Biological Activity

International Edition: DOI: 10.1002/anie.201810312
German Edition: DOI: 10.1002/ange.201810312

Furo[3,2-*b*]pyridine: A Privileged Scaffold for Highly Selective Kinase Inhibitors and Effective Modulators of the Hedgehog Pathway

*Václav Němec, Michaela Hylsová, Lukáš Maier, Jana Flegel, Sonja Sievers, Slava Ziegler, Martin Schroeder, Benedict-Tilman Berger, Apirat Chaikuad, Barbora Valčíková, Stjepan Uldrijan, Stanislav Drápela, Karel Souček, Herbert Waldmann, Stefan Knapp, and Kamil Paruch**

Abstract: *Reported is the identification of the furo[3,2-b]pyridine core as a novel scaffold for potent and highly selective inhibitors of cdc-like kinases (CLKs) and efficient modulators of the Hedgehog signaling pathway. Initially, a diverse target compound set was prepared by synthetic sequences based on chemoselective metal-mediated couplings, including assembly of the furo[3,2-b]pyridine scaffold by copper-mediated oxidative cyclization. Optimization of the subseries containing 3,5-disubstituted furo[3,2-b]pyridines afforded potent, cell-active, and highly selective inhibitors of CLKs. Profiling of the kinase-inactive subset of 3,5,7-trisubstituted furo[3,2-b]pyridines revealed sub-micromolar modulators of the Hedgehog pathway.*

Small molecules represent the majority of clinically profiled compounds[1] and identification of privileged scaffolds applicable in the synthesis of compounds with specific biological activity thus represents a key tool in chemical biology and drug discovery.[2] As numerous major post-translational signaling mechanisms in the cell rely on phosphorylation, protein kinases represent one of the therapeutically most important target classes.[3] Modulation of kinase activity can be utilized in modern anticancer therapy as well as in the treatment of other diseases. Currently over 40 small-molecule protein kinase inhibitors have been approved by the FDA for clinical use.[4] While the biological functions of few protein kinases have been thoroughly explored, the role of many others in signaling and their potential as drug targets is largely unexplored. Identification of potent and selective modulators of these kinases as chemical probes for functional studies (and as potential starting points for medicinal chemistry optimization) is therefore of significant importance.[5]

The majority of small-molecule protein kinase inhibitors are ATP mimetics, frequently containing heteroaromatic bioisosteres of purine. Interestingly, similar scaffolds can yield inhibitors with significantly different inhibitory activity.[6] While pyrazolo[1,5-*a*]pyrimidine represents a privileged scaffold,[7] kinase inhibitors possessing analogous furo[3,2-*b*]pyridine motif are very rare, as they are not typical ATP mimetic moieties. To date, only few examples of this scaffold have been published with a rather narrow substitution pattern.[8] In this report, we describe the identification of the furo[3,2-*b*]pyridine core as the central scaffold for two novel structurally related compound classes with distinct biological activity: highly selective inhibitors of cdc-like kinases (CLKs) and potent modulators of the Hedgehog pathway.

Initially, we prepared a small library of structurally diverse target compounds consisting of 3,5-disubstituted, 5,7-disubstituted and 3,5,7-trisubstituted furo[3,2-*b*]pyridines (**7**; Scheme 1).

Assembly of the furo[3,2-*b*]pyridine core by precedented intramolecular Heck[9] and Sonogashira[10] reactions proceeded uneventfully and provided the intermediates **2** and **4**. The compound **2** was converted into **3** (Scheme 1). Of note, chlorination of the N-oxide intermediate provided a significant part of the 2-chloro regioisomer. For compounds lacking substituents at position 3 (e.g., the desilylated N-oxide of **5**; see compound **S6** in the Supporting Information), the chlorination was even more problematic and it exclusively yielded the undesired 2-chloro isomer. In contrast, chlorination of the TMS-containing N-oxide of **5** (see compound **S7**) proceeded well and ultimately provided the desired **6** in good yield. Final amination and Suzuki couplings with the chlorides

[*] V. Němec, Dr. M. Hylsová, Dr. L. Maier, Prof. Dr. K. Paruch
Department of Chemistry, CZ-Openscreen
Masaryk University
Kamenice 5, Brno, 625 00 (Czech Republic)
E-mail: paruch@chemi.muni.cz

V. Němec, Dr. M. Hylsová, Dr. L. Maier, B. Valčíková, Dr. S. Uldrijan, S. Drápela, Dr. K. Souček, Prof. Dr. K. Paruch
International Clinical Research Centre
St. Anne's University Hospital
Pekařská 53, Brno, 656 91 (Czech Republic)

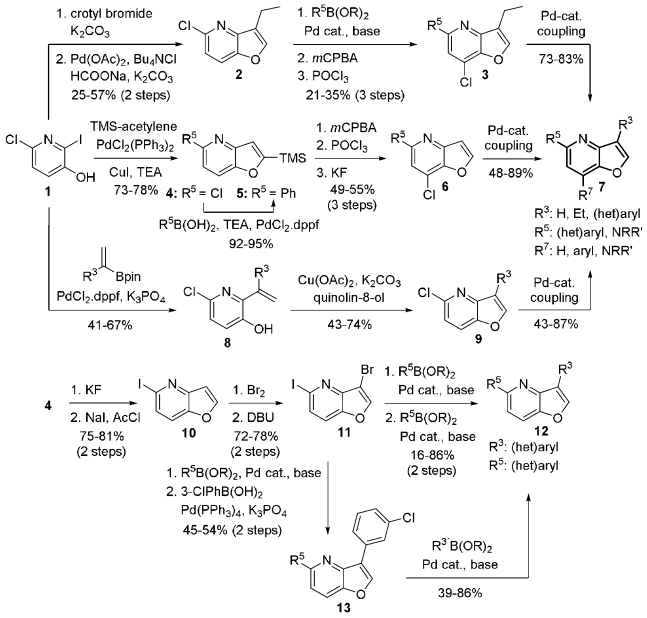
J. Flegel, Dr. S. Sievers, Dr. S. Ziegler, Prof. Dr. H. Waldmann
Max-Planck-Institute für Molekulare Physiologie
Abteilung Chemische Biologie
Otto-Hahn-Strasse 11, 44227 Dortmund (Germany)

M. Schroeder, B. T. Berger, Dr. A. Chaikuad, Prof. Dr. S. Knapp
Institute for Pharmaceutical Chemistry
Structural Genomics Consortium
Johann Wolfgang Goethe-University
Max-von-Laue-Strasse 15, 60438 Frankfurt am Main (Germany)

B. Valčíková, Dr. S. Uldrijan
Department of Biology, Faculty of Medicine
Masaryk University
Kamenice 5, Brno, 625 00 (Czech Republic)

S. Drápela, Dr. K. Souček
Department of Cytokinetics, Institute of Biophysics CAS
Královopolská 135, Brno, 612 65 (Czech Republic)

Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under: https://doi.org/10.1002/anie.201810312.



Scheme 1. Synthesis of an initial library of the substituted furo[3,2-*b*]pyridines **7** and modular assembly of the CLK inhibitors **12**. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, dppf = 1,1′-bis(diphenylphosphanyl)ferrocene, *m*CPBA = *m*-chloroperbenzoic acid, TEA = triethylamine, TMS = trimethylsilyl.

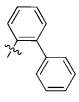
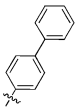
3 and **6** provided subsets of the compound **7** with N- and C-linked substituents at position 7.

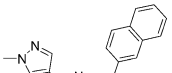
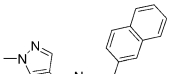
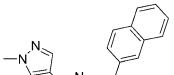
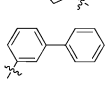
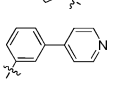
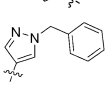
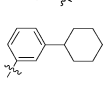
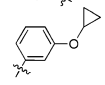
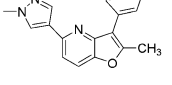
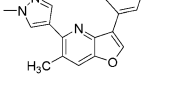
The synthesis of furo[3,2-*b*]pyridines with (hetero)aryls directly attached to position 3 proved more challenging. This particular compound class was neither known at that point nor available by directly applicable synthetic route. However, we were able to prepare the desired chloro compounds **9** (Scheme 1) using a slightly modified version of the Cu-mediated cyclization reported for benzofurans,[11] and subsequently converted these cyclization products into the corresponding target compounds **7a–h** (Table 1).

The three routes depicted in Scheme 1 provided a starting library of 20 compounds, and they were profiled against a panel of 206 human protein kinases at 1 μM concentration (Eurofins). In addition, IC_{50} values of the compounds **7i–k** and **7m–o**, analogues of known pyrazolo[1,5-*a*]pyrimidine-based inhibitors of CDK2[12] and PIM[13] kinases, were also determined. The CDK2 and PIM furo[3,2-*b*]pyridine inhibitors **7i–k** and **7m–o** were significantly less potent than the corresponding pyrazolo[1,5-*a*]pyrimidines (see Table S1 A and S1 B in the Suppporting Information). However, broad kinase panel profiling revealed that **7c** possesses attractive activity against members of the CLK and HIPK family (Table 1; see Tables S2 and S3).

CLK kinases regulate alternative mRNA splicing but their precise role in this process is poorly understood,[14] and CLK2 is an emerging therapeutic target in oncology.[15] To unravel the role of CLK kinases in splicing, selectivity of chemical inhibitors within the highly conserved splicing kinases subfamily, which includes CLKs, DYRKs, and

Table 1: IC_{50} values[a] for the selected compounds **7a–h** (R^7 = H) and **12a–j**.

Comp.	7a	7b	7c	7d	7e	7f	12a	12b	7g	7h	12c	12d
R^5												
R^3	H	Et										
CLK1	578	260	72	>3000	627	75	529	109	924	>3000	>3000	>3000
CLK2	2010	405	132	>3000	1114	69	>3000	106	2377	1282	>3000	>3000
CLK3	>3000	>3000	>3000	>3000	>3000	>3000	>3000	>3000	>3000	>3000	>3000	>3000
CLK4	645	345	63	>3000	369	52	1009	113	1058	4083	>3000	>3000
DYRK2	>3000	>3000	1000	>3000	>3000	>3000	>3000	>3000	>3000	>3000	>3000	>3000
HIPK1	>3000	>3000	861	>3000	2502	148	1099	127	>3000	>3000	>3000	>3000

Comp.	12e	12f	12g	12h	12i	12j	14	15	16
R^5									
R^3									
CLK1	9	8	10	9	49	16	>3000	1708	662
CLK2	21	20	15	55	59	5	>3000	664	>3000
CLK3	>3000	>3000	2299	>3000	>3000	>3000	>3000	>3000	>3000
CLK4	10	12	15	8	53	17	>3000	1325	698
DYRK2	>3000	1309	2013	>3000	>3000	>3000	>3000	>3000	>3000
HIPK1	278	187	199	768	1838	154	>3000	>3000	>3000

[a] All compounds were tested at Eurofins. Additional compounds are listed in Table S2.

SRPKs, would be required. However, the few reported examples of specific inhibitors for splicing kinases often retain dual activities of CLK and DYRK activity,[16] reflecting their highly conserved ATP binding pocket. We were intrigued by the lack of activity of the hit **7c** for the closely related DYRKs, whose inhibition may not always be therapeutically desirable,[17] and its exclusive selectivity within the splicing kinases for the CLKs. We thus steered the subsequent structure–activity relationship (SAR) optimization towards the development of potent and selective CLK inhibitors.

By the third route depicted in Scheme 1, we prepared an additional set of (16) 3,5-disubstituted furo[3,2-*b*]pyridines. For position 5, the 1-methyl-1*H*-pyrazol-4-yl motif was identified as optimal, whereas relatively large substituents (e.g. 2-naphthyl in compound **7f**) were preferred at position 3 (Table 1; see Table S2).

Since the most active hits contained (hetero)aryls at positions 3 and 5 of the furo[3,2-*b*]pyridine scaffold, we focused on the SAR development within this subseries. We envisioned that chemoselective manipulation of properly 3,5-dihalogenated furopyridines could provide a rapid and flexible access to these target compounds. However, Suzuki couplings of known the 3-bromo-5-chlorofuro[3,2-*b*]pyridine[18] under a variety of reaction conditions provided only practically inseparable mixtures of several components. Fortunately, Pd-catalyzed chemoselective couplings with newly prepared 3-bromo-5-iodofuro[3,2-*b*]pyridine (**11**) were successful and provided the desired intermediates with (hetero)-aryl substituents at position 5, and were finally converted into the additional target compounds **12** (Scheme 1). Additional analogues were flexibly prepared from the *m*-chlorophenyl intermediate **13**. Profiling of this set (59 compounds) revealed additional SAR trends (Table 1; see Table S2): 1. Analogues containing aromatic motifs with properly oriented substituents were found to be particularly active with high overall selectivity (see Table S4); 2. In contrast, the CLK inhibitory activity rapidly decreased upon increasing steric bulk (methylation) at positions 2, 6, or 7 (**14**–**16**); and also around the heterocycle at position 5 (**7g**–**h**).

X-ray crystal structures of **12h**, **12k**, **12l**, and **12m** in CLK1 (Figure 1A; see Figure S1) provided insight into the binding mode of this unusual ATP mimetic furopyridine scaffold and served as the basis for advanced SAR development. All inhibitors showed a conserved binding mode with CLK1 and, in contrast to most ATP competitive kinase inhibitors, they were anchored to the back pocket rather than the hinge region. The furo[3,2-*b*]pyridine served as only a weak ATP mimetic forming a single hydrogen bond between the furane oxygen and the main-chain L244, while in the backpocket the methylpyrazole group interacted with the catalytic Lys191. The structural data highlighted the advantage of weak ATP mimetic hinge interaction for selectivity: in comparison to the furo[3,2-*b*]pyridine **12j**, indeed, the stronger hinge binder pyrazolo[1,5-*a*]pyrimidine analogue (**S53**) showed comparable activity against CLKs but significantly worse selectivity (see Figure S2 and Table S5).

Kinome-wide screening and cell profiling revealed that **12f** was the most selective analogue with good activity in the cell (cellular BRET for CLK1 $IC_{50} = 51$ nM; Figures 1B,C; see

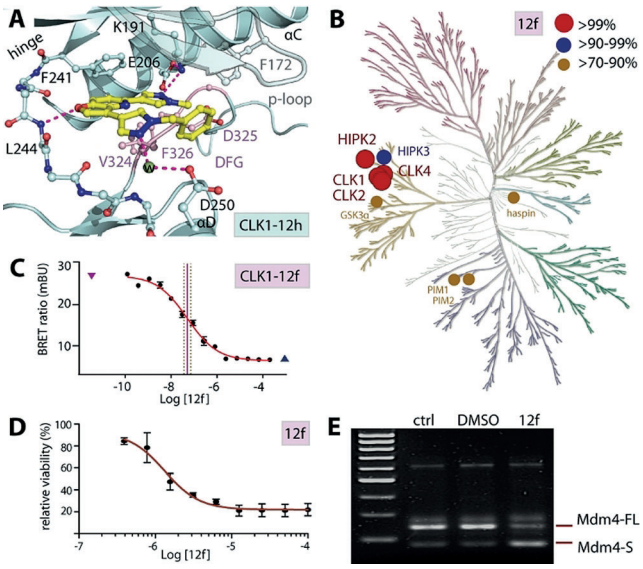
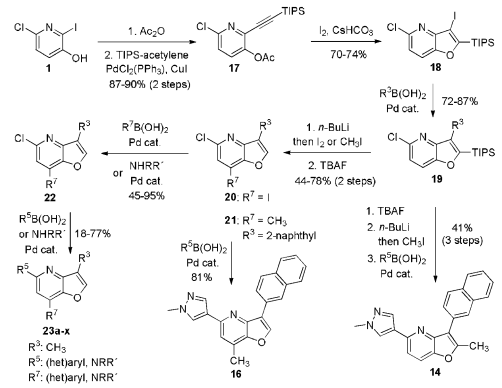


Figure 1. Characterization of furo[3,2-*b*]pyridine derivatives in CLK1. A) crystal structure reveals the binding mode of compound **12h** in CLK1 (pdb id 6I5I). B) Kinome tree representation of the selectivity of the lead compound **12f**. % Inhibition in enzyme kinetic assays is shown as sheres as indicated in the Figure capture. C) On-target activity of **12f** in CLK1 determined by NanoBRET assay. ▼ for control with no compound, and ▲ for background signal (see the Supporting Information for method). D) Cytotoxicity of **12f** for the breast cancer cell line MCF7. E) Modulation of alternative mRNA splicing of *Mdm4* detected by PCR.

Tables S6 and S7). Activity against off-target HIPKs was rather surprising, nonetheless in vitro kinase assays confirmed greater than 20-fold weaker affinities than for CLKs. In accordance with the previous reports on the role of CLKs in the splicing process,[19] we observed that **12f** profoundly affected the *Mdm4* alternative splicing and showed high activity in cytotoxicity assays using MCF7 breast cancer cells (Figure 1D,E; see Table S8). In addition, **12f** also has favorable pharmacokinetics (mouse, 10 mpk, IP: $C_{max} =$ 1.24 μM, $T_{1/2} = 58$ min; no acute toxicity observed), suggesting its potential use in in vivo models. Given its overall selectivity profile as well as its cellular activities, **12f** can be considered a quality probe[20] for CLK1, CLK2, and CLK4.

The observations summarized above served also as the basis for the design of a kinase-inactive furo[3,2-*b*]pyridine sub-library that was additionally profiled in a different biological context to explore potential applications of this series (see below). In addition, the set also contained compounds that could be used as negative controls for direct comparison for the on-target inhibitions of **12f**.

Specifically, we focused on manipulation of position 7, installing C- and N-linked substituents to prevent interaction with kinases. To produce target compounds **23**, we further utilized the route originally developed to prepare **16** (Scheme 2). Iodocyclization of the Sonogashira intermediate **17** provided **18**, which was selectively manipulated at position 3 by Pd-catalyzed couplings. Of note, the regioselectivity of the subsequent functionalization of position 7 again depended on the presence of the protecting group at position 2, while the TIPS-protected **19** was lithiated (and subsequently



Scheme 2. Synthesis of kinase-inactive sub-series **23** by regioselective lithiation. TBAF = tetra-*n*-butylammonium fluoride, TIPS = triisopropylsilyl.

methylated or iodinated) at position 7, the desilylated version of **19** (i.e. compound **9b**, R^3 = 2-naphthyl) underwent lithiation at position 2 and upon methylation provided the target compound **14**.

Investigation of activity in different cellular pathways revealed that the compounds **23** are nontoxic sub-micromolar inhibitors of the Hedgehog (Hh) pathway (see Table S9), and are crucial for embryonic development and tissue regeneration.[21] Binding of a Hh ligand to the transmembrane receptor Patched1 (PTC1) leads to the abrogation of Smoothened (SMO) suppression and its accumulation in the primary cilium. Subsequently, GLI transcription factors translocate into the nucleus and initiate the transcription of Hh specific genes.[21] Aberrant activation of Hh signaling is involved in medulloblastoma and basal cell carcinoma.[22] In an osteoblast differentiation assay using C3H10T1/2 cells for primary screening,[23,24] the most active compound, **23a** (Figure 2a), suppressed Hh-dependent osteogenesis with an IC_{50} of 300 ± 100 nM. In an orthogonal, GLI-dependent reporter gene assay using Shh-LIGHT2 cells **23a** inhibited the GLI-mediated response with an IC_{50} of 400 ± 100 nM (Figure 2b). In accordance with this observation, reverse-transcription quantitative PCR analysis (RT-qPCR) revealed that **23a** at a concentration of 0.5 μM reduces the expression of the Hh target genes *Gli1* and *Ptch1* by 55% and 63%, respectively (Figure 2c).

Most of the currently known Hh inhibitors target SMO.[25] In a competition experiment with the SMO antagonist BODIPY-cyclopamine, after treatment of cells with 30 μM **23a**, BODIPY-cyclopamine related fluorescence was not observed (Figure 2e). Quantitative analysis by flow cytometry (Figure 2d) proved this observation, and confirmed **23a** as a SMO binder.

In the Thermo Fisher SelectScreen kinase panel (454 kinases), **23a** inhibited only 5 kinases to 40–60% at 10 μM concentration (see Table S10A and S10B). It can be thus estimated that the corresponding IC_{50} values are at least tenfold higher than the effective concentration of the compound in the cell (Figure 2). Kinase off-target effects therefore should not be responsible for the observed cellular activity.

In summary, our synthetic methodology enables modular construction of furo[3,2-*b*]pyridines. Within the 3,5-disubsti-

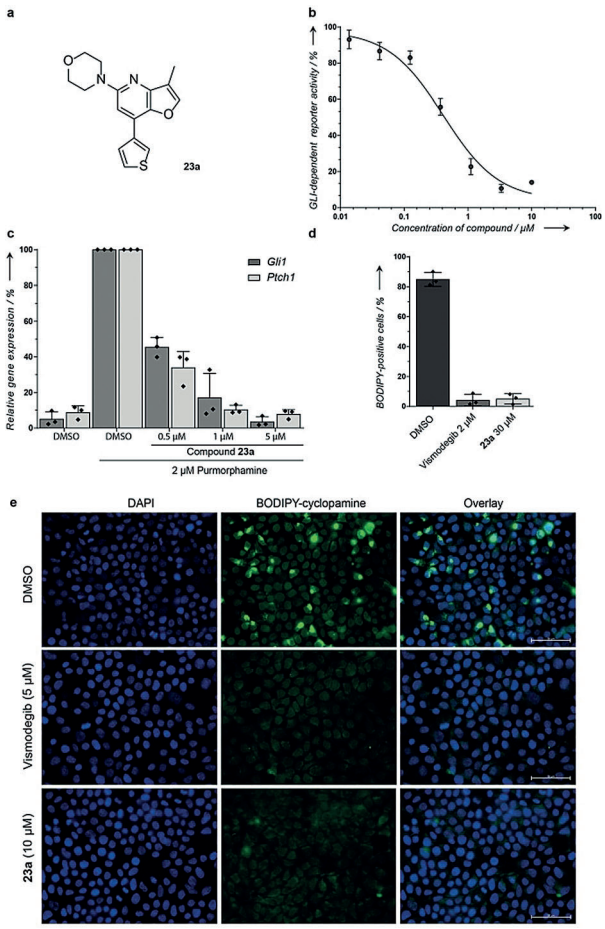


Figure 2. **23a** inhibits Hh signaling: a) Structure of **23a**. b) GLI-dependent reporter gene assay. Shh-LIGHT2 cells were treated with 2 μM purmorphamine and different concentrations of **23a** or DMSO as a control for 48 h prior to detection of Firefly (Fluc) and Renilla (Rluc) luciferase activity. The signal of the GLI-responsive Firefly luciferase was divided by the control signal of the Renilla luciferase. The value for cells which were treated with purmorphamine and DMSO, was set to 100%. Data are mean values of three biological replicates ± SD. c) RT-qPCR analysis of Hh target gene expression. NIH-3T3 cells were treated with 2 μM purmorphamine and different concentrations of the compound or DMSO as a control, for 48 h. After isolation of RNA and reverse transcription, qPCR was performed using primer for *Gli1* and *Ptch1* and *Gapdh* as a reference. Data were related to the value for cells, which were treated with DMSO, which was set to 100%. Data are mean values ± SD ($n = 3$). d) Quantitative SMO binding assay. HEK293T cells ectopically expressing SMO-BFP were treated with 5 nM BODIPY-cyclopamine and **23a** (30 μM) or vismodegib (5 μM) and DMSO as controls for 4 h. Cells were then analyzed by means of flow cytometry to quantify the BODIPY-cyclopamine fluorescence. Data are presented as the fraction of BODIPY-cyclopamine positive cells, of all transfected cells (BFP-positive) and are mean values ± SD of three biological replicates. e) Qualitative SMO binding assay. HEK293T cells ectopically expressing SMO were fixed and treated with 5 nM BODIPY-cyclopamine (green) and **23a** (30 μM) or vismodegib (5 μM) and DMSO as controls. To visualize the nuclei, cells were stained with DAPI (blue). Scale bar: 50 μm.

tuted subseries we identified potent and highly selective inhibitors of CLKs, exemplified by **12f** (**MU1210**). Activity of this series could be also optimized for other kinases such as HIPK and Haspin, as well as PIM which were identified as targets in selectivity screens of some analogues.

The structural and medicinal chemistry optimization highlights the utility of weak hinge binding motifs resulting in favorable selectivity profiles by interacting with the less conserved back pocket of kinases. Profiling of the kinase-inactive 3,5,7-trisubstituted subclass led to identification of **23a** (**MU1300**), a new effective modulator of the Hedgehog pathway.

Acknowledgements

The work was supported by the following grants: CZ-OPEN-SCREEN: National Infrastructure for Chemical Biology (Identification code: LM2015063), Preclinical Progression of New Organic Compounds with Targeted Biological Activity (CZ CZ.02.1.01/0.0/0.0/16_025/0007381), MUNI/E/0456/2018, and the National Program of Sustainability II (MEYS CR, project No. LQ1605). B-T.B., M.S., A.C., and S.K. are grateful for support by the SGC, a registered charity supported by AbbVie, Bayer Pharma AG, Boehringer Ingelheim, Canada Foundation for Innovation, Eshelman Institute for Innovation, Genome Canada, Innovative Medicines Initiative (EU/EFPIA) [ULTRA-DD 115766], Janssen, Merck KGaA, MSD, Novartis Pharma AG, Ontario Ministry of Economic Development and Innovation, Pfizer, São Paulo Research Foundation-FAPESP, Takeda, and Wellcome. A.C. is supported by the DFG network grant "Autophagy" SFB1177.

Conflict of interest

The authors declare no conflict of interest.

Keywords: biological activity · chemical probes · heterocycles · inhibitors · kinases

[1] 2017/2018 Parexel Biopharmaceutical R&D Statistical Sourcebook, PAREXEL International Corporation, Waltham, **2017**.
[2] a) H. Zhao, J. Dietrich, *Expert Opin. Drug Discovery* **2015**, *10*, 781 – 790; b) P. Schneider, G. Schneider, *Angew. Chem. Int. Ed.* **2017**, *56*, 7971 – 7974; *Angew. Chem.* **2017**, *129*, 8079 – 8083; c) C. D. Altomare, *Chem. Heterocycl. Comp.* **2017**, *53*, 239 and other subsequent articles in this thematic issue.
[3] R. Roskoski, *Pharmacol. Res.* **2015**, *100*, 1 – 23.
[4] a) http://www.brimr.org/PKI/PKIs.htm; b) J. M. Elkins, V. Fedele, M. Szklarz, K. R. A. Azeez, E. Salah, J. Mikolajczyk, S. Romanov, N. Sepetov, X. P. Huang, B. L. Roth, A. A. H. Zen, D. Fourches, E. Muratov, A. Tropsha, J. Morris, B. A. Teicher, M. Kunkel, E. Polley, K. E. Lackey, F. L. Atkinson, J. P. Overington, P. Bamborough, S. Müller, D. J. Price, T. M. Willson, D. H. Drewry, S. Knapp, W. J. Zuercher, *Nat. Biotechnol.* **2016**, *34*, 95 – 103.
[5] F. M. Ferguson, N. S. Gray, *Nat. Rev. Drug Discovery* **2018**, *17*, 353 – 376.
[6] a) R. Jorda, K. Paruch, V. Kryštof, *Curr. Pharm. Des.* **2012**, *18*, 2974 – 2980; b) P. Ciceri, S. Müller, A. O'Mahony, O. Fedorov, P. Filippakopoulos, J. P. Hunt, E. A. Lasater, G. Pallares, S. Picaud, C. Wells, S. Martin, L. M. Wodicka, N. P. Shah, D. K. Treiber, S. Knapp, *Nat. Chem. Biol.* **2014**, *10*, 305 – 312.
[7] a) S. Cherukupalli, R. Karpoormath, B. Chandrasekaran, G. A. Hampannavar, N. Thapliyal, V. N. Palakollu, *Eur. J. Med. Chem.* **2017**, *126*, 298 – 352; b) F. P. Lim, A. V. Dolzhenko, *Eur. J. Med. Chem.* **2014**, *85*, 371 – 390.
[8] a) L. Burgdorf, M. Schultz, T. Hofmann, B. Hodous, J. Potnick, A. E. Sutton, B. R. Huck , WO2012025187A2; b) L. Burgdorf, T. Ross, C. Deutsch , WO2013124025A1.
[9] B. M. Mathes, S. A. Filla, *Tetrahedron Lett.* **2003**, *44*, 725 – 728.
[10] a) A. Chartoire, C. Comoy, Y. Fort, *Tetrahedron* **2008**, *64*, 10867 – 10873; b) A. Jasselin-Hinschberger, C. Comoy, A. Chartoire, Y. Fort, *Eur. J. Org. Chem.* **2015**, 2321 – 2331.
[11] M. J. Moure, R. SanMartin, E. Dominguez, *Angew. Chem. Int. Ed.* **2012**, *51*, 3220 – 3224; *Angew. Chem.* **2012**, *124*, 3274 – 3278.
[12] K. Paruch, M. P. Dwyer, C. Alvarez, C. Brown, T. Y. Chan, R. J. Doll, K. Keertikar, C. Knutson, B. McKittrick, J. Rivera, R. Rossman, G. Tucker, T. O. Fischmann, A. Hruza, V. Madison, A. A. Nomeir, Y. Wang, E. Lees, D. Parry, N. Sgambellone, W. Seghezzi, L. Schultz, F. Shanahan, D. Wiswell, X. Xu, Q. Zhou, R. A. James, V. M. Paradkar, H. Park, L. R. Rokosz, T. M. Stauffer, T. J. Guzi, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6220 – 6223.
[13] M. P. Dwyer, K. Keertikar, K. Paruch, C. Alvarez, M. Labroli, C. Poker, T. O. Fischmann, R. Mayer-Ezell, R. Bond, Y. Wang, R. Azevedo, T. J. Guzi, *Bioorg. Med. Chem. Lett.* **2013**, *23*, 6178 – 66182.
[14] A. S. Deshmukh, M. Agarwal, S. K. Dhar, *Curr. Genet.* **2016**, *62*, 481 – 486.
[15] a) S. Y. Park, Y. Piao, C. Thomas, G. N. Fuller, J. F. de Groot, *Oncotarget* **2016**, *7*, 26793 – 26805; b) T. Yoshida, J. H. Kim, K. Carver, Y. Su, S. Weremowicz, L. Mulvey, S. Yamamoto, C. Brennan, S. Mei, H. Long, J. Yao, K. Polyak, *Cancer Res.* **2015**, *75*, 1516 – 1526.
[16] a) B. T. Mott, C. Tanega, M. Shen, D. J. Maloney, P. Shinn, W. Leister, J. J. Marugan, J. Inglese, C. P. Austin, T. Misteli, D. S. Auld, C. Thomas, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 6700 – 6705; b) Q. Zhou, A. F. Phoa, R. H. Abbassi, M. Hoque, T. A. Reekie, J. S. Font, R. M. Ryan, B. W. Stringer, B. W. Day, T. G. Johns, L. Munoz, M. Kassiou, *J. Med. Chem.* **2017**, *60*, 2052 – 2070; c) P. Jain, C. Karthikeyan, N. S. Moorthy, D. K. Waiker, A. K. Jain, P. Trivedi, *Curr. Drug Targets* **2014**, *15*, 539 – 550.
[17] a) S. B. Lee, V. Frattini, M. Bansal, A. M. Castano, D. Sherman, K. Hutchinson, J. N. Bruce, A. Califano, G. Liu, T. Cardozo, A. Iavarone, A. Lasorella, *Nature* **2016**, *529*, 172 – 177; b) Y. Imawari, R. Mimoto, S. Hirooka, T. Morikawa, H. Takeyama, K. Yoshida, *Cancer Sci.* **2018**, *109*, 363 – 372.
[18] Y. Seiji, A. Kazuaki, H. Yoshiro, Y. Hajime, S. Shunsaku, *J. Heterocycl. Chem.* **1998**, *35*, 1249 – 1255.
[19] P. L. Boutz, A. Bhutkar, P. A. Sharp, *Genes Dev.* **2015**, *29*, 63 – 80.
[20] S. Knapp, P. Arruda, J. Blagg, S. Burley, D. H. Drewry, A. Edwards, D. Fabbro, P. Gillespie, N. S. Gray, B. Kuster, K. E. Lackey, P. Mazzafera, N. C. O. Tomkinson, T. M. Willson, P. Workman, W. J. Zuercher, *Nat. Chem. Biol.* **2013**, *9*, 3 – 7.
[21] J. Briscoe, P. P. Therond, *Nat. Rev. Mol. Cell Biol.* **2013**, *14*, 416 – 429.
[22] P. A. Beachy, S. S. Karhadkar, D. M. Berman, *Nature* **2004**, *432*, 324 – 331.
[23] S. Peukert, K. Miller-Moslin, *ChemMedChem* **2010**, *5*, 500 – 512.
[24] X. Wu, S. Ding, Q. Ding, N. S. Gray, P. G. Schultz, *J. Am. Chem. Soc.* **2002**, *124*, 14520 – 14521.
[25] Y. Wang, Z. Zhou, C. T. Walsh, A. P. McMahon, *Proc. Natl. Acad. Sci. USA* **2009**, *106*, 2623 – 2628.

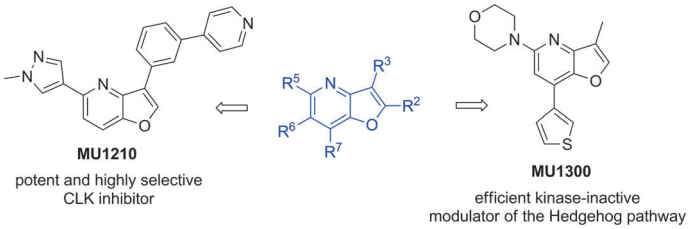
Manuscript received: October 3, 2018
Revised manuscript received: November 16, 2018
Version of record online: ■■ ■■, ■■■■

Communications

Biological Activity

V. Němec, M. Hylsová, L. Maier, J. Flegel, S. Sievers, S. Ziegler, M. Schroeder, B. T. Berger, A. Chaikuad, B. Valčíková, S. Uldrijan, S. Drápela, K. Souček, H. Waldmann, S. Knapp, K. Paruch* _____ ■■■■–■■■■

Furo[3,2-*b*]pyridine: A Privileged Scaffold for Highly Selective Kinase Inhibitors and Effective Modulators of the Hedgehog Pathway



Core competence: The furo[3,2-*b*]pyridine core has been identified as a novel scaffold for potent and highly selective inhibitors. A diverse target compound set was prepared by synthetic sequences based on chemoselective metal-mediated couplings. The 3,5-disubstituted furo[3,2-*b*]pyridine sub-series afforded potent, cell-active, and highly selective inhibitors of cdc-like kinases (CLKs). And the kinase-inactive subset of 3,5,7-trisubstituted furo[3,2-*b*]pyridines afforded submicromolar modulators of the Hedgehog pathway.

