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Back in Person: Frontiers in Medicinal Chemistry 2023

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Dedicated to Franz von Nussbaum for his outstanding dedication and great commitment as a former chairman of the Medicinal Chemistry Division of the German Chemical Society (GDCh).

The Frontiers in Medicinal Chemistry (FiMC) is the largest international Medicinal Chemistry conference in the German speaking area and took place from April 3rd to 5th 2023 in Vienna (Austria). Fortunately, after being cancelled in 2020 and two years (2021–2022) of entirely virtual meetings, due to the COVID-19 pandemic, the FiMC could be held in a face-to-face format again. Organized by the Division of Medicinal Chemistry of the German Chemical Society (GDCh), the Division of Pharmaceutical and Medicinal Chemistry of the German Pharmaceutical Society (DPhG), together with the Division of Medicinal Chemistry of the Austrian Chemical Society (GÖCH), the Austrian Pharmaceutical Society (ÖPhG), and a local organization committee from the University of Vienna headed by Thierry Langer, the meeting brought together 260 participants from 21 countries. The program included 38 lectures by leading scientists from industry and academia as well as early career investigators. Moreover, 102 posters were presented in two highly interactive poster sessions.

Introduction

The annual Frontiers in Medicinal Chemistry (FiMC) conference, which represents the largest international Medicinal Chemistry-focused meeting in the German speaking area, took place in Vienna (Austria) from April 3rd to 5th, 2023. The conference is usually co-organized by the Division of Medicinal Chemistry of the German Chemical Society (Gesellschaft Deutscher Chemiker; GDCh) and the Division of Pharmaceutical and Medicinal Chemistry of the German Pharmaceutical Society (Deutsche Pharmazeutische Gesellschaft; DPhG), supported by a local organization committee. Since this year's edition of the FiMC extraordinarily took place in Austria, the organization of the meeting was also supported by the Division of Medicinal Chemistry of the Austrian Chemical Society (Österreichische Chemische Gesellschaft; GÖCH) and the Austrian Pharmaceutical Society (Österreichische Pharmazeutische Gesellschaft; ÖPhG).

The meeting was opened by Gerhard Hessler (Chairman of the GDCh Division of Medicinal Chemistry) and Thierry Langer (Chairman of the local organization committee). Gerhard Hessler welcomed the 260 participants from academia and industry in "Vienna, one of the most beautiful cities in the world" and thanked all 21 sponsors for supporting the FiMC. Then, Thierry Langer took over giving a short overview on the University of Vienna, which is, with more than 88 000 students, the biggest German speaking university and follows the slogan "Genuinely curious. Since 1365". Finally, Gerhard Hessler gave an enthusi-

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astic outlook on the upcoming three-day conference with its 38 lectures, 102 posters, and various scientific awards.

Medicinal Chemistry Highlights and Fresh Case Studies

The first session on 'Medicinal Chemistry Highlights & Fresh Case Studies' was chaired by Darryl McConnell (Boehringer Ingelheim) and started with a talk from Joachim Bröker (Boehringer Ingelheim). He presented the discovery of the *in vivo* active covalent $KRAS^{G12C}$ inhibitor BI-0474 (**1**, Figure 4 below).[1] The fragment that lead to **1** was identified through a 2nd site fragment-based HSQC NMR screen, in which the 1st site (the so-called switch I/II pocket) was blocked by a covalent fragment binding to an engineered cysteine (S39C). The identified aminocyanothiophene/aminothiazole hits that reversibly bound to the switch II pocket were then grown towards Cys12 and finally linked to an acrylamide warhead, in order to achieve irreversible binding to $KRAS^{G12C}$. Next, *in vivo* efficacy data and PD biomarker modulation results for compound **1** were presented. While **1** showed poor oral bioavailability, it was further optimized to orally bioavailable BI-1823911 (structure not disclosed), which is currently in clinical trials.[2]

The second presentation was given by Andreas Blum (Merck KGaA) about his team's discovery of M4205 (**2**, also referred to as IDRX-42, Figure 4), a selective inhibitor of mutated KIT protein kinases. He started by outlining the unmet need for second line treatments of gastrointestinal stromal tumors (GIST) due to KIT resistance mutations. The team aimed to develop a compound active against KIT harboring mutations in exons 13 and 17 and a superior safety profile over the multikinase inhibitor sunitinib. A high-throughput screening (HTS) of ~350k compounds yielded a hit with high selectivity that was optimized for potency and metabolic stability. He then explained that one major hurdle in the efforts were opposing trends in efflux, solubility and hERG inhibition, which eventually could be overcome by key compound **2**. This inhibitor has a high kinome selectivity and KIT mutant coverage combined with a favorable ADME (absorption, distribution, metabolism, and excretion) profile. Andreas Blum showed efficacy data in cell line-derived xenograft (CDX) and patient-derived xenograft (PDX) models and reported that no cardiac toxicity was observed in guinea pigs and beagles. Currently, compound **2** is being developed by IDRx and entered phase 1 clinical trials.[3]

Michael Hahn (Bayer) held the last talk of the first session and presented his team's efforts in the discovery of BAY2586116, a TASK-1 and TASK-3 channel blocker. He started by introducing obstructive sleep apnea (OSA), a disorder with a large patient population which is thought to be linked to the TASK family (tandem pore acid sensitive K^+ channel) of ion channels. His team performed a HTS of ~4 Mio. compounds and optimized a hit to an *in vivo* chemical probe enabling proof of concept in a pig OSA model. He explained that TASK-1/3 blockers are not suitable for systemic administration due to potential central nervous system (CNS) side effects and that a topical administration (nasal) was aimed for. He then presented structure-activity relationships (SAR) on brain penetration and duration of action, and the identification of BAY2586116, which is currently in clinical phase 2.[4]

For this talk, Michael Hahn received the NextGenMedChem best talk award, and an extended version of the research project will be presented in the MedChemCASES webinar series in September 2023.

PhD Prize Award Ceremony

In the following session chaired by Tatjana Ross (Merck KGaA) and Gerhard Hessler (Sanofi), the PhD prizes were awarded to Alaa Alhayek (Hirsch group, Helmholtz Institute for Pharmaceutical Research Saarland (HIPS)) and Li Gao (Thorn-Seshold group, LMU Munich).

Alaa Alhayek was awarded for her work on the exploration of bacterial metalloproteinases as promising drug targets. In the light of the current antibiotic resistance crisis, the elaboration of new concepts such as antivirulence agents ("pathoblockers") in anti-infective drug discovery is of particular importance. In her thesis, Alaa Alhayek identified and characterized inhibitors of bacterial collagenases,[5] a class of extracellular proteases acting as virulence factors. Through a screening approach, she identified hydroxamate- and diphosphonate-based inhibitors, including several FDA-approved diphosphonate-containing drugs. Afterwards, SAR studies led to a diphosphonate series, exemplified by inhibitor **3** (Figure 4) with low micromolar potency. These compounds showed activity in several *in vitro* and *in vivo* infection models as well as limited cytotoxicity and off-target activity on human matrix metalloproteinases (MMPs).

Li Gao was awarded for his investigations on photoswitchable drugs enabling the spatiotemporal control of microtubule-dependent biology. To overcome the limitations of classical azobenzene-based photoswitches, including metabolic instability and incompatibility with green and yellow fluorescent protein (GFP/YFP) imaging, Li Gao designed styrylbenzothiazole (SBT)-based switches. These GFP/YFP-orthogonal and metabolically stable scaffolds were incorporated into tubulin inhibitors ("SBTubs"), as exemplified by SBTubA4P (**4**, Figure 4), which allowed for precise and reversible photomodulation of microtubule-dependent processes in cell culture and *in vivo* models.[6] Analogous photoswitches were successfully incorporated into epothilone-based microtubule stabilizers (STEpo) enabling the photocontrol of microtubule dynamics and cell division.[7]

We congratulate the award winners (see Figure 1) for their excellent achievements and wish them the very best for their future careers.

New Chemistry and Modern MedChem Methods

Daniele Leonori (RWTH Aachen) opened this session, which was chaired by Peter Ettmayer (Boehringer Ingelheim), with exciting

Figure 1. PhD prize winners at the FiMC 2023. Alaa Alhayek (middle) and Li Gao (right). Gerhard Hessler (left) chaired the award ceremony and handed over the certificates.

applications of his new organic synthesis methodologies to Medicinal Chemistry. At the beginning, he drew the attention to a fairly novel topic: the usage of boron radicals in synthetic chemistry. He showcased interesting examples of such reactions like the Minisci-type borylation of azines.[8] Furthermore, the group discovered a safe alternative to classical ozonolysis employing excited nitroarenes. The latter can be used to promote the cleavage of olefins upon blue light irradiation.[9] Finally, he gave insights into some unpublished results of his group: a novel approach towards azepanes and several transformations of the corresponding azepine intermediates.

Charlotte Griffiths-Jones (Astex Pharmaceuticals) presented an excellent overview on the nanoscale high throughput experimentation (HTE)-C–H-functionalization platform at Astex and its importance in fragment-based drug discovery.[10] She explained the company's nanogram-to-gram workflow on a photoredox-mediated cross-dehydrogenative coupling of a fragment in a 1536-well format.[11] After initial HTE optimization, the conditions could be upscaled to generate numerous derivatives and to explore the SAR around the fragment rapidly. With this approach, they were able to quickly access important growth vectors in fragments. To obtain larger quantities, the reaction conditions were transferred into flow reactors which gave rise to multigram amounts.

Nuno Maulide (University of Vienna) started his talk by revisiting the well-known topic of olefination reactions involving ylides. However, in contrast to the well-established chemistry around phosphorus-ylides, his group focused on the reactions of sulfur-ylides and their applications in modern synthetic chemistry.[12] He nicely pointed out mechanistic similarities and differences between the two species as well as the stereochemical outcome of their different olefination reactions. He then switched topics and presented his group's insights into the so-called inverse hydride shuttle catalysis.[13] With this principle, the group is able to access complex ring systems, such as indolizidine bicycles, *via* a multicomponent reaction involving a nitro-olefin, an amine and an aldehyde. The formed cyclobutane intermediate is then converted to the bicyclic ring system *via* boron-based Lewis acid catalysis.

Molecular Glues and Degraders

The 'Molecular Glues and Degraders' session was chaired by Michael Gütschow (University of Bonn) and was opened with a talk given by Georg E. Winter from the Research Center for Molecular Medicine (CeMM) of the Austrian Academy of Science (Vienna). The beginning of the presentation was focused on a study, in which Winter and co-workers identified functional E3 ligase hotspots and resistance mechanisms to small molecule degraders. Application of haploid genetics enabled to demonstrate that hotspot mutations cluster in substrate receptors of hijacked ligases, for which mutation type and frequency correlate with gene essentiality. Interestingly, the identified hotspots were also shown to be mutated in samples from patients that relapse from degrader treatment.[14] The second part of the talk was dedicated to the discovery of tempered α,β-unsaturated indolinone electrophiles as novel drug-like ligands of the E3 ligase DCAF11, enabling targeted protein degradation (TPD) *via* the ubiquitin-proteasome system.[15] Finally, the concept of intramolecular bivalent glues was introduced by the example of the BRD4-targeted sulfonamide-based degrader **5** (Figure 4), which bivalently binds both bromodomains of BRD4 and thereby stabilizes the interaction with DCAF16, a substrate recognition component of CUL4-DDB1 E3 ubiquitin ligases.[16]

Nicole Trainor from the Walter and Eliza Hall Institute of Medical Research (WEHI, Melbourne, Australia) focused her talk on strategies to achieve oral bioavailability in Proteolysis Targeting Chimera (PROTAC) degrader development. This is a major challenge, as PROTACs often possess high molecular weight and other physicochemical properties beyond those typically observed for orally active drugs. Although several E3 ligases can be utilized for chemically induced TPD, to date, oral bioavailability has only been reported for cereblon-mediated PROTACs. In her talk, Nicole Trainor reported on the discovery of orally bioavailable SMARCA2-targeted PROTACs, which co-opt the E3 ligase VHL (Von-Hippel-Lindau). Optimization of the physicochemical properties of a SMARCA bromodomain ligand with subsequent structure-guided and property-driven optimization of the bivalent degraders led to ACBI2 (**6**, Figure 4), which achieves preferential degradation of SMARCA2 over its close homologue SMARCA4 in cells and potent *in vivo* degradation when applied orally.[17] Since several cancer types are dependent on SMARCA2, the development of highly active and selective SMARCA2-targeted PROTACs is a promising strategy for the development of new anti-cancer drugs.

In the final talk of this session, Finn K. Hansen (University of Bonn) reported on the development of PROTACs targeting HDAC6, a lysine deacetylase that has been associated with the pathogenesis of cancer and neurodegeneration. For the synthesis of hydroxamic acid-based HDAC6 PROTACs, the Hansen group developed a solid-phase supported protocol, using hydroxamic acids immobilized on resins (HAIRs).[18] This approach enabled the straightforward solid-phase parallel synthesis of potent and selective HDAC6 degraders that showed promising antiproliferative activity *via* inducing apoptosis in myeloid leukemia cell lines.[19] The last part of the talk was focused on the development of the first selective non-

hydroxamate HDAC6 degraders that utilize a difluoromethyl-1,3,4-oxadiazole warhead as a zinc-binding group, exemplified by compound **7** (Figure 4).[20] Very recently, the Hansen group was also able to elucidate the binding mode of difluoromethyl-1,3,4-oxadiazoles, which is characterized by a mechanism-based, and essentially irreversible inhibition of HDAC6.[21]

Young Investigators

The session chaired by Nina Schützenmeister (University of Vienna) started with the presentation from Oliver Thorn-Seshold (LMU Munich) on new synthetic disulfides as tumor-selective redox-responsive prodrugs. A series of duocarmycin prodrugs based on dichalcogenides were highlighted.[22] These cyclic dichalcogenides are relatively stable under "normal reducing conditions" (e.g. to reduction by monothiols) but could be easily reduced by high turnover thioreductases, thereby releasing the cargo.[23] Whereas other bioreductive prodrugs are known, these are the first examples of bioreductive prodrugs addressing the thiol/disulfide manifold, which has been postulated to play a role in some types of cancers. These prodrugs (e.g. P-SS66C-CBI-TMI (**8**, Figure 4)) were tested *in vitro* and in mouse models of pancreatic and breast cancers where they showed promising results.[24]

Matthias Gehringer (University of Tübingen) gave the second presentation of this session on the discovery of a selective covalent chemical probe for the protein kinase S6K2, a barely studied p70 ribosomal protein S6 kinase, which may play an important role in cancer drug resistance. A selective inhibitor targeting this protein would be of great value to study the function of this kinase. Following a structure-based approach, the structure of PF-4708671,[25] a known S6K1 inhibitor, and the linker/acrylamide covalent warhead of BLU9931,[26] a known FGFR4 inhibitor, were combined to obtain the first putative covalent inhibitors of S6K2. S6K1 and S6K2 are very similar, but differ in a cysteine in the hinge region, which is only present in S6K2. The initial acrylamide-based inhibitors showed only weak potency, which was rationalized by a steric clash between the linker and the protein. Therefore, second-generation inhibitors bearing non-canonical electrophilic warheads, based on nucleophilic aromatic substitution (S_NAr) chemistry,[27] were designed and synthesized. SAR investigations led to highly potent and selective S6K2 inhibitors such as compound **9** (Figure 4).[28]

The session continued with a presentation by Christina Lamers (University of Leipzig) on cyclic peptide inhibitors of the complement system C3. The inhibition of the complement system has turned into a highly interesting approach to treat a number of clinical conditions.[29] In 2021, a new compound class represented by pegylated C3 inhibitor pegcetacoplan (Empaveli, Apellis®)[30] was approved for the treatment of paroxysmal nocturnal hemoglobinuria (PNH). Another compound in clinical development is Cp40-AMY101 and both of these inhibitors are based on the cyclic peptide compstatin (Cp05). The crystal structure of Cp40 in complex with its target Complement C3b and the elucidation of the molecular determinants for binding using kinetic analyses were presented.[31] These results helped to understand previous SAR campaigns leading to Cp40 and revealed a crucial role of a structural water for inhibitor binding. With this information, a further optimization campaign was conducted introducing so far unexplored amino acid variations, which led to derivatives with improved drug-target residence time. These studies also served to rationalize the different affinities observed among species orthologues and will provide support for further improvement of this class of complement inhibitors.

The next presentation by Lennart Brewitz (University of Oxford) focused on inhibitors of the SARS-CoV-2 main protease (M^{pro}). The recent approvals of nirmatrelvir and ensitrelvir for the treatment of SARS-CoV-2 validate the relevance of M^{pro} inhibition as a therapeutic strategy.[32] Most of the known M^{pro} inhibitor programs rely on covalent binders of diverse chemical nature, targeting the active site Cys145. The presentation focused on the development of two classes of covalent inhibitors: ß-lactams and (non-activated) alkynes. Using crystallography and mass spectrometry analysis,[33] the intermediates generated upon reaction of Cys145 and ß-lactams where characterized, demonstrating that this type of inhibition is not suitable for productive SAR generation. Therefore, the strategy was changed to synthesize nimatrelvir-derived inhibitors with alkyne warheads. Molecular modeling was used to understand the difference between the more common nitrile-based and alkyne-based inhibitors and to develop improved alkyne inhibitors such as **10** (Figure 4), which according to MS and X-ray crystallography bind covalently to the M^{pro} catalytic cysteine by forming a vinyl thioether.[34]

Steffen Pockes (University of Regensburg) presented a fragment-based approach for the identification of caspase-2 inhibitors, which are becoming increasingly important for the potential treatment of Alzheimer's disease.[35] Up to date, most of the known caspase-2 inhibitors are of peptidic nature, which poses a challenge on developing them as CNS therapeutics. Therefore, a fragment-based screen was undertaken, using a chloroacetamide-based covalent fragment library from Enamine. Caspase-3 was used as a counter screen allowing the identification of several caspase-2 selective inhibitors, for which target engagement and covalent binding could be shown using mass spectrometry peptide sequencing.

The session was finalized with the contribution of Gwenaëlle Jézéquel (Helmholtz Institute for Pharmaceutical Research Saarland) on a new class of inhibitors of the virulence factor Elastase B (LasB) in *Pseudomonas aeruginosa*, an important Gram-negative pathogen with high priority for the WHO. LasB is an extracellular metalloprotease associated with increased mortality, and it is a validated target to disarm bacteria. During fragment growing and optimization of thiol-based inhibitors, new heterocycles were identified as a suitable scaffold[36] and used as starting points for a Medicinal Chemistry optimization program. Several zinc binding moieties, such as phosphoric and hydroxamic acids were introduced into these structures leading to potent protease selective inhibitors, for which an X-ray structure was obtained.[37] Phosphonate inhibitors (e.g. HIPS 6872 (**11**, Figure 4)) were more stable and non-toxic and

showed improvement of survival *in vivo* in a *Galleria mellonella* model.

Innovation Award

The Innovation Award ("Innovationspreis in Medizinischer/Pharmazeutischer Chemie") is jointly awarded by the Medicinal Chemistry Divisions of the German Chemical Society (GDCh) and the German Pharmaceutical Society (DPhG) to an excellent young investigator with outstanding contributions to the field. This year, Matthias Schiedel (Figure 2), formerly from the University of Erlangen-Nürnberg, since June 2023 Professor at the TU Braunschweig, received the award in honor of his work on selective ligands and degraders targeting G-protein coupled receptors (GPCRs) at their intracellular allosteric binding site (IABS). We congratulate our new NextGenMedChem colleague on this outstanding achievement.

After a general introduction on the award and a laudation by the session chairs Christian Ducho (Saarland University) and Christian Kuttruff (Boehringer Ingelheim), Matthias Schiedel presented his work in an award lecture. Normally, GPCRs are activated by extracellular ligands inducing a conformational shift to trigger intracellular signaling cascades. Recently, however, several IABS-targeted GPCR ligands have been identified. Based on vercirnon, an intracellular antagonist of the chemokine receptor CCR9, the Schiedel group developed high-affinity CCR9 ligands such as AAA30 (**12**, Figure 4) and fluorescently labelled analogs that were used for NanoBRET binding assays and fluorescence microscopy. Moreover, CCR9 PROTACs were developed to provide a full chemical biology toolbox for this receptor.[38] Following up on this pioneering work, the Schiedel group developed fluorescently labelled intracellular ligands for a variety of other GPCRs giving rise to an unprecedent NanoBRET-based screening platform for IABS binders.[39]

Figure 2. Innovation award winner at the FiMC 2023: Matthias Schiedel (middle). Christian Ducho (left) and Christian Kuttruff (right) chaired the award ceremony and handed over the certificate.

Lunch Workshops and Seminars

During the lunch break on the second day of the conference, BioSolveIT kindly invited conference participants to an interactive workshop. The aim of the workshop was to expand the skill portfolio of a Medicinal Chemist with the help of computational methods: ligand design, decorating fragments to satisfy unoccupied binding sites, find scaffold replacements and mine synthesizable compounds from billion-sized chemical spaces. For this, real-life examples were investigated with the drug discovery platforms SeeSAR and infiniSee.

The lunch break on the third conference day was filled by a talk given by Susana Tomasio from Collaborative Drug Discovery (CDD). In her presentation, she introduced CDD Vault as a comprehensive, cloud-based informatics platform that is hosted through an intuitive interface. With features like real-time collaboration, advanced visualization, and powerful data analysis tools, CDD Vault makes it easy to organize and share large amounts of data within teams or with collaboration partners.

In Silico Solutions in MedChem

The session was chaired by Gerhard Hessler (Sanofi) and started with a talk by Sharon Bryant from Inte:Ligand. She presented the NeuroDeRisk IL Profiler,[40] a collaboration between industrial and academic partners under the "Innovative Medicines Initiative". Due to the resource intensity of neurotoxicity assessment, compounds are usually profiled only late in the drug discovery process. Hence, there is a huge need for predictive *in silico* tools to fill this gap. The NeuroDeRisk IL profiler mainly assesses three areas: convulsant & seizure-inducing effects, psychological and psychiatric side effects and peripheral nervous system toxicity. It uses the 3D pharmacophore profile of ligands and matches it to the 3D pharmacophore profiles of known neurotoxicity targets or outcome-based models from pharmacovigilance databases. The tool is available *via* KNIME or *via* their website.[41]

The second talk of the session was given by Friedemann Schmidt and described how Sanofi utilizes predictive modeling during the design-make-test (DMT) cycle. A manifold of different methods (QSAR/Machine Learning, QM methods and multi-scale modelling)[42] were applied and made available to the multi-disciplinary project teams through several internal platforms. He also showed a case study of this workflow applied to the kinase SGK1,[43] where safety liabilities (e.g., mutagenicity and photolability) of the initial lead needed improvements. Each of the liabilities was found to be linked to a scaffold or decoration using ADME-toxicity models *in silico* and these findings were included in the next optimization cycle to arrive with a suitable pre-candidate profile.

In the last talk Franca Klingler (now at Isomorphic labs) presented a collaboration between BioSolveIT and Genentech. They applied a synthon-based docking approach, which they call 'Chemical Space Docking' to efficiently leverage ultra-large databases via docking. That method was applied to identify inhibitors of ROCK1 kinase from almost one billion commercially

available synthesis-on-demand compounds. From 69 synthesized molecules, 39% had K_i values below 10 μM. Two leads were crystallized with the ROCK1 protein, and structures showed excellent agreement with the docking poses.[44] Very interesting is the efficiency of that method compared to the computational power needed for conventional docking of fully enumerated libraries, thus enabling the virtual screening of much bigger libraries.

Next-Generation Drugs

This session was organized by the NextGenMedChem team and chaired by Eleonora Diamanti (University of Bologna) and Julien Lefranc (Merck KGaA). First, Stefanie Flohr (Novartis) talked about the discovery of LNP023 (**13**, Figure 4) as the first-in-class orally bioavailable serine protease factor B (FB) inhibitor for the treatment of rare, alternative complement pathway driven diseases.[45] FB is a trypsin-like serine protease and a major challenge of the presented study was to gain selectivity over related proteases. To this end, Flohr and co-workers targeted a unique feature of FB located in the protease S1 pocket. Starting with a HTS screen, followed by a substantial SAR campaign aimed at optimizing the potency and ADME properties of the initial hit molecules, inhibitor **13** was identified as a candidate compound for further studies. The high potency ($IC_{50} = 10$ nM), selectivity, and favorable pharmacokinetic (PK) profile allowed to test the *in vivo* efficacy of **13** in a pharmacodynamic (PD) model and to progress into clinical trials (currently phase III).

James Crawford (Genentech) focused his talk on the discovery of tool compounds to tackle the transcriptional enhanced associate domain (TEAD) protein family. In his presentation, he highlighted the identification and characterization of a potent small molecule (**14**, Figure 4) that targets the *S*-palmitoylation site of TEAD, also referred to as the lipid pocket (LP). This approach enables a modulation of the Hippo signaling pathway that is dysregulated in many human cancers. A co-crystal structure of compound **14** with the TEAD2-YAP-binding domain (YBD) proved engagement of the TEAD LP and it also indicated that **14** mimics *S*-palmitoylation. Finally, the compound was shown to effectively limit tumor growth in a xenograft mouse model, thus demonstrating the high therapeutic potential of the TEAD LP as a drug target site.[46]

As the last speaker of this session, Sophie Bertrand (GSK) gave an overview on the discovery and optimization of potent, slow-dissociating inhibitors of the type III phosphatidylinositol 4-kinase (PI4KB). The PI4KB is a lipid kinase indispensable for human rhinovirus (HRV) replication. The therapeutic concept behind this study is that a pulmonal application of a PI4KB inhibitor will reduce HRV replication in the lungs, thereby preventing HRV-induced asthma and chronic obstructive pulmonary disease (COPD) exacerbations. After in-depth SAR and structure-kinetic relationship (SKR) studies, followed by an improvement of compound solubility, Bertrand and co-workers identified a lead compound having an extremely slow dissociation rate with a residence time of more than 2,000 min. The final candidate was tested in PK studies, and less than 5% of the dose remained in the lung at 24 hours, thus minimizing the risk of macrophage toxicity upon repeated dosing. Finally, *in vivo* target engagement was verified for the lead PI4KB inhibitor.

Plenary Lecture

The second day finished with a plenary lecture from Dirk Trauner (University of Pennsylvania) chaired by Julien Lefranc (Merck KGaA). Dirk Trauner gave an overview of his work on photopharmacology, in which he showed the use of azobenzene photoswitches to activate or deactivate different types of target proteins like GPCRs, as exemplified by dopamine receptors, or even protein kinases.[47] Azobenzenes are known to adopt either *cis* or *trans* conformations about the N=N bond and they can be isomerized from one to the other using light of certain wavelengths. The Trauner group has been successfully using this property to design novel molecules that will only be active in one of the two forms (*cis* or *trans*) and will switch from the inactive to the active form upon light irradiation. This strategy can also be used on a tethered approach, where the ligand is covalently linked to the receptor.[48]

In the second part of his presentation, Dirk Trauner switched gears and moved to natural product synthesis and went through one of his recent works in the field: the total synthesis of tetrodotoxin.[49] This work led to one of the shortest syntheses of tetrodotoxin (TTX, **15**, Figure 4) in 22 steps with an overall yield of 11%. The group is still working on further optimizing their synthesis, in order to be able to deliver larger quantities of the natural product.

Translational Science Case Studies

The 'Translational Science Cases Studies' session was chaired by Thierry Langer (University of Vienna) and started with a contribution from Peter Nussbaumer (Lead Discovery Center Dortmund), who presented two studies illustrating the translation of academic research into a pharmaceutical application. The first program focused on the development of NET (neutrophil extracellular trap) formation inhibitors. NETs are DNA/protein complexes, which are split off from the cells in a neutrophil cell death pathway called NETosis. A 38-week high content screen of approximately 190k compounds in primary human neutrophils was carried out. After triage, clustering, and selection for known mechanisms, three validated hit classes were identified.[50] Using a pegylated derivative, Gasdermin D could be identified as the potential target, although the exact mode of action could not be determined.[51] The asset is now outlicensed to a Boston biotech company and being further developed. The second case study comprised inhibitors of the DNA-directed RNA polymerase POLRMT, which is relevant in mitochondrial transcription. Using a new assay principle, 430k compounds were screened and triaged, leading to two hit series. Optimization was done in the coumarin hit series, for which steep SAR and poor *in vitro* ADME was initially observed.

Several modifications leading to compounds with improved ADME profile and *in vivo* PK (e.g. front runner LDC04857 (**16**, Figure 4)) were presented and their allosteric binding mode could be elucidated by CryoEM.[52] *In vivo* proof-of-concept could be shown in multiple xenograft models and no toxicity was observed in a 4-week study in mice.

The following presentation by Rolf Müller from the HIPS in Saarbrücken showcased three examples for the identification of innovative natural product-based anti-infectives arising from myxobacteria. First, a bioactivity-based workflow for the discovery of cystobactamides,[53] a novel class of broad-spectrum antibiotics effective against Gram-negative and multidrug-resistant strains was presented. This compound class is currently being developed by the INCATE (Incubator for Antibacterial Therapies in Europe) consortium. Secondly, the discovery of corallopyronin A (**17**, Figure 4), an α-pyrone antibiotic, which acts on a translocator protein situated in the membrane of Gram-negative bacteria was described. Thanks to genetic engineering, this molecule can be produced in large quantities to support preclinical characterization including *in vivo* studies.[54] The third class of antibiotics are chlorotonils, chlorinated macrolides which are isolated from *Sporangium cellulosum*. Besides broad antibacterial activity, these compounds display antimalarial properties. Semisynthetic derivatization, enabled by supply of chlorotonil through fermentation, led to the identification of improved derivatives which are now in preclinical development.[55]

The session continued with a contribution from Gerald Platzer from MAG-Lab, who presented a workflow for studying protein-drug interactions in solution using NMR and selective isotopic labelling of proteins. By these means, nonpolar C–H interactions upon ligand binding can be observed. The application of this technology for the target proteins FKPB12 and NSD3 showcased the determination of key protein-ligand interactions with atomistic resolution.[56]

The final presentation by Jörg Rademann from the FU Berlin, described small-molecule inhibitors of pneumolysin (PLY), a pore-forming cytolysin involved in pneumonia. Using a virtual screening approach, small-molecule pore blockers (PB) were identified and their binding mode was confirmed by CryoEM.[57] An SAR campaign, which included derivatives obtained by scaffold-hopping, led to the identification of PB-3 (**18**, Figure 4), a reversible-covalent binder with superior chemical stability, solubility, and a prolonged residence time, that could be formed in a protein-templated Knoevenagel condensation.[58] The binding site for this class of compounds could be determined by mutation experiments and the specificity for PLY could be confirmed. Compound **18** showed efficacy in preventing cytolysis and cell death in human lung epithelial cells also during infection with *Streptococcus pneumoniae*. These promising results are currently being applied to cytolysins of other bacteria with pharmacological relevance.

RNA Modifying Enzymes

The session on RNA modifying enzymes was chaired by Yann Foricher (Sanofi) and opened by a talk of Harald Schwalbe (University of Frankfurt), who belongs to the "International Covid19-NMR Consortium" (https://covid19-nmr.de). He showed the identification of binders targeting the RNA genome of SARS-CoV-2. To this end, the DSI (Diamond-SGC-iNEXT)-poised library, which is composed of 768 highly different and easily modifiable fragments, was screened against 20 viral RNA elements from the untranslated part of the viral genome and 25 different SARS-CoV-2 proteins.[59] The workflow for the identification of novel binders started with an initial NMR-based screening, followed by computational methods to further elucidate the ligand-target interactions. This led to the identification of screening hits with affinities in the double-digit micromolar range. From there, hit optimization resulted in nanomolar binders with antiviral activities targeting the SARS-CoV-2 frameshift element.

Andrea Rentmeister (University of Münster) presented a novel and efficient optochemical strategy for directly controlling mRNA translation. This approach, which does not require any genetic modifications, is based on photo-cleavable groups (FlashCap) that interfere with the initiation stage of the mRNA translation. These photo-cleavable groups (e.g. 3,4-dimethoxy-2-nitrobenzyl (DMNB) or 6-nitropiperonyl-methyl (NPM)), that are synthetically installed at the 5' cap of the mRNA, can be released by short light exposure. Several examples were presented, where this new approach of light-induced activation of photo-caged mRNA enabled the spatio-temporally controlled translation of the protein of interest.[60]

The final talk of this session was given by Mark Helm (University of Mainz) and was focused on the enzyme DNMT2, a member of the DNA methyltransferase (MTase) family that represents a potential target for cancer treatment. DNMT2 requires *S*-adenosyl-*L*-methionine (SAM) as the cofactor to transfer a methyl group to the 5-position of the cytidine base. Mark Helm presented the SAR work done around DNMT2 inhibitors that are based on modifications of the natural binder *S*-adenosyl-*L*-homocysteine (SAH). These studies resulted in the identification of new synthetic DNMT2 inhibitors with a *N*-adenosyl-2,4-diaminobutyric acid (Dab) scaffold. Finally, he introduced electron-deficient aryl (i.e. S_NAr) warheads covalently targeting a cysteine to gain potency and selectivity over other SAM-dependent MTases.[61]

Friedrich Stolz Award

The following Friedrich Stolz Award ceremony chaired by Franz von Nussbaum (Nuvisan) was another highlight of the conference. As a pioneer and role model in Medicinal Chemistry, Friedrich Stolz was trained as both, a pharmacist and a chemist. His work in industry and academia had a tremendous translational impact highlighted by the invention of the drug aminophenazon (Pyrazolon®) and the first total synthesis of adrenalin. The prize is awarded alternately to individuals or teams from

industry and academia in recognition of outstanding dedication, scientific discoveries, or innovative technologies in Medicinal Chemistry with a clear translational potential. This year, Rolf Hartmann from the HIPS institute in Saarbrücken was honored with the Friedrich Stolz Award (Figure 3) for his pioneering research in two completely different fields, i.e., inhibitors of steroid hormone biosynthesis and pathoblockers, which has led to several drug candidates and the foundation of successful spin-off companies. The award comes with a prize money of 5,000 euros, a lecture at the Frontiers in Medicinal Chemistry conference and two additional lectures at a university and a company within Germany.

After a laudation by Anna Hirsch (HIPS), Rolf Hartmann spotlighted his impressive achievements in the field of steroid hormone biosynthesis inhibitors in an award lecture. The talk started with the presentation of pioneering work on aromatase (CYP19A1) inhibitors of the aminoglutethimide type.[62] Subsequently, the four enzymes 11β-hydroxylase (CYP11B1), aldosterone synthase (CYP11B2), 17β-hydroxysteroid dehydrogenase type 1 (17β-HSD1) and type 2 (17β-HSD2) were introduced as more recent targets pursued by the Hartmann group, which resulted in a remarkable number of 175 publications from 2005 to 2023. In the following presentation of case studies, Rolf Hartmann highlighted the development of selective aldosterone synthase inhibitors such as SL242 (**19**, Figure 4), which showed promising *in vivo* activity.[63] This program was continued in his spin-off company ElexoPharm in collaboration with MSD to develop treatments for cardiovascular diseases. Next, successful work on 11β-hydroxylase inhibitors, which suppress cortisol biosynthesis and may be used as treatments of Cushing's syndrome and to promote wound healing, was presented.[64] The last part of the lecture focused on 17β-HSD1 and 2, for which four potential indications were explored. While development of 17β-HSD1 inhibitors blocking estradiol synthesis was pursued for endometriosis and breast cancer treatment,[65] 17β-HSD2 inhibitors that block oxidative estrogen/androgen deactivation were developed for osteoporosis and bone fracture healing.[66]

Congratulations to Rolf Hartmann on the exceptional achievements throughout his career.

Figure 3. Prize winner of the Friedrich Stolz-Award at the FiMC 2023: Rolf Hartmann (middle). Anna Hirsch (left) and Franz von Nussbaum (right) chaired the award ceremony and handed over the certificate.

Medicinal Chemistry Case Studies (I)

The first afternoon session on 'Medicinal Chemistry Case Studies' was chaired by Stefan Laufer (University of Tübingen) and started with a talk given by Hideyo Takahashi (University of Tokyo), who highlighted the role of axial chirality in drugs. With his group, he investigated the atropisomerism in benzodiazepine derivatives. 1,4-Benzodiazepine-2-ones and triazolobenzodiazepines were synthesized with the addition of an extra methyl substituent in position 9 and 10, respectively, in order to freeze their conformation. The presence of axial chirality was then confirmed by chiral HPLC and ^{1}H NMR. The synthesized 1,4-benzodiazepin-2-ones and triazolobenzodiazepines bearing an extra methyl group exist as pairs of enantiomers [(a^1R, a^2S) and (a^1S, a^2R)], which was confirmed by X-ray analysis. The absolute configuration of the active stereoisomers was deduced from circular dichroism (CD) spectra. Affinity investigations towards the $GABA_A$ receptor revealed that 1,4-benzodiazepines, including triazolobenzodiazepines, bind to this receptor in the (a^1R, a^2S) configuration. Thus, triazolam should also bind to the $GABA_A$ receptor in the (a^1R, a^2S) conformation, although behaving achirally due to the rapid conformational change.[67]

During the next talk, Les Burnett (Revolution Medicines) presented the discovery of RMC-5552 (**20**, Figure 4), a selective bi-steric inhibitor of the mTOR complex 1 (mTORC1) for the treatment of mTORC1-activated tumors.[68] Their goal was to develop an mTORC1 inhibitor that acts as a potent suppressor of 4EBP1 and S6K phosphorylation and shows selectivity over mTORC2 and lipid kinases. The bi-steric inhibitor RapaLink-1 provided an attractive starting point with an approximate 3–4-fold selectivity for inhibition of mTORC1 over mTORC2.[69] RapaLink-1 connects an FKBP-FRB (FK506-binding protein-rapamycin-binding) allosteric mTOR inhibitor based on rapamycin with an active-site (orthosteric) inhibitor based on sapanisertib. The Medicinal Chemistry optimization focused on modifications in the rapamycin core, changes around the chemical handle, as well as the exploration of optimal linker length and modifications at the active site inhibitor. This focused work resulted in compound **20**, a potent and selective inhibitor of hyperactivated mTORC1 signalling in cancer. The compound shows anti-tumor activity as single agent and combinatorial anti-tumor activity with $KRAS^{G12C}$ inhibitors in preclinical models. Compound **20** is currently being evaluated in clinical trials.

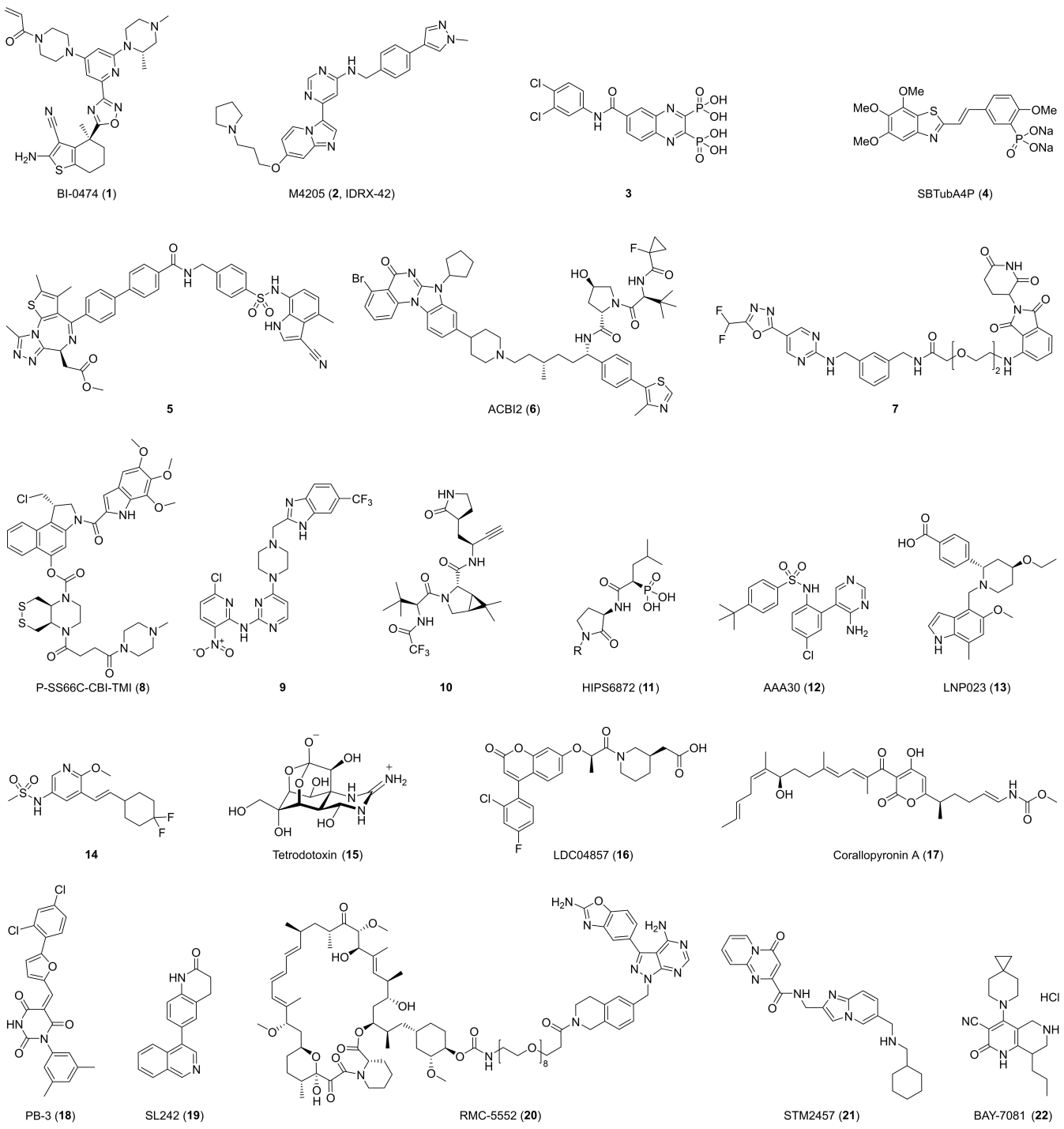

Figure 4. Chemical structures of selected compounds presented at the FiMC 2023 conference.

Medicinal Chemistry Case Studies (II)

The second afternoon session was chaired by Thierry Langer (University of Vienna). It started with a talk from Daniel Merck (LMU Munich), who presented the development of diverse chemical tools for the transcription factor Nurr1, which is expressed in the CNS and possesses neuroprotective and anti-neuroinflammatory properties. Starting from an amodiaquine fragment and by means of microscale analogue library synthesis, novel Nurr1 agonists with superior potency compared to the lead compound were obtained.[70] In addition, unpublished data on the discovery of additional chemical tools to study Nurr1 were presented, including an AI driven Nurr1 agonist design and a fragment-based screen, among others.

The second talk was delivered by Matthew Fyfe (Storm Therapeutics) on the discovery of the SAM competitive METTL3 methyl transferase inhibitor STM2457 (**21**, Figure 4), which is currently in clinical trials.[71] The m^{6}A methyltransferase METTL3

has been linked to the initiation and maintenance of acute myeloid leukemia (AML). An HTS screen of 250k compounds delivered STM1760, a micromolar hit that was optimized in only seven months into key compound **21**. The inhibitor shows high selectivity against other methyl transferases, kinases, GPCRs and ion channels. It was shown that inhibition of METTL3 *in vivo* with **21** prevents AML expansion, reduces the number of key leukemia stem cells and it leads to impaired engraftment and prolonged survival in various mouse models of AML.

Then, Michael Gütschow (University of Bonn) presented the discovery of extremely potent cathepsin B inhibitors bearing inversely oriented covalent warheads. Cathepsin B is a lysosomal protease that is involved in angiogenesis and metastasis. The impact of dipeptide nitriles and azadipeptide nitriles as cysteine protease inhibitors was studied.[72] The electrophilic azanitrile warhead is subjected to the reversible nucleophilic attack of the active site cysteine to give an isothiosemicarbazide adduct. Several carboxylic acid containing peptides bearing inversely oriented warheads were designed that would leverage the interaction with the occluding loop. During the talk, SAR understanding of several peptides and mechanistic aspects of the covalent modifications were presented.

The last talk was delivered by Daniel Meibom (Bayer) on the discovery of BAY-7081 (**22**, Figure 4), a potent, selective, and orally bioavailable PDE9A inhibitor.[73] PDE9A is a phosphodiesterase (PDE) believed to be a key regulator of cGMP (cyclic guanosine monophosphate) levels. The inhibition of PDE9A might be relevant for the treatment of CNS disorders, sickle cell disease, and heart failure. An HTS was performed to yield a cyanopyridone-based hit with good *in vivo* rat PK but limited selectivity against different PDEs. The Medicinal Chemistry optimization focused on potency and selectivity improvement, while also addressing poor solubility. The compounds suffered from low bioavailability and high clearance due to glucuronidation of the lactam core. Thus, an alternative screening hit belonging to another subseries was revisited and combining features of both classes resulted in a new starting point without glucuronidation issues. Further SAR on the piperidine head group delivered more potent derivatives resulting in compound **22**, a potent PDE9A inhibitor with acceptable to good PDE panel selectivity, high aqueous solubility, and BID (*bis in die* = twice a day) PK profile.

Closing Remarks and Poster Prizes

Following the sessions on 'Medicinal Chemistry Case Studies', the poster prizes were awarded. Overall, four of the 102 presented posters were honored with the FiMC 2023 best poster awards. Max E. Huber (FAU Erlangen-Nürnberg) was awarded for his poster on a Chemical Biology toolbox targeting the chemokine receptor CCR9, Tonia Kirschner (Technical University of Dortmund) for her poster on the development of first-in-class covalent $KRas^{G13C}$ inhibitors, Lukas Schneider (University of Zürich) for his poster on novel BODIPY-based photothermal agents for cancer treatment, and Josef Braun (Technical University of Munich) for his poster on palladium-labile prodrugs for the prevention of implant-associated bacterial biofilms. Congratulations to all poster prize winners! The awardees were further invited to a job shadowing at Boehringer Ingelheim, organized by Christian Kuttruff and the NextGenMedChem team.

After the poster prizes, María Méndez Pérez (Sanofi) announced that Michael Hahn (Bayer AG) has been selected from the many outstanding speakers as the winner of this year's NextGenMedChem award for the best talk of the conference. We were delighted that he accepted our offer to give his extended talk on the discovery of BAY2586116, a TASK-1 and TASK-3 channel blocker for the treatment of obstructive sleep apnea in a MedChemCASES webinar, which will take place in September 2023.

Finally, after three days full of outstanding science, the conference was closed by Thierry Langer and Gerhard Hessler with concluding remarks acknowledging all the organizers, the scientific advisory board, and of course all attendees and speakers for their great contributions.

We look forward to the Frontiers in Medicinal Chemistry Conference 2024, which will take place from 17th to 20th of March 2024 in Munich (Save the date!, see Figure 5).

Recent and Upcoming Activities of the NextGenMedChem Group

As a part of the NextGenMedChem 'Job shadowing in industry' program, which is intended to enable young scientists and students to discover the world of Medicinal Chemistry in industry, all four FiMC poster prize winners (Max E. Huber, Tonia Kirschner, Lukas Schneider and Josef Braun) were invited for a job shadowing at the Boehringer Ingelheim site in Biberach an der Riß.

The MedChemCASES webinar series, organized by the NextGenMedChem group, features outstanding Medicinal Chemistry case studies from industry and academia several times per year. One of the highlights of last year was the presentation given by Brian Lanman (Amgen) on the development of the first $KRAS^{G12C}$ inhibitor sotorasib. Outstanding

Figure 5. Save the date for the Frontiers in Medicinal Chemistry Conference 2024 in Munich.

academic research was presented by Anna Hirsch (HIPS) who showcased their approaches for addressing unusual anti-infective targets. With the permanently increasing number of participants, we will continue to offer you very exciting Medicinal Chemistry case studies on a regular basis (stay tuned on: www.gdch.de/medchemcases or the LinkedIn group of the GDCh MedChem Division).

For the last two years, the NextGenMedChem team organized one of the sessions at the FiMC: Next Generation Drugs. We will continue this still young but very nice tradition at the FiMC 2024 and look forward to seeing you in Munich.

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Conflict of Interests

The authors declare no conflicts of interest.

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