

## Chemical Scaffolds

Pd<sup>II</sup>-Mediated Oxidative Amination for Access to a 9-Azabicyclo[4.2.1]nonane Compound Library and Anatoxin-aRafid S. Dawood,<sup>[a,b]</sup> Suresh R. Chidipudi,<sup>[a]</sup> Daniel C. O'Connor,<sup>[a]</sup> William Lewis,<sup>[a]</sup> Daniel Hamza,<sup>[c]</sup> Christopher A. Pearce,<sup>[c]</sup> Geraint Jones,<sup>[c]</sup> Ross P. Wilkie,<sup>[a]</sup> Irene Georgiou,<sup>[a]</sup> Thomas E. Storr,<sup>[a]</sup> Jonathan C. Moore,<sup>\*[a]</sup> and Robert A. Stockman<sup>\*[a]</sup>

**Abstract:** Intramolecular oxidative amination of readily accessible aminocyclooct-4-enes provides rapid and regioselective access to the 9-azabicyclo[4.2.1]nonane framework characteristic of the natural product anatoxin-a (1). This has enabled the syn-

thesis of sp<sup>3</sup>-rich chemical scaffolds suitable for diversification. A library of 881 lead-like compounds is reported alongside a formal synthesis of anatoxin-a (1).

## Introduction

The structure of anatoxin-a (1) was unambiguously determined in 1977 through the combination of X-ray crystallographic<sup>[1]</sup> and spectroscopic<sup>[2]</sup> analysis. This potent neurotoxin is produced by certain strains of the freshwater blue-green algae *Anabena flos-aquae* and has been responsible for fatal poisoning of animal life.<sup>[3]</sup> Also known as "Very Fast Death Factor", anatoxin-a (1) causes death by respiratory paralysis with an LD<sub>50</sub> (intraperitoneal, mouse) of 0.2 mg/kg, with a survival time of 4–7 minutes.<sup>[4]</sup> The natural compound acts as a mimic for acetylcholine and is a potent and irreversible agonist for the nicotinic acetylcholine receptor (nAChR).<sup>[5]</sup> As acetylcholine deficiency is implicated in diseases such as Alzheimer's, analogues of anatoxin-a (1) possessing lower levels of toxicity may have potential in the treatment of neurological disorders.<sup>[6]</sup> Paired with its significant biological properties, the compound's unusual structure has prompted much synthetic interest; a number of distinct approaches to anatoxin-a (1) and its analogues have been devised.<sup>[7]</sup> Since the topic was reviewed in 2006,<sup>[8]</sup> there have been a considerable number of total/formal syntheses reported including our own two-directional approach<sup>[9]</sup> and a contemporary example (2016) that utilises a novel formal amide insertion strategy.<sup>[10]</sup> One commonly employed approach is to construct the 9-azabicyclo[4.2.1]nonane framework through the ring closure of an aminocyclooct-4-ene (Figure 1), however there are drawbacks to each of the methods reported to date.

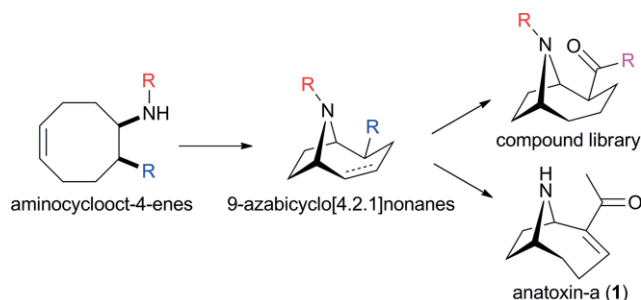


Figure 1. Ring closure of aminocyclooct-4-enes for the synthesis of anatoxin-a (1) and chemical scaffolds for library generation.

An aminocarbonylation strategy was reported by Ham in 1998,<sup>[11]</sup> however this heterocyclisation was observed not to be regioselective. A series of reports by Parsons<sup>[12]</sup> saw the development of a selenium-mediated ring closure, however this approach requires stoichiometric quantities of toxic phenylselenenyl chloride. Ho<sup>[13]</sup> reported a catalytic palladium mediated cyclisation of a corresponding *trans*-derivative, although yields were hampered by the formation of an undesired tricyclic side-product.

## Results and Discussions

As part of our studies into the synthesis of chemical scaffolds for drug discovery,<sup>[14]</sup> we set out to develop a catalytic and selective protocol for the heterocyclisation of aminocyclooct-4-enes. It was envisaged that a regioselective and high-yielding protocol would expedite entry to series of 9-azabicyclo[4.2.1]nonane derived chemical scaffolds that could be further derivatised to generate a lead-like compound library. Small molecule libraries are highly desired in early-stage probe- and drug-discovery screening programmes<sup>[15]</sup> and as part of our work under the European Lead Factory<sup>[16]</sup> we have been engaged in the development of facile synthetic routes to chemical scaffolds that are suitable for diversification into high Fsp<sup>3</sup> (frac-

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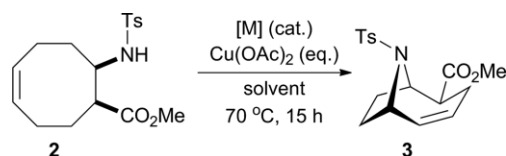
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tion of sp<sup>3</sup>-hybridised carbon atoms)<sup>17</sup> compound libraries. For these purposes we were drawn to the simplicity and concise nature of the heterocyclisation approach to the 9-azabicyclo[4.2.1]nonane framework. We set out to investigate ring closure of the key precursor **2** under classical oxidative amination conditions with Pd(OAc)<sub>2</sub>, using Cu(OAc)<sub>2</sub> as the terminal oxidant (Table 1).

Table 1. Catalyst/solvent optimisation. Reactions were performed on a 0.1 mmol scale. Yields were determined by quantitative <sup>1</sup>H NMR spectroscopy with 1,3,5-trimethoxybenzene as an internal standard.



Entry	[M] (mol-%)	Cu(OAc) <sub>2</sub> [equiv.]	Solvent	Yield
1	Pd(OAc) <sub>2</sub> (5)	2.1	THF	30%
2	Pd(OAc) <sub>2</sub> (5)	2.1	PhMe	37%
3	Pd(OAc) <sub>2</sub> (5)	2.1	MeCN	95%
4	Pd(OAc) <sub>2</sub> (5)	2.1	DMF	99%
5	Pd(OAc) <sub>2</sub> (2.5)	2.1	DMF	43%
6	–	2.1	DMF	–
7	[RuCl <sub>2</sub> ( <i>p</i> -cymene)] <sub>2</sub> (2.5)	2.5	DMF	–
8	[RhCp*Cl <sub>2</sub> ] <sub>2</sub> (2.5)	2.5	DMF	–

Moderate yields of the desired product **3** were obtained using THF and PhMe as solvents (30% and 37% respectively). Changing to MeCN (Entry 3) gave an excellent conversion but DMF was found to be the superior solvent for this transformation, providing access to the 9-azabicyclo[4.2.1]nonane ring system with complete selectivity and quantitative conversion (Entry 4). Reducing the palladium loading to 2.5 mol% had a significantly detrimental effect on the yield (43%) and when the reaction was performed in the absence of palladium (Entry 6) or in the presence of Ru<sup>II</sup> and Rh<sup>III</sup> complexes (Entries 7–8), no cyclisation products could be detected. With the optimised conditions in hand, the substrate scope of the transformation was investigated (Figure 2).

Initially we attempted exchanging the *N*-tosyl functionality for the more readily de-protected carboxybenzyl (Cbz) group. In this case, the desired product **4** was obtained in a moderate yield of 39%. Benzoyl protection was considerably better tolerated, yielding the desired product **5** in a much improved 75%. The electron rich *N*-benzyl substrate was observed to react with poor selectivity and the targeted 9-azabicyclo[4.2.1]nonane **7** could not be isolated from the complicated mixture of products. We were however able to obtain the over-oxidised dienyl derivative **8** and the bicyclo[3.3.1]nonane derivative **9**, albeit in modest yields in each case. Sulfonamides were found to be the highest yielding and most selective substrates, which is consistent with reports from the literature on many other palladium-mediated alkene aminations.<sup>[18]</sup> The *N*-mesyl and -tosyl derivatives **6** and **3** were obtained in 79% and 93% respectively. In light of these results, *N*-tosylated precursors were selected to further investigate the substrate scope of the transformation with regard to the R<sup>2</sup> substituent (Figure 2). We were delighted to obtain a good yield of 84% for the Weinreb amide functional-

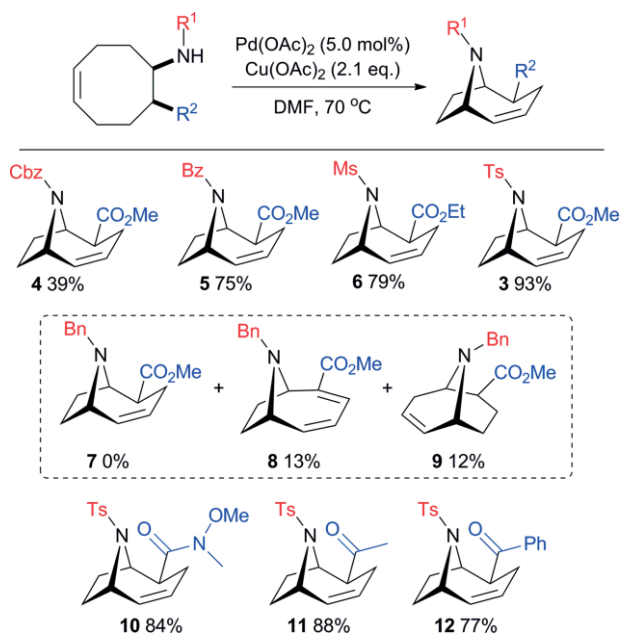


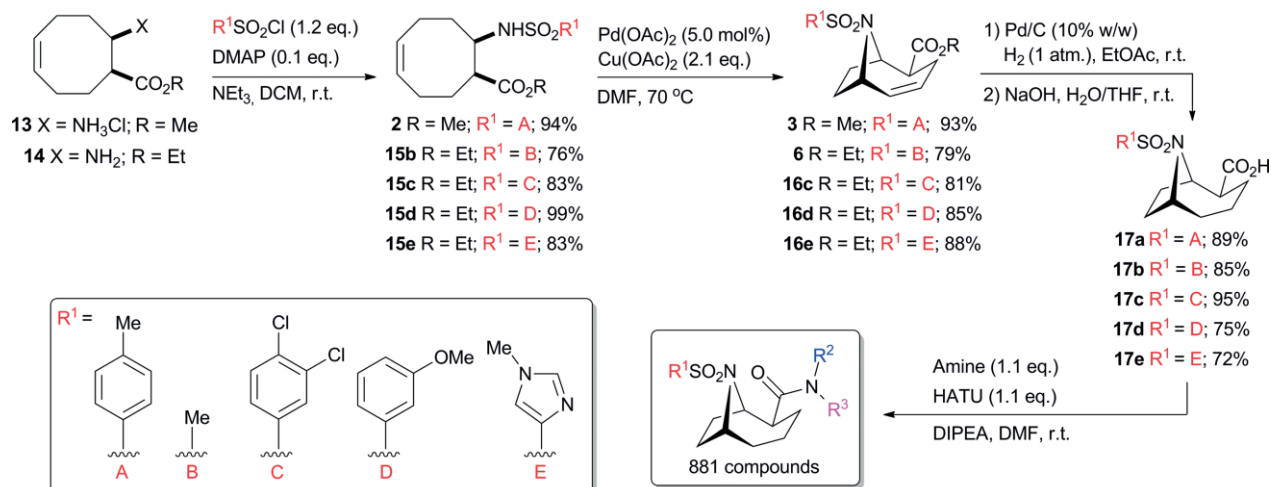
Figure 2. Investigation into the substrate scope of the transformation. Yields are for isolated material obtained following column chromatography.

ised derivative **10**, which could likely serve as a useful intermediate for the synthesis of side chain-modified anatoxin-a (**1**) derivatives. Performing alkylation prior to ring closing was also demonstrated to be a viable strategy, with the methyl and phenyl ketones **11** and **12** being isolated in 88% and 77% respectively.

It was deemed prudent to focus the efforts of library synthesis on the high yielding and selective *N*-sulfonyl substrates. Furthermore, it was anticipated that the inherent stability of the sulfonamide functionality would help safeguard against the expected toxicity of the *N*-H derivatives. It was decided that the strategy for library synthesis would involve a series of sulfonylation reactions for decoration of the first point of diversity, with R<sup>2</sup> becoming the main diversity generating vector to be explored. As such, the β-amino esters **13/14** were prepared according to a modified procedure of Choi<sup>[19]</sup> and then treated with a range of sulfonyl chlorides. The selected examples represent alkyl, aryl (electron poor and rich) and heteroaryl sulfonamide substitutions (Scheme 1, A–E). In each case sulfonylation proceeded smoothly and the products **2/15b–e** were isolated in 76–99% yield. Under our optimised conditions, the oxidative amination of **2/15b–e** gave excellent yields (79–93%) and regioselectivities (> 20:1).

Next, to increase the “lead-likeness” of the final library the metabolically labile alkene functionality was removed via hydrogenation over palladium on carbon. In the penultimate step of library synthesis, base-mediated ester hydrolysis was employed to yield the carboxylic acid functionalised scaffolds **17a–e** in good to excellent yields (72–95% over two steps).

With the acids **17a–e** in hand, the feasibility of a library synthesis via HATU-mediated amidation in plate-format was investigated. From the 5 scaffolds **17a–e**, 15 test reactions were performed using a selection of cyclic, acyclic and aromatic amines (See Supporting Information). The reaction mixtures were ana-



Scheme 1. The synthesis and derivatisation of chemical scaffolds for the generation of a 9-azabicyclo[4.2.1]nonane compound library.

lysed by UPLC, filtered and purified by preparative HPLC, with purities of 85–100% as determined by LCMS. The stability of the amidation products was assessed by comparison of the <sup>1</sup>H NMR spectra obtained before and after storage in DMSO-d<sub>6</sub> at room temp. for 7 days. In each case no significant change could be observed. By utilising the general strategy for library synthesis described herein, a library of 881 9-azabicyclo[4.2.1]nonane derivatives were produced (ca. 0.1 mmol each) to be incorporated into the European Lead Factory's screening programme. Computational assessment of the library indicates that it is largely Lipinski's rule of five compliant, with an average molecular weight of 445.6 Da and cLogP of 2.48. The library also has a high degree of three-dimensionality and bond-saturation, with an average Fsp<sup>3</sup> of 0.56 (Figure 3). In recent years there has been increased recognition of the importance of Fsp<sup>3</sup> when designing compound libraries for lead identification. Increased bond saturation in general, as a measure of complexity, has been shown to correlate well with clinical success as compounds transition through the drug-discovery process.<sup>[17]</sup> With an average Fsp<sup>3</sup> of 0.56, this library compares favourably to compounds in the discovery phase (average Fsp<sup>3</sup> = 0.36) and to marketed drugs (average Fsp<sup>3</sup> = 0.47).<sup>[17]</sup>

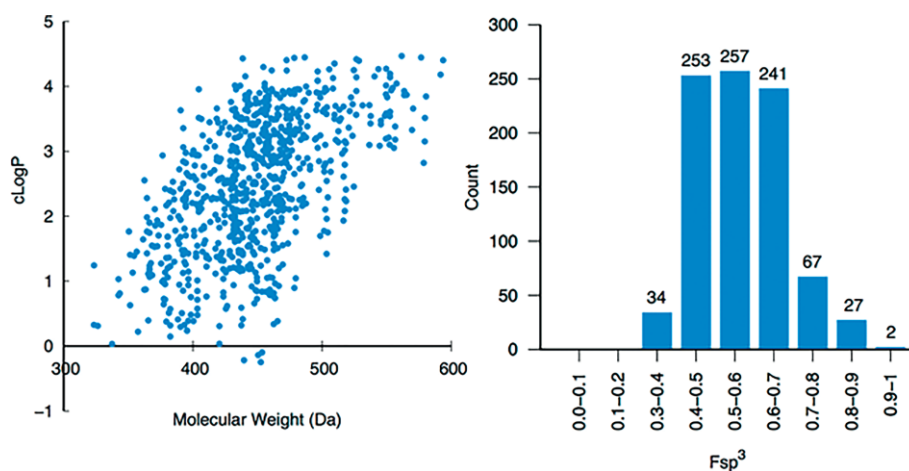
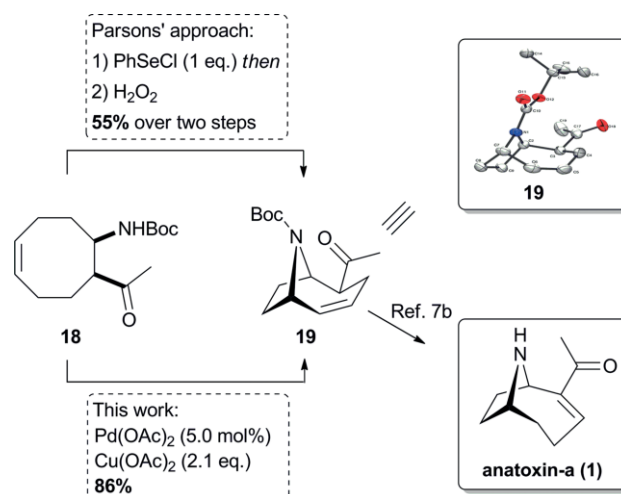


Figure 3. cLogP vs. MW (left) and Fsp<sup>3</sup> (right) plots of the produced 881 membered compound library.

We were also compelled to apply the oxidative amination conditions to the synthesis of anatoxin-a (1). Parsons' 2000 synthesis<sup>[12a]</sup> utilised a selenium-mediated ring closure of the



Scheme 2. Application of the optimised oxidative amination conditions to the formal synthesis of anatoxin-a (1).

N-Boc methyl ketone **18** to construct the 9-azabicyclo[4.2.1]-nonane framework (Scheme 2). The intermediate selenide was not isolated but instead treated with H<sub>2</sub>O<sub>2</sub>, promoting oxidation and elimination to yield the key aza-bridged bicycle **19** in 55% over two steps. Interestingly, despite the report that PdCl<sub>2</sub>, Pd(OAc)<sub>2</sub> and RhCl<sub>3</sub> were unsuccessful at bringing about the heterocyclisation of **18**, we were delighted to observe that utilisation of our optimised oxidative amination conditions allowed the isolation of **19** in a much improved 86% yield. This was achieved in a single synthetic operation and constitutes a useful refinement to the seminal work of Parsons<sup>[12a]</sup> and Rapoport.<sup>[7b]</sup>

## Conclusions

In conclusion, an improved method for the intramolecular oxidative amination of aminocyclooct-4-enes is reported for formation of the biologically relevant 9-azabicyclo[4.2.1]nonane framework. The reaction is generally high yielding, has good substrate scope and proceeds under a cheap and “ligand-free” catalytic manifold. The protocol was applied to the synthesis of a series of chemical scaffolds, which were further derivatised to form a lead-like 881 membered compound library. The oxidative amination methodology was then applied to a formal synthesis of anatoxin-a (**1**), facilitating an improved yield and increased operational simplicity.

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- [1] C. S. Huber, *Acta Crystallogr., Sect. B* **1972**, *28*, 2577–2582.  
 [2] J. P. Devlin, O. E. Edwards, P. R. Gorham, N. R. Hunter, R. K. Pike, B. Stavric, *Can. J. Chem.* **1977**, *55*, 1367–1371.  
 [3] a) W. W. Carmichael, D. F. Biggs, P. R. Gorham, *Science* **1975**, *187*, 542–544; b) L. Krienitz, A. Ballot, K. Kotut, C. Wiegand, S. Pütz, J. S. Metcalf, G. A. Codd, S. Pflugmacher, *FEMS Microbiol. Ecol.* **2003**, *43*, 141–148; c) B. Puschner, B. Hoff, E. R. Tor, *J. Vet. Diagnostic Investig.* **2008**, *20*, 89–92.

- [4] K. L. Swanson, H. Rapoport, R. S. Aronstam, E. X. Albuquerque, *ACS Symp., Ser.* **1990**, *418*, 107–118.  
 [5] C. E. Spivak, B. Witkop, E. X. Albuquerque, *Mol. Pharmacol.* **1980**, *18*, 384–394.  
 [6] S. Wonnacott, T. Gallagher, *Mar. Drugs* **2006**, *4*, 228–254.  
 [7] For total/formal syntheses of anatoxin-a, see references 8–10 and further references therein. For approaches to anatoxin derivatives please see: a) N. A. Magnus, L. Ducry, V. Rolland, S. Wonnacott, T. Gallagher, *J. Chem. Soc. Trans.* **1997**, *1*, 2313–2318; b) F. J. Sardina, M. H. Howard, A. M. P. Koskinen, H. Rapoport, *J. Org. Chem.* **1989**, *54*, 4654–4660; c) P. Thomas, P. A. Brough, T. Gallagher, S. Wonnacott, *Drug Dev. Res.* **1994**, *31*, 147–156; d) D. Simoni, R. Rondanin, P. Marchetti, C. Rullo, R. Baruchello, G. Grisolia, G. Barbato, R. Giovannini, C. Marchioro, A. M. Capelli, C. Virginio, A. Bozzoli, P. A. Borea, S. Merighi, D. Donati, *Bioorg. Med. Chem. Lett.* **2011**, *21*, 5423–5427; e) D. B. Kanne, L. G. Abood, *J. Med. Chem.* **1988**, *31*, 506–509; f) F. I. Carroll, X. Hu, H. A. Navarro, J. Deschamps, G. R. Abdрахmanova, M. I. Damaj, B. R. Martin, *J. Med. Chem.* **2006**, *49*, 3244–3250; g) E. Wright, T. Gallagher, C. G. V. Sharples, S. Wonnacott, *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2867–2870; h) H. Gohlke, S. Schwarz, D. Gündisch, M. C. Tilotta, A. Weber, T. Wegge, G. Seitz, *J. Med. Chem.* **2003**, *46*, 2031–2048; i) M. H. Howard, F. J. Sardina, H. Rapoport, *J. Org. Chem.* **1990**, *55*, 2829–2838.  
 [8] For reviews on synthetic approaches to anatoxin-a and its derivatives see: a) H. L. Mansell, *Tetrahedron* **1996**, *52*, 6025–6061; b) V. Rodriguez, S. Moura, E. Pinto, C. M. P. Pereira, R. C. Braga, *Quim. Nova* **2006**, *29*, 1365–1371.  
 [9] a) S. J. Roe, R. A. Stockman, *Chem. Commun.* **2008**, 3432–3434; b) S. J. Roe, D. L. Hughes, P. Aggarwal, R. A. Stockman, *Synthesis* **2009**, 3775–3784.  
 [10] M. Kono, S. Harada, Y. Hamada, T. Nemoto, *Tetrahedron* **2016**, *72*, 1395–1399.  
 [11] C.-Y. Oh, K.-S. Kim, W.-H. Ham, *Tetrahedron Lett.* **1998**, *39*, 2133–2136.  
 [12] a) P. J. Parsons, N. P. Camp, N. Edwards, L. R. Sumoreeah, *Tetrahedron* **2000**, *56*, 309–315; b) P. J. Parsons, N. P. Camp, J. M. Underwood, D. M. Harvey, *Tetrahedron* **1996**, *52*, 11637–11642; c) P. J. Parsons, N. P. Camp, J. M. Underwood, D. M. Harvey, *J. Chem. Soc., Chem. Commun.* **1995**, 1461–1462.  
 [13] T.-L. Ho, E. Zinurova, *Helv. Chim. Acta* **2006**, *89*, 134–137.  
 [14] a) M. J. Rawling, T. E. Storr, W. A. Bawazir, S. J. Cully, W. Lewis, M. S. I. T. Makki, I. R. Strutt, G. Jones, D. Hamza, R. A. Stockman, *Chem. Commun.* **2015**, *51*, 12867–12870; b) T. E. Storr, S. J. Cully, M. J. Rawling, W. Lewis, D. Hamza, G. Jones, R. A. Stockman, *Bioorg. Med. Chem.* **2015**, *23*, 2621–2628; c) R. S. Dawood, I. Georgiou, R. P. Wilkie, W. Lewis, R. A. Stockman, *Chem. Eur. J.* **2017**, *23*, 11153–11158; d) S. J. Cully, T. E. Storr, M. J. Rawling, I. R. Abeyseena, D. Hamza, G. Jones, C. A. Pearce, A. Quddus, W. Lewis, R. A. Stockman, *Bioorg. Med. Chem.* **2016**, *24*, 5249–5257.  
 [15] a) J.-L. Reymond, M. Awale, *ACS Chem. Neurosci.* **2012**, *3*, 649–657; b) A. W. Hung, A. Ramek, Y. Wang, T. Kaya, J. A. Wilson, P. A. Clemons, D. W. Young, *Proc. Natl. Acad. Sci. USA* **2011**, *108*, 6799–6804; c) J.-L. Reymond, R. van Deursen, L. C. Blum, L. Ruddigkeit, *Med. Chem. Commun.* **2010**, *1*, 30–38.  
 [16] European Lead Factory, <https://www.europeanleadfactory.eu>, (accessed 12 February 2018).  
 [17] F. Lovering, J. Bikker, C. Humblet, *J. Med. Chem.* **2009**, *52*, 6752–6756.  
 [18] E. M. Beccalli, G. Broggin, M. Martinelli, S. Sottocornola, *Chem. Rev.* **2007**, *107*, 5318–5365.  
 [19] W. Lee, S. Kwon, P. Kang, I. A. Guzei, S. H. Choi, *Org. Biomol. Chem.* **2014**, *12*, 2641–2644.

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