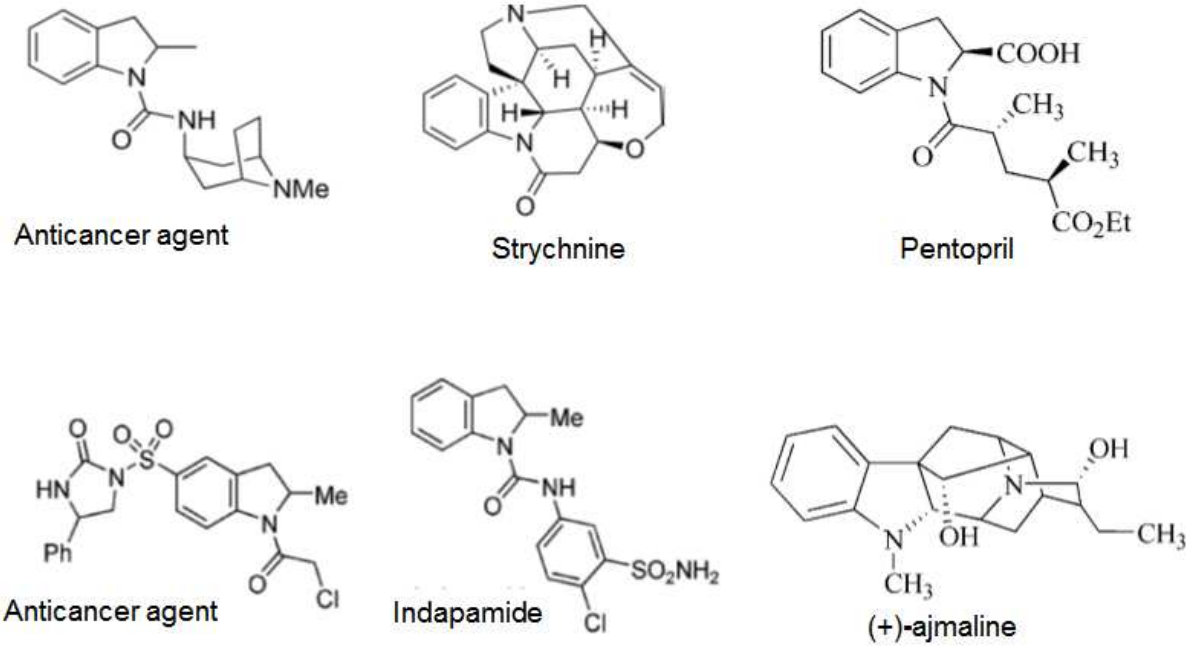
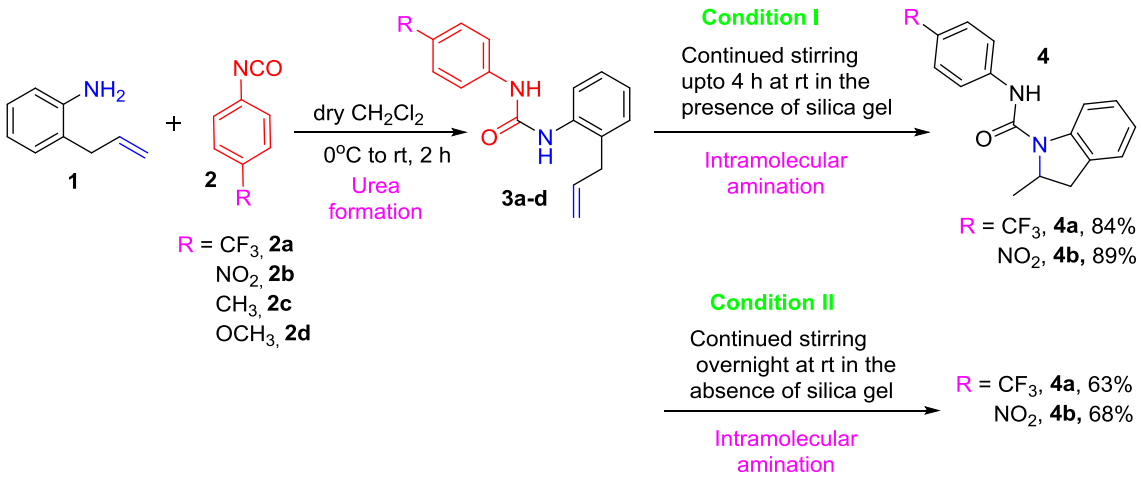


Figure 1. Representative compounds containing the indoline.

Results and Discussion

We have adopted a very simple one-pot synthetic approach for indoline derivatives. O-allylic aniline was reacted with aryl isocynates having electron-withdrawing groups, in dry CH_2Cl_2 under nitrogen atmosphere and stirred in the presence and absence of silica gel to give a single indoline product **4** in high yield (Scheme 1). Initially conditions were optimized by using precursors O-allylic aniline **1** and 4-(Trifluoromethyl)phenyl isocyanate **2a** for successful transformation to indoline derivative **4a**. The reaction was monitored on thin-layer chromatography (TLC). In the first two hours, urea formation (**3a**) was complete, and then the reaction was stirred for four hours in the presence of silica gel at room temperature to fully convert the urea moiety to the indoline derivative **4a**.



Scheme 1. Synthesis of indoline derivatives **4 (a-d)**.

Presumably, this reaction proceeds on the surface of silica gel that promotes cyclisation and results in intramolecular amination by a nucleophilic attack of the urea on terminal alkene, followed by internal proton transfer for the final indoline product (see Figure 2 for possible mechanism). In another experiment, the reaction was stirred in the absence of silica gel at room temperature to fully convert the urea moiety to indoline derivative **4a** but the reaction was carried out overnight and the yield was low as compared to the reaction performed in the presence of silica gel. In the second case, the reaction might proceed due the presence of the electron-withdrawing group that makes the urea derivative a hydrogen bond donor, and the first step is intramolecular proton transfer to alkene, followed by nucleophilic attack of nitrogen atom.

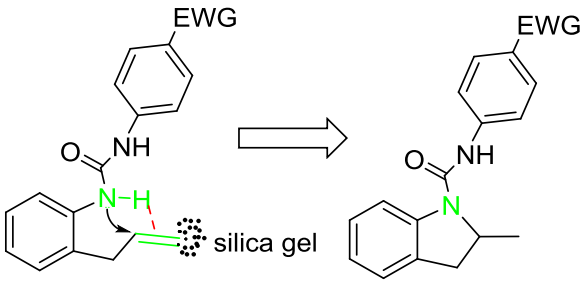
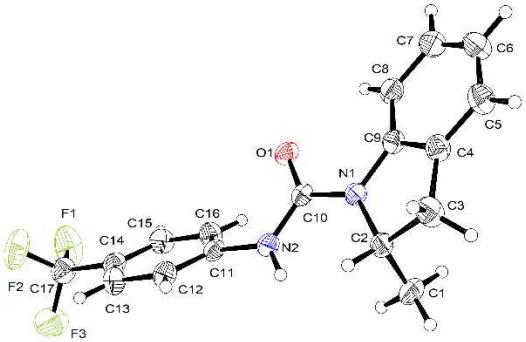
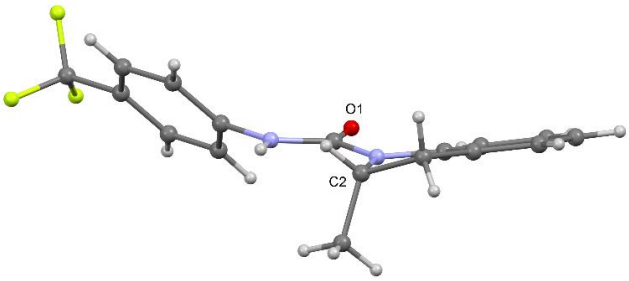


Figure 2. Possible pathway for indoline formation as a result of intramolecular amination through internal proton transfer from urea hydrogen bond donor to terminal end of alkene activated through silica gel.

In the third experiment, the reaction was stopped after two hours on completion of urea formation (**3a**) and the product was purified for characterization which clearly showed the urea moiety **3a** (see Supporting Information). However, during purification of **3a** on the silica gel column, we also observed the formation of indoline **4a** alongside which also shows that silica promotes cyclisation. The same conditions used for **4a** synthesis, were applied for the synthesis of indoline derivative **4b** using substrate **2b**, again noting the electron-withdrawing nature of the aryl group, and the reaction also generated good yields. Cyclisation was also attempted in the presence and absence of silica gel using substrates **3c, d** which also contain electron donating groups on the aromatic ring (see Supporting information for characterization data of **3c, d**). However, only minor traces of cyclic products **4c, d** (R = -CH_3, -OCH_3) were observed at TLC plate. Presumably, the electron donating groups on the aryl ring might quench the ability of urea derivatives to act as hydrogen bond donors resulting in minor traces. These results show that this methodology is effective for the substrates of electron deficient nature. Indolines **4a** and **4b** were crystallized from CH_3CN at room temperature and their X-ray analysis clearly shows the cyclisation products with an "in plane" orientation of the carbonyl group relative to the aromatic part of the indoline framework[14] that might be essential for potent biological activities.[4a] In the indole groups, the five-membered is in half-envelope conformation (Figure 3) with atom C2 as the flap. The largest atomic deviations from the least-squares planes through both the indole and carbonyl groups are by the flap atoms (C2) at 0.190(3)Å for **4a** and 0.230(2)Å for **4b**. The carbonyl oxygen atoms are located on the opposite side of the plane.



(a)



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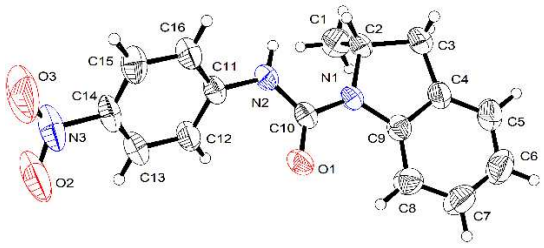
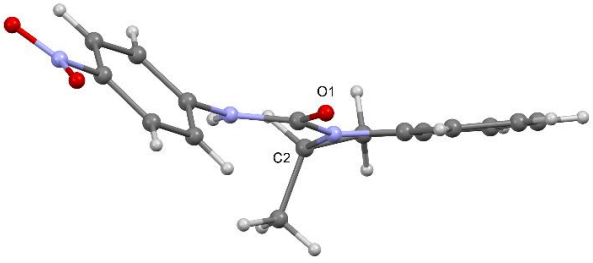


(b)



(d)

Figure 3. X-ray structure of indolines for (a) **4a** and (b) **4b** showing thermal ellipsoids at 50% probability. The view along the planes of the carbonyl group and indoline moieties for (c) **4a** and (d) **4b**.

Conclusion

Indolines with specific conformation are an important part of many pharmacologically important compounds, natural products and represent a class of biologically active compounds. Conventional synthesis depends largely on metal catalysis and iodine reagents with associated toxicity and purification problems and there is therefore need for a metal-, reagent-free and environmentally friendly method to be developed. We report the first facile metal- and reagent-free synthesis of indoline derivatives **4a** and **b**. The synthesis proceeds through intramolecular amination between the urea nucleophile and unactivated alkene. Fast ring closure occurs in the presence of pre-dried silica gel and gives good yields of indoline products with an "in plane" orientation of the carbonyl group relative to the aromatic part of the indoline framework. We anticipate that this facile synthesis of indoline derivatives, mediated by the hydrogen bond donor nature of ureas, can play an important role in designing more promising derivatives with potential for use in biological trials

Experimental Section

All the solvent and chemicals were purchased from Sigma Aldrich, Alfa Aesar, Acros Organic and FluoroChem and were used without further purification. The reactions were carried out under nitrogen atmosphere. Thin-layer chromatography (TLC) was performed on pre-coated aluminium sheets of Merck silica gel 60 F254 (0.20 mm) and visualised by UV radiation (254 nm). ^{1}H NMR and ^{13}C NMR spectra were measured on Bruker DPX 300, 400 or 500 apparatus. Mass spectrometric measurements were performed by the EPSRC Mass Spectrometry Facility in Swansea University on a Waters Xevo G2-S and on a Thermo Scientific LTQ Orbitrap XL machine for high-resolution mass spectroscopy (HRMS).

General procedure for the preparation of Indoline derivatives

To a stirred solution of an aryl isocyanate (1.0 equiv) in dry CH_2Cl_2 at 0 °C under N_2, the corresponding allylamine (1.0 equiv) was added. The reaction was allowed to warm to room temperature and stirred for 4 hours in the presence of silica gel (500 mg, here is important to mention that more than this amount of silica gel have no effect on yield). In another experiment, the reaction was stirred overnight in the absence of silica gel. For the workup separately, the reaction mixture was then diluted with CH_2Cl_2, washed with water, HCl (1 N), $NaHCO_3$ (sat.) and brine, dried with anhydrous $MgSO_4$. The mixture was filtered, and the filtrate was concentrated under vacuum. The residue was purified through silica gel flash chromatography (eluents: hexanes and ethyl acetate).

Synthesis of *2*-allyl aniline (1)

In a 100-mL 2-neck round bottom flask, a solution of N-allylaniline (5.0 g, 37.5 mmol) in m-xylene (70 mL) was first cooled at −78 °C and then was added boron trifluoride etherate (5.6 mL, 45 mmol) under inert nitrogen atmosphere. After 5 min, the solution was warmed to room temperature. After 15 min, heated to 180 °C. After 72 h, the reaction was cooled down to room temperature and quenched with 2M NaOH solution (80 mL) at 0 °C. The organic layer was separated and the aqueous

layer was extracted with diethyl ether (70 mL × 3). All the combined organic layers were washed with brine solution and then dried over anhydrous $MgSO_4$ and then concentrated in vacuo. The residue was purified by flash column chromatography to give as a yellow oil, 71% yield. Pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 – 7.14 (m, 2H), 6.89 (td, *J* = 7.4, 1.2 Hz, 1H), 6.78 (dd, *J* = 7.8, 0.9 Hz, 1H), 6.09 (ddt, *J* = 16.5, 10.3, 6.2 Hz, 1H), 5.32 – 5.18 (m, 2H), 3.76 (s, 2H), 3.42 (dt, *J* = 6.1, 1.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.01, 145.01, 136.11, 136.11, 130.3, 130.30, 127.69, 127.69, 124.10, 124.10, 118.96, 118.96, 116.25, 115.95, 36.59; HRMS *m/z:* calcd 133.0891 g/mol. observed 134.096,

2-methyl-N-(4-(trifluoromethyl)phenyl)indoline-1-carboxamide (4a)

To a stirred solution of 4-(Trifluoromethyl)phenyl isocyanate (0.711g, 3.7mmol, 1.0 equiv) in dry CH_2Cl_2 (10mL) at 0 °C under N_2, the o-allylamine (0.5g, 3.7mmol ,1.0 equiv) was added. The reaction was allowed to warm to room temperature and stirred for four hours in the presence of predried silica gel (500 mg). The reaction mixture was then diluted with CH_2Cl_2, washed with water, HCl (1 N), $NaHCO_3$ (sat.) and brine, dried with anhydrous $MgSO_4$. The mixture was filtered, and the filtrate was concentrated under vacuum. The residue was purified through silica gel flash chromatography (eluents: hexanes and ethyl acetate). 84% yield. White crystalline solid, mp = 187-189°C; ^{1}H NMR (300 MHz, Acetone) δ 8.33 (s, 1H), 7.99 (d, *J* = 7.8 Hz, 1H), 7.88 (d, *J* = 8.5 Hz, 2H), 7.63 (d, *J* = 8.5 Hz, 2H), 7.27 – 7.13 (m, 2H), 6.96 (td, *J* = 7.4, 1.0 Hz, 1H), 4.91 – 4.78 (m, 1H), 3.44 (dd, *J* = 15.9, 9.1 Hz, 1H), 2.73 (d, *J* = 15.9 Hz, 1H), 1.34 (d, *J* = 6.3 Hz, 3H). ^{13}C NMR (126 MHz, Acetone) δ 151.70, 143.68, 143.67, 142.51, 130.05, 127.14, 125.67, 125.02, 122.34, 119.49, 115.83, 54.91, 35.99, 20.3; ESI HRMS *m/z:* calcd 320.1136 g/mol, Observed 321.1252g/mol.

2-methyl-N-(4-nitrophenyl)indoline-1-carboxamide (4b)

To a stirred solution of 4-Nitrophenyl isocyanate (0.623g, 3.7mmol, 1.0 equiv) in dry CH_2Cl_2 (10mL) at 0 °C under N_2, the o-allylamine (0.5g, 3.7mmol, 1.0 equiv) was added. The reaction was allowed to warm to room temperature and stirred for four hours in the presence of predried silica gel (500 mg). The reaction mixture was then diluted with CH_2Cl_2, washed with water, HCl (1 N), $NaHCO_3$ (sat.) and brine, dried with anhydrous $MgSO_4$. The mixture was filtered, and the filtrate was concentrated under vacuum. The residue was purified through silica gel flash chromatography (eluents: hexanes and ethyl acetate), 89% Yield. Yellow crystalline solid, mp = 157-159°C; ^{1}H NMR (300 MHz, Acetone) δ 8.58 (s, 1H), 8.29 – 8.13 (m, 2H), 7.99 (d, *J* = 7.7 Hz, 1H), 7.97 – 7.89 (m, 2H), 7.32 – 7.09 (m, 2H), 6.99 (td, *J* = 7.4, 1.0 Hz, 1H), 4.88 (dqd, *J* = 11.0, 6.3, 1.8 Hz, 1H), 3.46 (dd, *J* = 15.9, 9.1 Hz, 1H), 2.76 (d, *J* = 15.9 Hz, 1H), 1.35 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (126 MHz, Acetone) δ 151.32, 146.46, 142.25, 142.22, 130.20, 127.19, 125.08, 124.51, 122.64, 118.94, 115.98, 55.04, 35.98, 20.40; ESI HRMS *m/z:* calcd 297.1113g/mol, observed 298.1188g/mol.

Crystal Structure Determination

Single-crystal X-ray diffraction data were recorded at ambient temperature using an Agilent SuperNova Dual Atlas diffractometer equipped with a mirror monochromator using Mo Kα (λ = 0.71073Å) radiation. Generally, H atoms were inserted in idealized positions and refined using a riding model, with Uiso(H) values equal to 1.2 or 1.5 times the Ueq value of the atom to which it is bonded and with methyl groups

allowed to rotate about the C-C bond. Structure solution and refinement were performed using SHELXS-2013 and SHEXL-2018 respectively.

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References

1. a) Kuehne, M. E.; Bornmann, W. G.; Marko, I.; Qin, Y.; Le-Boulluec, K. L.; Frasier, D. A.; Xu, F.; Mulamba, T.; Ensinger, C. L.; Borman, L. S.; Huot, A. E.; Exon, C.; Bizzarro, F. T.; Cheung, J. B.; Bane, S. L.; Org Biomol Chem 2003, 1, 2120; b) Zhang, H.; Boonsombat, J.; Padwa, A. Org Lett 2007, 9, 279; c) Bui, T.; Syed, S.; Barbas III, C. F. J Am Chem Soc. 2009, 131, 8758; d) Wang, T.; Xu, Q.; Yu, P.; Liu, X.; Cook, J. M.; Org Lett 2001, 3, 345; e) Iyengar, R.; Schildknegt, K.; Morton, M.; Aube, J. J Org Chem 2005, 70, 10645.
2. Rakhit, A.; Hurley, M. E.; Tipnis, V.; Coleman, J.; Rommel, A.; Brunner, H. R. J Clin Pharmacol 1986, 26, 156.
3. a) Kunz, R. K.; MacMillan, D. W. C. J Am Chem Soc. 2005, 127, 3240; b) Andersson, F.; Hedenstrçm, E. Tetrahedron Asymmetry 2006, 17, 1952; c) Hartikka, A.; Arvidsson, P. I. J Org Chem 2007, 72, 5874; d) Pietruszka, J.; Simon, R. C. ChemCatChem 2010, 2, 505.
4. a) Bermudez, J.; Dabbs, S.; Joiner, K. A.; King, F. D. J Med Chem 1990, 33, 1929; b) Adachi, S.; Koike, K.; Takayanagi, I. Pharmacology 1996, 53, 250; c) Horton, D. A.; Bourne, G. T.; Smythe, M. L. Chem Rev 2003, 103, 893.
5. Chang, L.; Podoll, J. D.; Wang, W.; Walls, S.; Orourke, C. P.; Wang, X.; J Med Chem 2014, 57, 3803.
6. Danilenko, V. N.; Simonov, A. Y.; Lakatosh, S. A.; Kubbutat, M. H. G.; Totzke, F. Schachtele, C.; Elizarov, S.; M. Bekker, O. B.; Printsevskaya, S. S.; Luzikov, Y. N. et al. J Med Chem 2008, 51, 7731.
7. Chessari, G.; Buck, I. M.; Day, J. E. H.; Day, P. J.; Iqbal, A.; Johnson, C. N.; Lewis, E. J.; Martins, V.; Miller, D.; Reader, M. et al. J Med Chem 2015, 58, 6574.
8. Sato, K. Takahagi, H. Yoshikawa, T. Morimoto, S. Takai, T. Hidaka, K. Kamaura, M. Kubo, O. Adachi, R. Ishii, T. et al. J Med Chem 2015, 58, 3892.
9. a) Bergmeier, S. C. Tetrahedron 2000, 56, 2561; b) Lyons, T. W.; Sanford, M. S. Chem Rev 2007, 110, 1147; c) Donohoe, T. J.; Callens, C. K. A.; Flores, A.; Lacy, A. R.; Rathi, A. H. Chem Eur J 2011, 17, 58; d) Ye, K-Y.; Pombar, G.; Fu, N.; Sauer, G. S.; Keresztes, I.; Lin, S. J Am Chem Soc 2018, 140, 2438; e) Ahmed, N.; Khatoon, S.; Shirinfar, B. ChemElectroChem 2018, 5, 1245; e) Triandafillidi, I.; Tzaras, D. I.; Kokotos, C. G. ChemCatChem 2018, 10, 2521; f) Triandafillidi, I.; Kokotos, C. G. Org Lett 2017, 19, 106; g) Theodorou, A.; Kokotos, C. G. Adv Synth Catal 2017, 359, 1577; h) Theodorou, A.; Triandafillidi, I.; Kokotos, C. G. Adv Synth Catal 2018, 360, 951; i) Islam, M.; Kariuki, B. M.; Shafiq, Z.; Wirth, T.; Ahmed, N. Eur J Org Chem 2018, 10.1002/ejoc.201801688; j) Martins, G. M.; Shirinfar, B.; Hardwick, T.; Ahmed, N. ChemElectroChem 2018, 10.1002/celc.201801466; k) Ahmed, N.; Khatoon, S. ChemistryOpen 2018, 7, 576.
10. a) Lira, R.; Wolfe, J. P. J Am Chem Soc 2004, 126, 13906; b) Alexanian, E. J. Lee, C. Sorensen, E. J. J Am Chem Soc 2005, 127, 7690; c) Sherman, E. S.; Chemler, S. R.; Tan, T. B.; Gerlits, O.; Org Lett 2004, 6, 1573; d) Zabawa, T. P.; Kasi, D.; Chemler, S. R. J Am Chem Soc 2005, 127, 11250; e) Nicolaou, K. C.; Roecker, A.

J.; Pfefferkorn, J. A.; Cao, G.-Q. J Am Chem Soc 2000, 122, 2966; f) Yin, Y.; Zhao, G. Heterocycles 2006, 68, 23; g) Gleave, D. M.; Brickner, S. J.; Manninen, P. R.; Allwine, D. A.; Lovasz, K. D.; Rohrer, D. C.; Tucker, J. A.; Zurenko, G. E.; Ford, C. W. Bioorg Med Chem Lett 1998, 8, 1231; h) Gleave, D. M.; Brickner, S. J. J Org Chem 1996, 61, 6470; i) Liu, D. Zhao, G. Xiang, L. Eur. J Org Chem 2010, 3975.

11. a) Correa, A.; Tellilu, I.; Dominguez, E.; SanMartin, R. J Org Chem 2006, 71, 8316; b) Lovick, H. M.; Michael, F. E. J Am Chem Soc 2010, 132, 1249; c) Mizar, P.; Burelli, A.; Gunther, E.; Softje, M.; Farooq, U.; Wirth, T. Chem Eur J 2014, 20, 13113; d) Moriyama, K.; Izumisawa, Y.; Togo, H. J Org Chem 2012, 77, 9846.
12. a) Banerjee, A. K.; Mimo', M. S. L.; Vegas, W. J. V. *Russian Chemical Reviews* 2001, 70, 971; b) Clive, D. L. J.; Farina, V.; Singh, A.; Wong, C. K.; Kiel, W. A.; Menchen, S. M. *J Org Chem* 1980**,** 45, 2120.
13. Beckett, N. S.; Peters, R.; Fletcher, A. E. *et al. N Engl J Med* 2008, 358, 1887.
14. CCDC 1877878 (**4a**), 1877879 (**4b**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.