Synthesis of *meta*-Substituted Arene Bioisosteres from [3.1.1]Propellane

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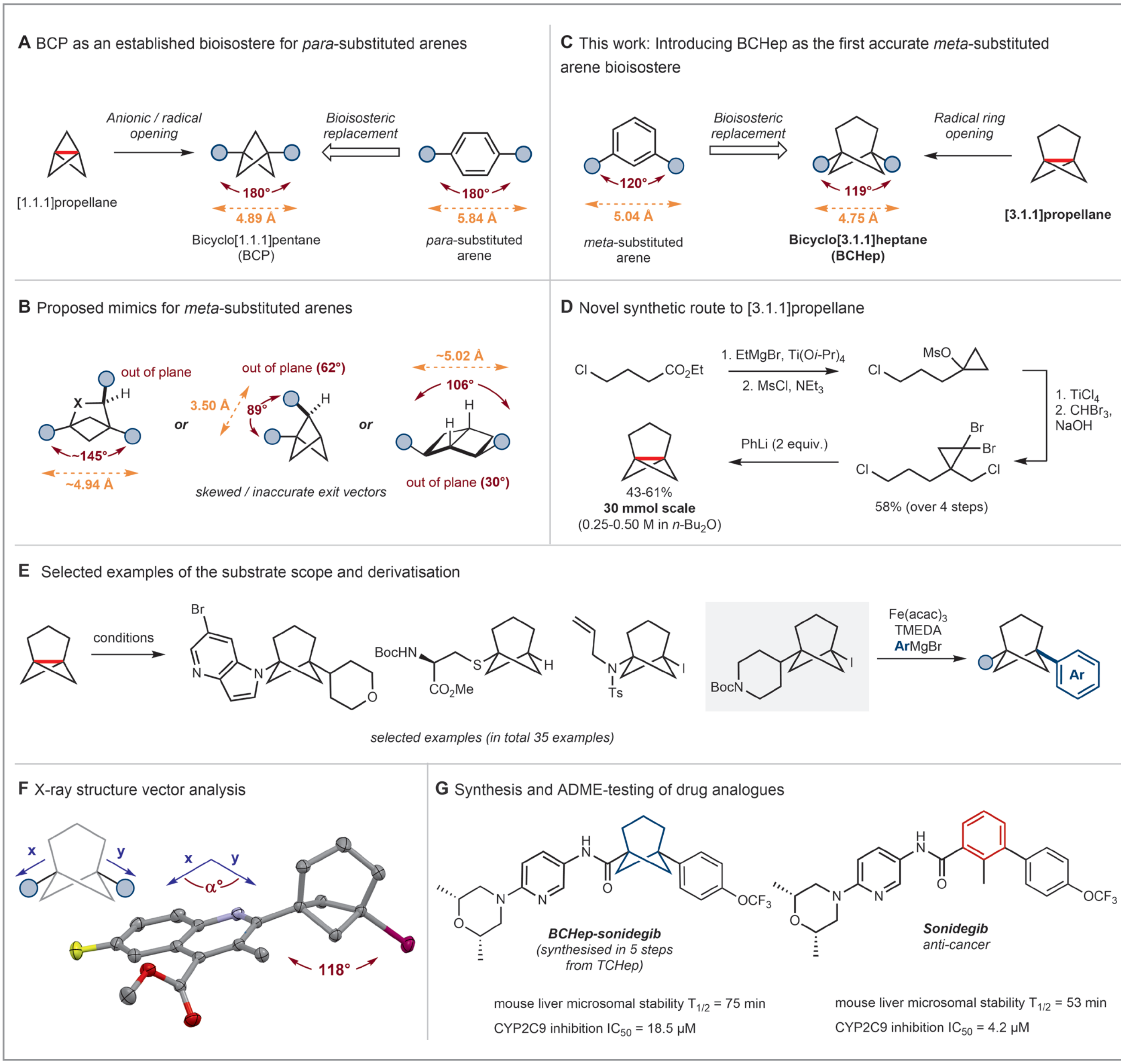
Bicyclo[1.1.1]pentanes (BCPs) have emerged as important structures in drug development as bioisosteres for *para*-substituted benzene rings. The group of Professor Ed Anderson at the University of Oxford (UK) has had a long-standing interest in the molecule [1.1.1]propellane, the usual precursor to a BCP, from both synthetic and mechanistic perspectives. "BCPs display increased solubility and metabolic stability compared to their aromatic parents, while retaining the 180° substitution geometry and, often, bioactivity (Scheme 1A),"[1,2] said Professor Anderson, adding: "BCPs have spearheaded an armada of small-ring cage hydrocarbons that 'escape the aromatic flatland' through their three-dimensionality, which has been linked to higher clinical success rates of drug candidates.[3,4] However, a bioisostere for *meta*-substituted arenes that accurately mimics their 120° substitution geometry has, to date, been absent from this collection (Scheme 1B)."

Prof. Anderson stated that an obvious extension of his group's research into ring-opening reactions of [1.1.1]propellane was to explore its next stable higher congener, namely [3.1.1]propellane, which they recognised could lead to a bicyclo[3.1.1]heptane product, that perfectly mimics the geometry of a *meta*-substituted benzene (Scheme 1C). The group faced two questions: whether [3.1.1]propellane could indeed serve as a versatile precursor to bicyclo[3.1.1]heptanes (BCHeps), and whether BCHeps would bestow equivalent property benefits as BCPs in drug candidates. Before these questions could be addressed, the first challenge was to prepare [3.1.1]propellane on a synthetically useful scale, as previous approaches from the 1980s and 1990s delivered only milligram quantities, hindering synthetic explorations.[5,6]

A scalable synthesis of [3.1.1]propellane was first developed by the group (Scheme 1D). Masters student Nils Frank commented: "We were inspired by the tetrahalide propellane synthesis strategy established by Szeimies, and were able to replace a number of awkward synthetic steps in the known approaches to [3.1.1]propellane by employing a Kulinkovich cyclopropanation/rearrangement sequence. This streamlined the chemistry and offered easy access to the required tetrahalide precursor, with only one column purification required."

By overcoming this synthetic bottleneck, the door was opened to explore the reactivity of [3.1.1]propellane. Nils Frank and postdoc Dr Jeremy Nugent trialled a range of methodologies applicable to [1.1.1]propellane ring-opening on [3.1.1]propellane. "Our group's own methodology was easily translated onto [3.1.1]propellane, such as the photoredox-catalyzed addition of organic halides," Nils explained (Scheme 1E). He continued: "We were fortunate that even a complex three-component metallaphotoredox reaction reported by the MacMillan group for [1.1.1]propellane proved possible to carry out on [3.1.1]propellane without much modification. However, many reactions failed – especially anionic methodologies that are successful on the smaller [1.1.1] system." Prof. Anderson added: "Our long-standing collaboration with computational chemists Alistair Stirling and Prof. Fernanda Duarte revealed the source of this reactivity difference. We believe this derives from the unique abilities of three-membered rings to stabilise electron density; as [3.1.1]propellane features one less cyclopropane than [1.1.1]propellane, this disfavours reactions with anions."[7]

The ring-opening reactions of [3.1.1]propllane delivered a wide variety of BCHep products (Scheme 1E), several of which proved suitable for X-ray crystallography. This enabled DPhil student Helena Pickford to confirm the predicted 120° angle between the bridgehead substituents (Scheme 1F). DPhil student Bethany Shire then found that iodo-BCHeps can be cross-coupled with aryl Grignards in excellent yields using an iron-catalysed Kumada cross-coupling developed previously in the group.[8] "Derivatising the BCHep iodides was significant, as this opened up the rapid synthesis of BCHep pharmaceutical analogues," said Prof. Anderson. The group was thus able to prepare analogues of the anti-cancer drug Sonidegib (Scheme 1G) and the anti-seizure drug URB597. Collaboration with Prof. Paul Brennan enabled evaluation of a range of physicochemical and pharmacokinetic properties, which indeed revealed increased resistance towards metabolic degradation – one of the main hoped-for benefits of the BCHep. Promising data on improved membrane permeability were also observed. Prof. Anderson concluded: "These measurements were crucial to validate the design principle of the BCHep, and we hope will inspire medicinal chemists to test this structure in drug design settings."



Scheme 1 Synthesis of *meta*-substituted arene bioisosteres from [3.1.1]propellane

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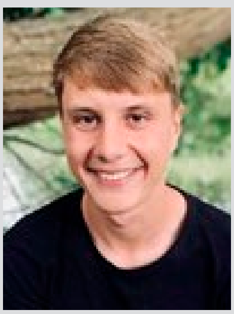

N. Frank

Nils Frank received his BSc degree from the Karlsruhe Institute of Technology (Germany) in 2020, during which time he also undertook an internship in the group of Professor Tobias Ritter at the Max Planck Institute for Coal Research (Germany), working on thianthrenation chemistry. He joined the group of Professor Anderson at the University of Oxford (UK) from 2020 to 2022, where he graduated with an MRes degree. In addition to his work on [3.1.1]propellane synthesis and reactivity, he also researched cycloaddition reactions of thiophene *S*,*S*-dioxides. In 2022, he joined F. Hoffmann-La Roche AG (Basel, Switzerland) for a one-year internship in medicinal chemistry before commencing his doctoral studies.

Dr. J. Nugent

Jeremy Nugent received his PhD from The Australian National University (Australia) in 2016 working with Professor Martin Banwell on the synthesis of various natural products. After a further year working as a postdoctoral fellow with Prof. Banwell, and a short stint with Vertex Pharmaceuticals, he moved to the University of Oxford (UK) to take up a Marie Skłodowska-Curie Fellowship working with Professor Ed Anderson. There, he developed new methods to synthesise bicyclo[1.1.1]pentanes and bicyclo[3.1.1]heptanes, important motifs in drug discovery. In 2022, he joined Samsara Eco (Australia) as Head of Chemistry.

Dr. B. R. Shire

Bethany Shire received her MChem degree from the University of Oxford (UK) in 2017; during this time, she explored enynamide cycloisomerisations with Prof. Edward Anderson. She then joined the EPSRC Synthesis for Biology and Medicine Centre for Doctoral Training (SBM CDT) at Oxford, and completed her DPhil studies in 2022 on catalytic methods for the synthesis of bicyclo[1.1.1]pentanes under the supervision of Prof. Anderson. She was then awarded an EPSRC Doctoral Prize to conduct further research into the applications of bicycloalkyl groups as bioisosteres.

Dr. H. D. Pickford

Helena Pickford received her MChem degree in 2017 from the University of Oxford (UK), where she worked on the synthesis of trigoxyphin natural products with Profs. J. Robertson and L. Wong. In 2022, she completed her DPhil as part of the EPSRC Synthesis for Biology and Medicine Centre for Doctoral Training (SBM CDT) at the University of Oxford. Her work involved the synthesis of heteroatom-substituted bicyclo[1.1.1]pentanes under the supervision of Prof. Anderson. Helena then joined the group of Prof. Matt Fuchter at Imperial College London (UK), where her research currently includes the synthesis of photoswitchable pharmaceuticals.

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Dr. P. Rabe

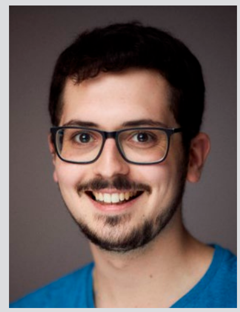
Patrick Rabe is a senior postdoctoral researcher in the Chemistry Research Laboratory at the University of Oxford (UK). In 2016, Patrick finished his PhD at the Kekulé Institute of Organic Chemistry and Biochemistry at the University of Bonn (Germany) on “Mechanistic Studies on Bacterial Terpene Synthases” with Prof. Jeroen S. Dickschat. For his doctoral thesis he received the 2017 Dechema doctoral award. Since 2017 he has been working in the group of Prof. Chris Schofield at Oxford (UK) on time-resolved crystallography and spectroscopy studies on oxygenases, with a fellowship funded by the Deutsche Akademie für Naturforscher Leopoldina (2017–2019).

Dr. A. J. Sterling

Alistair Sterling received his DPhil from the University of Oxford (UK) in 2021 under the supervision of Profs. Fernanda Duarte and Ed Anderson. Following postdoctoral studies with Prof. Duarte funded by an EPSRC Doctoral Prize, he joined the group of Prof. Martin Head-Gordon at the Lawrence Berkeley National Lab and the University of California, Berkeley (USA), where his research interests include theoretical physical organic chemistry and reaction development.

Dr. T. Zarganis–Tzitzikas

Tryfon Zarganis–Tzitzikas obtained his B.Sc. in chemistry from Aristotle University of Thessaloniki (Greece) in 2010 and his M.Sc., summa cum laude, in synthetic organic chemistry in 2012 at the same university. In 2017, he obtained his Ph.D., cum laude, in medicinal chemistry under the guidance of Prof. Alexander Dömling in the Group of Drug Design at the University of Groningen (Netherlands). His thesis focused on innovative multicomponent reactions and their use in medicinal chemistry. Tryfon then joined Symeres B.V. as a medicinal chemist working on immuno-oncology projects. Since 2014, he has been a co-founder and CSO of TelesisPharma B.V. (Netherlands), a company focusing on exploring novel synthetic routes to APIs using multicomponent reactions. In 2018, he joined Prof. Paul Brennan’s group at the Oxford Drug Discovery Institute (UK) as a senior postdoctoral scientist focusing on dementia targets, funded by Alzheimer’s Research UK.



T. Grimes

Thomas Grimes received his MChem degree from Durham University (UK) in 2017. He spent the final year of his degree in the epigenetics department at GSK in Stevenage (UK), working on the synthesis of BD2 selective BET bromodomain inhibitors. Following his degree, he worked for two years as a contract chemist based at the Eli Lilly Erl Wood site where he worked on a variety of Eli Lilly and Elanco projects. He joined the Alzheimer‘s Research UK Oxford Drug Discovery Institute at the University of Oxford (UK) as a Research Assistant in 2019 to work on the design of NLRP3 inflammasome inhibitors, and in 2022 began his DPhil within the same group under the supervision of Prof. Paul Brennan.

Dr. R. C. Smith

Russell C. Smith received his PhD in organic chemistry from the University of Illinois Urbana Champaign (USA) under the tutelage of Professor Scott Denmark focusing on the mechanistic understanding of the silicon-based cross-coupling reaction. He then traversed out to California to conduct his postdoctoral studies with Professor Brain Stoltz at the California Institute of Technology (USA) on efforts toward the total synthesis of ineleganolide. His professional career began at Janssen PRD in San Diego, CA (USA) as a medicinal chemist working in the area of immunology for over 9 years. Russell then returned to the Midwest in early 2020 to transition to AbbVie, joining the Centralized Organic Synthesis (COS) group where he currently holds the position of Senior Scientist II. He has recently been involved in the development of novel on-DNA method developments and applications while maintaining productive and active collaborations between the pharmaceutical and academic sectors.

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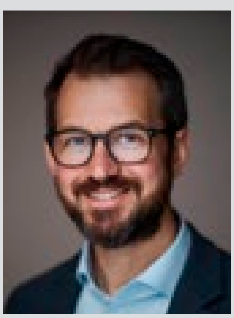
Professor C. J. Schofield

Chris Schofield's research centres on contributing to a chemistry-based understanding of systems of biological importance, including mechanisms of antibiotic resistance and the regulation of genetic machinery. An important aspect of his work has concerned enabling the exploitation of basic science results for societal/medicinal benefit, including for treatment of infectious diseases and hypoxia-related diseases (e.g. anaemia and cancer). Two current major research fields of the group are antibiotics/antibiotic resistance and the biochemistry and biology of oxygenases and hypoxia.



Professor P. E. Brennan

Paul Brennan received his PhD in organic chemistry from UC Berkeley (USA). Following post-doctoral research at the University of Cambridge (UK), Paul spent eight years working in the pharmaceutical industry at Amgen and Pfizer. In 2011, Paul joined the Structural Genomics Consortium at the University of Oxford (UK). Over the course of his career, Paul has worked on most major classes of drug targets: kinases, GPCRs, ion-channels, metabolic enzymes, and epigenetic proteins. Paul is currently Professor of Medicinal Chemistry and Chief Scientific Officer of the Alzheimer's Research UK Oxford Drug Discovery Institute in the Centre for Medicines Discovery at the University of Oxford. His research is focused on finding new treatments for dementia.

Professor F. Duarte

Fernanda Duarte is an Associate Professor in the Department of Chemistry at the University of Oxford (UK), a position she has held since 2018 following appointments at the University of Edinburgh, UK (Chancellor's Fellow), the University of Oxford (Newton Fellow), and Uppsala University, Sweden (PDRA). She leads a diverse team of researchers working at the interface of organic chemistry, supramolecular catalysis, and computational chemistry. Her research interests are centred on the prediction of chemical reactivity in the condensed phase, combining classical, quantum and machine-learning approaches. Her group has also developed a series of computational software to facilitate molecular design and reaction mechanism exploration. She has published over 60 peer-reviewed scientific publications and received several awards, most recently including the 2022 Novartis Early Career Award in Chemistry, and the 2021 RSC Harrison-Meldola Memorial Prize.

Professor E. A. Anderson

Ed Anderson is Professor of Organic Chemistry at the University of Oxford (UK). He began his independent career as an EPSRC Advanced Research Fellow in 2007, during which time he was appointed as Associate Professor at Jesus College, Oxford in 2009, and then as Professor in 2016. His research interests encompass a wide range of synthetic organic chemistry, including natural product total synthesis, transition-metal catalysis and mechanistic study, bicyclo[1.1.1]pentanes and related small rings, antiparasitic natural products, the chemistry of ynamides and yndiamides, and EPR spectroscopy in nucleic acids. He is a recent recipient of the Novartis Chemistry Lectureship (2018), and RSC Bader Award (2020).

