Access to a Diverse Array of Bridged Benzo[1,5]oxazocine and Benzo[1,4]diazepine Structures.

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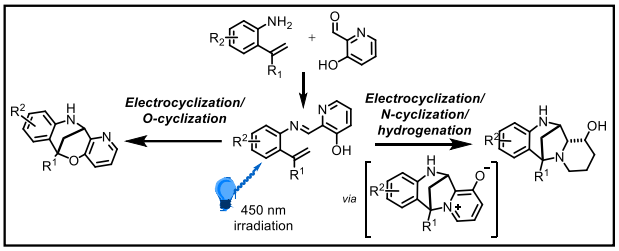


ABSTRACT: The preparation of bridged benzo[1,5]oxazocines and benzo[1,4]diazepines is demonstrated from simple aniline and aldehyde starting materials. A one-pot condensation/6π electrocyclization is followed by an intramolecular trapping of the 2,3-dihydroquinoline intermediate by nitrogen or oxygen nucleophiles to give bridged 7- and 8-membered products. Using 3-hydroxypyridinecarboxaldehydes result in a stable zwitterionic structure, which can undergo a diastereoselective reduction under hydrogenative conditions. A similar cyclisation/hydrogenation pathway with excellent diastereoselectivity is also demonstrated from 2-pyridyl substituted 1,2,3,4-tetrahydroquinolines.

Medium-sized heterocycles, particularly 7- and 8-membered nitrogen-heterocycles are widely prevalent in natural products and bioactive compounds. As such, their activity and preparation are subject to ongoing investigation in the pharmaceutical industry. Within this class of heterocycles, benzoxazocines and benzodiazepines are two of the most commonly encountered ring systems, being developed as treatments for depression, pain management,[1] MK2 inhibitors,[2] hepatitis C,[3] sonic hedgehog modulators,[4] anticancer agents[5] and T-type calcium channel blockers,[6] amongst others (**Figure 1a**).

Bridged heterocyclic rings represent complex three-dimensional structures, with unique geometries and increased rigidity. Owing to their complexity, many methods to prepare bridged heterocyclic compounds have been developed.[7] Many of these methods are not general and typically require significant pre-functionalization of starting materials, or complex multi-step syntheses. In recent years, several more general approaches have been reported to generate bridged oxazocine and diazepine structures, such as dearomatization,[7b, 8] [4+3] cycloaddition[9] and Michael-addition/cyclization methodologies,[10] enabling the design of natural product-resembling molecules in underexplored chemical space. Despite the increasing wealth of synthetic methods for the generation of complex three-dimensional molecular scaffolds, there remains a necessity for straightforward and broadly tolerant methods to generate ring systems that can be diversified and readily functionalized for structure-activity relationship exploration in drug discovery programmes. In this context, we previously reported the preparation of 1,2,3,4-tetrahydroquinolines through a visible light-mediated 6π-electrocyclization of diarylimines,[11] formed *in situ* from 2-vinylanilines and (hetero)aromatic aldehydes, in which the product of the cyclization reaction could be trapped by an alcoholic solvent. Building upon this methodology, we hypothesized that the *in situ* generation of the same intermediates could undergo intramolecular trapping from an appended nucleophile, giving alternative products containing 7- and 8-membered rings (**Figure 1b**).

Initial studies towards this goal used the commercially available 2-isopropenylaniline with 2-hydroxy-4-nitrobenzaldehyde in a one-pot condensation/electrocyclization/1,4-conjugate addition, under blue light-irradiation, yielding the desired benzo[1,5]oxazocine product **1** in 93% isolated yield. Control reactions and a brief solvent screen (see SI) found that DCE is the best solvent for this transformation. It was also noted that the superstoichiometric MeOH additive previously necessary for intermolecular trapping of the 6π intermediate did not compete with oxazocine formation, with no observation of the 4-methoxy-substituted tetrahydroquinoline. We had previously seen benefits in imine solubility and inhibition of oxidation pathways in the presence of MeOH, thus we concluded that its presence would aid generality of the reaction.

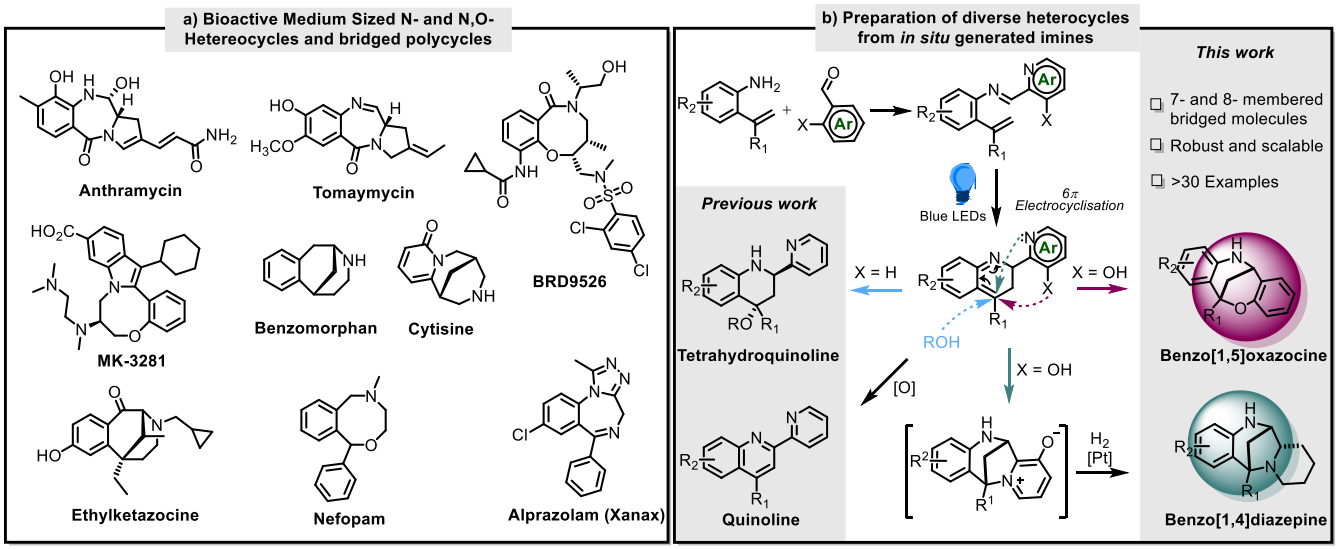
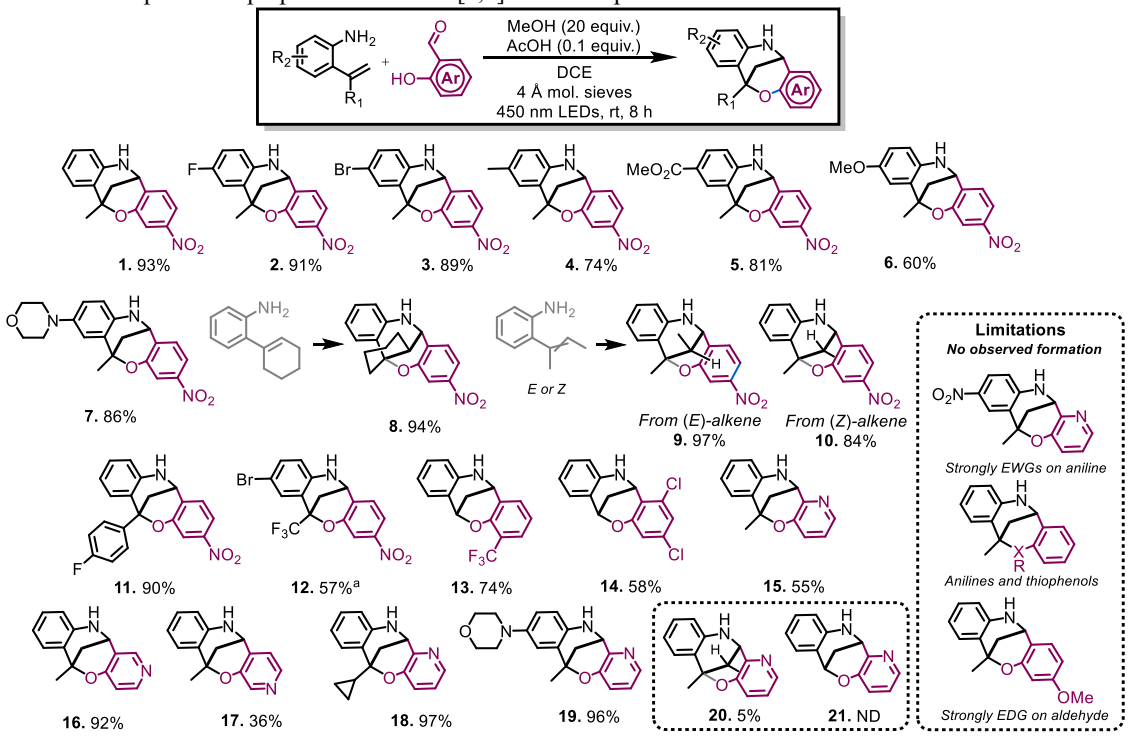


Figure 1. a) Examples of nitrogen and oxygen containing bioactive 7- and 8-membered polycyclic heterocycles. b) Previously reported visible light-mediated 6π-electrocyclization methodology for the preparation of 1,2,3,4-tetrahydroquinoline products and this work; a 6π-electrocyclization followed by intramolecular nucleophilic trapping by O- or N-nucleophiles.

Using our conditions, subsequent work explored the scope of this transformation with regards to both aniline and hydroxyaldehyde components (**Scheme 1**). Using 2-hydroxy-4-nitrobenzaldehyde, tolerance to variation of the substitution within the aniline was probed. Substitution with halogen (4-F, 4-Br), electron-donating (4-Me, 4-MeO) and electron-withdrawing (4-MeO_2C) groups all led to cyclization to the desired oxazocine in excellent yields (**2**-**7**). Using a trisubstituted alkene starting material introduces an additional stereocenter in products **8**-**10**. Notably single diastereomers are observed with the relative configuration at the bridgehead determined by the (*E*)- or (*Z*)-geometry of the starting alkene. Alternatively, substitution of the alkene with phenyl and trifluromethyl groups led to products **11** and **12** respectively, although a longer reaction time was necessary for the electron withdrawing -CF_3 substituent. Variation of the benzaldehyde condensation partner enabled the preparation of trifluoromethyl- and dichloro- products **13** and **14**. The use of regioisomeric pyridine substituted aldehydes could also be incorporated into the products (**15**-**17**). Quantitative yields of 6-cyclopropyl (**18**) and 8-morpholino-substituted (**19**) benzo[1,5]oxazoline products could also be obtained from prefunctionalized aniline substrates. Limitations of the reaction were also uncovered upon investigation of the substrate scope with, strongly electron-withdrawing groups on the aniline, as well as electron donating groups such as methoxy on the aldehyde inhibiting the electrocyclization. Nitrogen and sulfur-based trapping agents also did not lead to product formation.

Scheme 1. Substrate scope for the preparation of benzo[1,5]oxazocine products. [a]72h reaction time.



As part of the substrate scope exploration, a second product was formed with the use of pyridine-2-carboxaldehydes. In the preparation of **15**, a major byproduct was observed and isolated in 40% yield, whilst attempted generation of products **20** and **21** did not lead to the anticipated benzo[1,5]oxazoline as the major observed product. Instead, the major product of the reaction of 2-vinylaniline and 3-hydroxypyridine-2-carboxaldehyde was characterized as the zwitterionic structure **22** by a combination of 1D and 2D NMR spectroscopy experiments, indicating that cyclization to the bicycle had occurred through the pyridine nitrogen (**Figure 2a**). Experimental derivatization of this structure was performed through reactions of **22** in a Pt/C mediated hydrogenation of the pyridine to the corresponding piperidine fused product **23** as a single diastereomer, while treatment with ethyl chloroformate gave quantitative formation of pyridinium **24** in the absence of base (**Figure 2B**). Given the stability of **22** and ease of reduction of the pyridinium ring, these zwitterionic structures were proposed to act as an isolatable intermediate in a two-step synthesis of bridged benzo[1,4]diazepines.

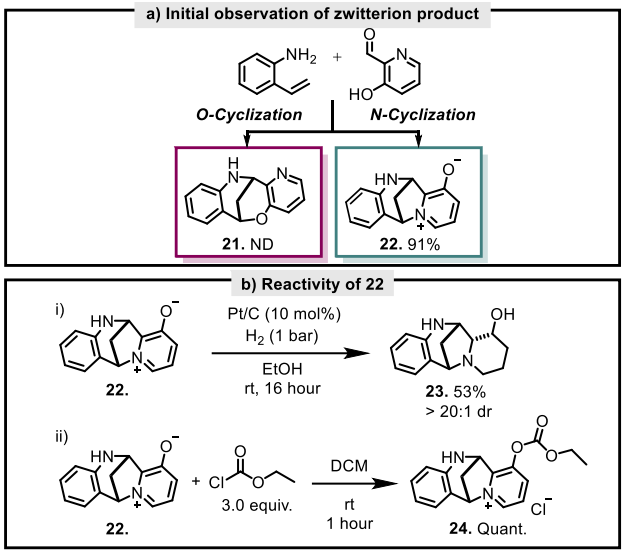
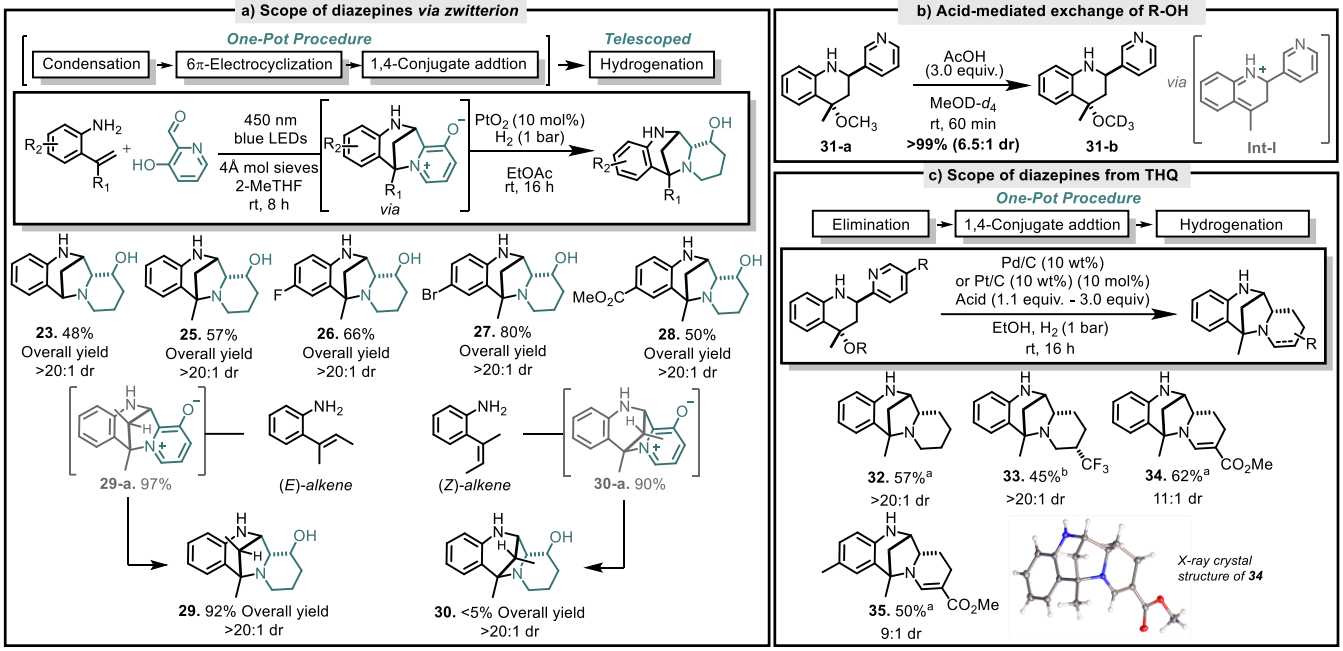


Figure 2. a) Expected and obtained products from 2-vinylaniline and 3-hydroxy-2-pyridinecarboxaldehyde condensation/cyclization. b) Reactivity of **22** towards i) hydrogenation and ii) nucleophilic substitution.

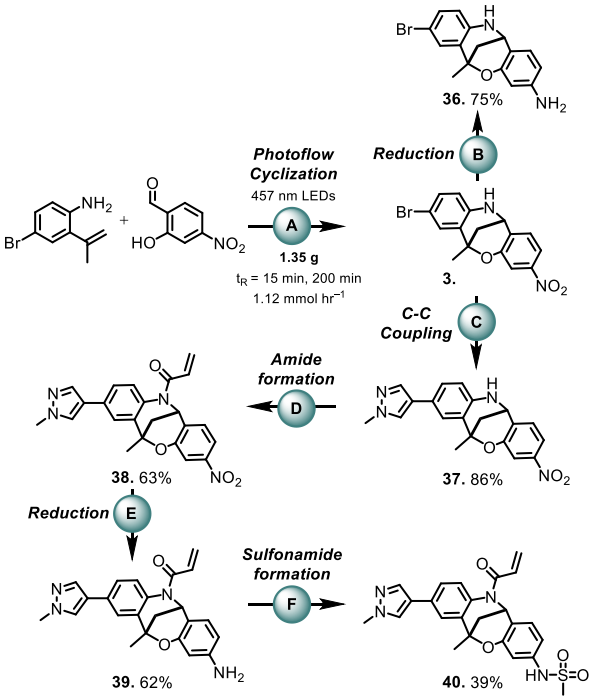
Based on the formation of these interesting bridged structures, further work explored the scope with regards to the multistep preparation of bridged benzo[1,4]diazepines (**Scheme 2a**). Following a short optimization, initial formation of zwitterionic products was identified as most efficient in 2-MeTHF. In the absence of MeOH, allowing for a simple filtration to isolate these intermediates as stable solids, which can be directly telescoped into the hydrogenation reactions. Using this protocol, substitution of mono- and di-substituted alkenes could be utilized within this procedure, with good overall yields for the corresponding diazepines, given the complexity of the products (**23, 25**). Simple substitution on the aniline ring was also well tolerated in products **26**-**28** with exceptional diastereoselectivity seen in all cases. Use of trisubstituted alkenes with an (*E*)- or (*Z*)-geometry successfully generated the stable intermediate zwitterionic species **29-a** and **30-a** respectively, in which the bridgehead methyl group is orientated towards the phenyl (**29-a**) or towards the pyridinium (**30-a**). Reduction of the pyridinium ring in **29-a** to **29** was facile, giving an excellent overall yield of the desired product, however **30** was not formed from **30-a** in appreciable yields, with the reaction sluggish and anticipated to be hindered by a steric effect of the bridgehead methyl. Considering the observed quaternization of the pyridine, subsequent studies explored alternative methods to utilize this reactivity to access diazepines.

A series of ^{1}H NMR experiments into the stability of 4-methoxy substituted tetrahydroquinolines, formed through our previously reported procedure, indicated that in the presence of acid, exchange of the -OR group could take place presumably via the iminium species **Int-I** (**Scheme 2b**). It was proposed that this exchange could be utilized through cyclization of the pendant pyridyl group into **Int-I**. The resultant pyridinium species could then be hydrogenated *in situ* to give bridged benzo[1,4]diazepine products. Using either heterogeneous palladium or platinium catalysts, exemplars of this method for the preparation of bridged benzo[1,4]diazepine products from tetrahydroquinoline starting materials is demonstrated in **Scheme 2c**, whereby partial or full reduction of the pyridine ring was observed. This reaction can be used for the generation of alternative substitution on the newly formed ring. The products were formed with excellent diastereoselectivity, with the relative configuration within **34** confirmed by single crystal X-ray diffraction.

Scheme 2. Substrate scope for the preparation of benzo[1,4]diazepine products. a) Multistep procedure from aldehyde and aniline starting materials. b) Exchange of alcohol observed in the presence of AcOH. c) Examples demonstrating hydrogenation from tetrahydroquinolines to 1,4-diazepines. [a]Pd/C (10 mol%), AcOH (3.0 equiv.). [b]Pt/C (10 mol%), diphenylphosphate (1.1 equiv.).



Scheme 3. Preparation of **3** using photoflow conditions, followed by iterative functionalization reactions for diversification to drug-like molecule **40**. a) Aniline (1 equiv.), aldehyde (1.1 equiv.), AcOH (10 mol%), MeOH (20 equiv.), DCE, 457 nm LEDs, 25 °C, t_R = 15 min. b) **3** (1 equiv.), Pt/C (10 mol%), H_2 (1 bar), DCM, 25 °C. c) **3** (1 equiv), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (1.2 equiv.), Cs_2CO_3 (3 equiv.), Pd(dppf)Cl_2.DCM (5 mol%), 1,4-dioxane/H_2O (2:1), 90 °C. d) **37** (1 equiv.), acryloyl chloride (1.1 equiv.), Et_3N (2 equiv.), THF, 0 °C. e) **38** (1 equiv.), Fe powder (10 equiv.), NH_4Cl (20 equiv.), THF/MeOH/H_2O (4:2:1), 90 °C. f) **39** (1 equiv.), MsCl (2 equiv.), pyridine (1.8 equiv.), DCM, 90 °C.



We believed that the reaction could be suited to continuous flow conditions and set out to scale up using a photoflow reactor, demonstrating a proof-of-principle gram scale generation of **3** using a commercially available reaction set-up. From **3**, using typical batch conditions, orthogonal functionalization is possible to give aniline product **36** or the pyrazole-bearing **37**, through hydrogenation and cross-coupling respectively. Further reactions such as amidation (**38**), iron-mediated reduction (**39**) and introduction of a sulfonamide were performed to prepare **40** indicating the feasibility of functionalizing the reactive sites using commonly found reactions used in the synthesis of pharmaceutically relevant compounds (**Scheme 3**).

In conclusion, the development of cascade cyclization procedures for the preparation of bridged benzo[1,5]oxazocine and benzo[1,4]diazepine products from simple aniline and aromatic aldehydes is reported. The reactions are high-yielding and generate complex, saturated heterocyclic ring systems with multiple vectors for further functionalization. A proof-of-principle synthesis of multigram quantities of the products using a photoflow setup followed by functionalization of reactive handles to access drug-like molecules was demonstrated. This chemistry will provide access to previously underexplored ring systems which are relevant in medicinal chemistry.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Procedures, structural analysis and NMR spectra for new and for some known compounds (PDF)

Accession Codes

Accession Code CCDC 2277416 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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REFERENCES

[1] S. Mitra, T. S. Banerjee, S. K. Hota, D. Bhattacharya, S. Das, P. Chattopadhyay, *Eur. J. Med. Chem.* **2011**, *46*, 1713-1720.

[2] A. U. Rao, D. Xiao, X. Huang, W. Zhou, J. Fossetta, D. Lundell, F. Tian, P. Trivedi, R. Aslanian, A. Palani, *Bioorg. Med. Chem. Lett.* **2012**, *22*, 1068-1072.

[3] F. Narjes, B. Crescenzi, M. Ferrara, J. Habermann, S. Colarusso, M. del Rosario Rico Ferreira, I. Stansfield, A. C. Mackay, I. Conte, C. Ercolani, S. Zaramella, M.-C. Palumbi, P. Meuleman, G. Leroux-Roels, C. Giuliano, F. Fiore, S. Di Marco, P. Baiocco, U. Koch, G. Migliaccio, S. Altamura, R. Laufer, R. De Francesco, M. Rowley, *J. Med. Chem.* **2011**, *54*, 289-301.

[4] a) G. I. Schaefer, J. R. Perez, J. R. Duvall, B. Z. Stanton, A. F. Shamji, S. L. Schreiber, *J. Am. Chem. Soc.* **2013**, *135*, 9675-9680; b) G. Liu, W. Huang, J. Wang, X. Liu, J. Yang, Y. Zhang, Y. Geng, W. Tan, A. Zhang, *J. Med. Chem.* **2017**, *60*, 8218-8245.

[5] a) I. Chatterjee, K. Ali, G. Panda, *ChemMedChem* **2023**, *18*, e202200617; b) K. N. V. Sastry, S. R. Routhu, S. G. Datta, N. Nagesh, B. N. Babu, J. B. Nanubolu, C. G. Kumar, R. A. Maurya, A. Kamal, *Org. Biomol. Chem.* **2016**, *14*, 9294-9305.

[6] R. Siegrist, D. Pozzi, G. Jacob, C. Torrisi, K. Colas, B. Braibant, J. Mawet, T. Pfeifer, R. de Kanter, C. Roch, M. Kessler, O. Corminboeuf, O. Bezençon, *J. Med. Chem.* **2016**, *59*, 10661-10675.

[7] a) S. Bera, B. Chatterjee, D. Mondal, *Eur. J. Org. Chem.* **2018**, *2018*, 5337-5354; b) J. A. Leitch, T. Rogova, F. Duarte, D. J. Dixon, *Angew. Chem. Int. Ed.* **2020**, *59*, 4121-4130; c) T. Wu, W. Tang, *Chem. Eur. J.* **2021**, *27*, 3944-3956.

[8] a) S. Mondal, R. Paira, A. Maity, S. Naskar, K. B. Sahu, A. Hazra, P. Saha, S. Banerjee, N. B. Mondal, *Tetrahedron Lett.* **2011**, *52*, 4697-4700; b) Y.-Q. Gao, Y. Hou, L. Zhu, J. Chen, R. Li, S.-Y. Zhang, Y.-P. He, W. Xie, *Chem. Commun.* **2020**, *56*, 6739-6742; c) Z. Zhang, H. Han, L. Wang, Z. Bu, Y. Xie, Q. Wang, *Org. Biomol. Chem.* **2021**, *19*, 3960-3982.

[9] a) H. Lam, Z. Qureshi, M. Wegmann, M. Lautens, *Angew. Chem. Int. Ed.* **2018**, *57*, 16185-16189; b) J. Feng, M. Zhou, X. Lin, A. Lu, X. Zhang, M. Zhao, *Org. Lett.* **2019**, *21*, 6245-6248.

[10] a) G. Yin, T. Ren, Y. Rao, Y. Zhou, Z. Li, W. Shu, A. Wu, *J. Org. Chem.* **2013**, *78*, 3132-3141; b) R. Gurubrahamam, K. Nagaraju, K. Chen, *Chem. Commun.* **2018**, *54*, 6048-6051; c) B. S. Vachan, M. Karuppasamy, G. Jan, N. Bhuvanesh, C. U. Maheswari, V. Sridharan, *J. Org. Chem.* **2020**, *85*, 8062-8073.

[11] G. J. Sherborne, P. Kemmitt, C. Prentice, E. Zysman-Colman, A. D. Smith, C. Fallan, *Angew. Chem. Int. Ed.* **2023**, *62*, e202207829.