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

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Abstract: Small-ring cage hydrocarbons are common bioisosteres for *para*-substituted benzene rings in drug design, exhibiting superior pharmacokinetic properties compared to the parent aromatics. In contrast, scaffolds mimicking *meta*-substituted arenes are lacking due to the challenge of synthesising saturated isosteres that accurately reproduce the substituent vectors of the corresponding arene. Here we report the use of [3.1.1]propellane as a convenient and scalable precursor to bicyclo[3.1.1]heptanes (BCHeps), hydrocarbons whose bridgehead substituents map precisely onto the geometry of *meta*-substituted benzenes. This precursor undergoes a range of radical-based transformations to generate medicinally-relevant carbon- and heteroatom-substituted BCHeps, including BCHep pharmaceutical analogues. Comparison of ADME properties of the latter reveals improved metabolic stability relative to their parent drugs, validating the potential of this *meta*-arene analogue as an sp^3-rich motif in drug design.

Main Text: Strategies for the structural modification of lead molecules that improve pharmacokinetic properties and metabolic stability are increasingly sought in drug development (*1*). One example is the replacement of aromatic rings with non-classical bioisosteres such as small-ring cage hydrocarbons (*2-5*). Such structures display a higher fraction of saturated carbon atoms compared to the parent arenes (Fsp^3, corresponding to greater three-dimensionality), a property linked to greater clinical success rates (*6*). Amongst these motifs, the replacement of planar *para*-substituted arenes with bicyclo[1.1.1]pentanes (BCPs, Fig. 1A), which have similar dimensions and identical substituent vectors to the parent aromatic, has emerged as a popular strategy (*7-9*). For instance, substitution of the fluorinated arene in the Alzheimer's treatment avagacestat with a BCP resulted in an analogue that maintained the bioactivity of the parent compound, but displayed an improved pharmacokinetic profile (*7*). More generally, cage hydrocarbons expand the vector space around a molecular core, offering new opportunities in drug design.

Meta-substituted arenes are also commonplace in pharmaceuticals and agrochemicals (*10*). However, in stark contrast to the numerous sp^3-rich bioisosteres for *ortho*- and *para*-substituted arenes (*7-9, 11*), a geometrically-accurate bioisostere for *meta*-arenes is yet to be discovered. Recent reports on the use of (hetero)bicyclo[2.1.1]hexanes (*12-16*) and bridge-substituted BCPs (*17-19*) have contributed to this arena (Fig. 1B). However, those motifs fail to recreate the bond vectors displayed in the *meta*-substituted aromatic, and a precise and accessible mimic remains absent from the arsenal of the medicinal chemist.

Here we report a solution to this challenge in the form of the saturated carbocycle bicyclo[3.1.1]heptane (BCHep, Fig. 1C), the bridgehead substituent vectors of which precisely replicate those of the parent *meta*-arene (~119° and ~120° respectively). While BCHeps have been prepared by ring expansion of BCPs (*20*) and by cyclization of cyclohexane dicarboxylates (*21*), these approaches can be limited in substituent scope or involve lengthy synthetic sequences. We show that BCHeps can instead be conveniently and directly accessed from [3.1.1]propellane (**1**), a homologue of [1.1.1]propellane (**2**) which is widely used as the near-ubiquitous source of BCPs (*22*). We found **1** to be a versatile precursor that undergoes a variety of radical-based transformations to access a wide range of functionalized BCHeps, including drug analogues. Profiling of the ADME properties of these analogues reveals that, like BCPs, BCHeps significantly improve physicochemical properties compared to their arene parents. As such, we anticipate that this novel scaffold should offer a readily accessible bioisostere for broad implementation in drug discovery programmes.

Higher [n.1.1]propellanes such as **1** have to date been of predominantly theoretical interest (*23, 24*); these elusive molecules have likely been overlooked in synthetic and medicinal chemistry due to the challenge of their synthesis and reported instability (*25, 26*). We devised a strategy to synthesise **1** on multigram scale (Fig. 1D), which began with Kulinkovich cyclopropanation of commercially available γ-chloroester **3** (*27*). Mesylation of the resulting alcohol **4**, followed by $TiCl_4$-mediated cyclopropyl–allyl chlorinative rearrangement and dibromocyclopropanation, afforded cyclopropane **5** in 58% yield over four steps on >30 mmol scale with only one chromatographic purification. Reaction of **5** with two equivalents of phenyllithium generated **1** in yields of 43–61% after distillation; the resulting solution of **1** (0.25–0.50 M in dibutyl ether) can be stored at –20 °C for several months with negligible decomposition.

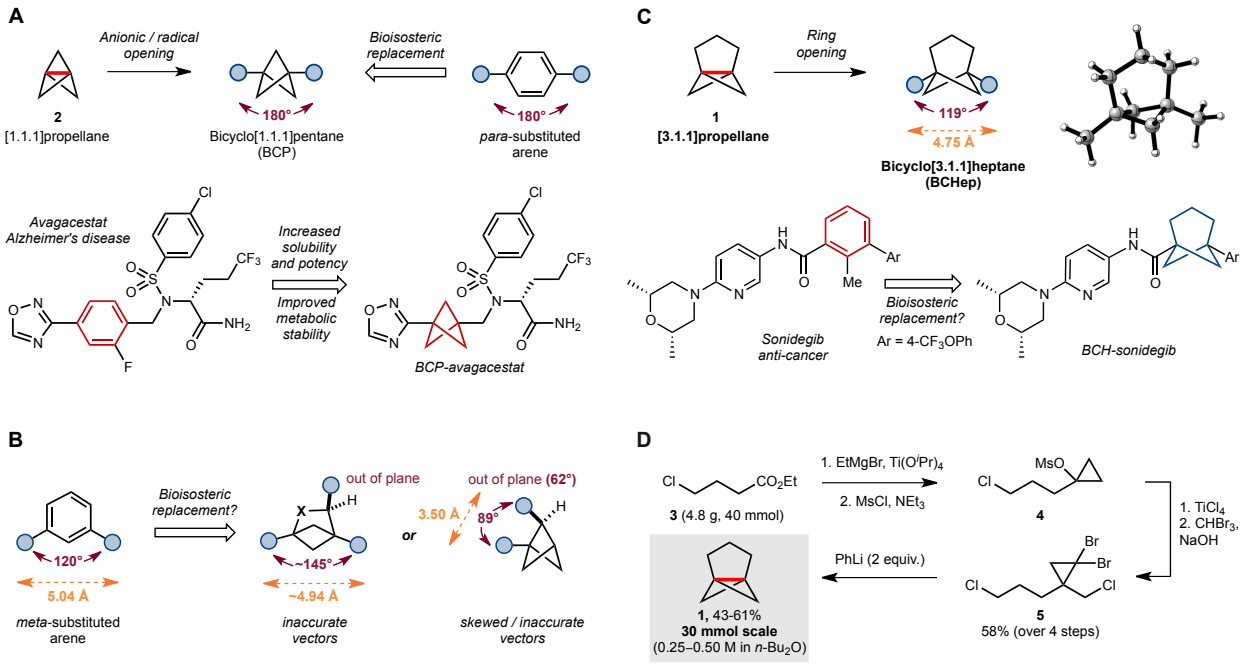


Fig. 1. Comparison of *para*- and *meta*-substituted arene bioisosteres, and synthesis of [3.1.1]propellane. (**A**) Bicyclo[1.1.1]pentanes (BCPs) derived from [1.1.1]propellane (**2**) are bioisosteres for *para*-substituted benzene rings, (**B**) Previous mimics of *meta*-substituted arenes, which do not accurately reproduce the geometry of the aromatic, (**C**) This work: Bicyclo[3.1.1]heptanes (BCHeps) derived from [3.1.1]propellane (**1**) exactly mimic the geometry of *meta*-substituted arenes, (**D**) A multigram scale synthesis of [3.1.1]propellane.

Previous reports on the chemistry of **1** detail only one reaction – the addition of thiophenol to generate BCHep phenyl thioether (*26*). As a prelude to exploring the wider reactivity of **1**, we first compared the calculated reaction barriers for the addition of a prototypical radical ($CH_3^{\bullet}$) and nucleophile (NH_2^-) with those for **2** (Fig. 2A) (*28*). These calculations predict that **1** should be

similarly susceptible to the addition of radicals to the inter-bridgehead C–C bond ($\Delta\Delta G^{\ddagger}$ = –1.1 kcal mol^{-1} between **1** and **2**), but that the reaction of **1** with anions is less favourable ($\Delta\Delta G^{\ddagger}$ = +5.4 kcal mol^{-1}). This in part may relate to the greater increase of charge density inside the propellane cage in anionic additions, which can be better accommodated by **2** due to the presence of a third three-membered ring that enables enhanced charge delocalization (*28, 29*). Our calculations therefore suggest that **1** should be amenable to the same panoply of radical functionalization chemistry established in the [1.1.1]propellane/BCP arena.

This theoretical analysis correlated well with experimental findings. We first explored atom transfer radical addition (ATRA) reactions, which are a powerful method to access disubstituted BCPs from **1**. Both Et_3B-initiated (*30*) and $Ir(ppy)_3$-catalyzed (*31*) addition of a variety of C–I bonds to **1** proceeded efficiently to afford diverse BCHep scaffolds (Fig. 2B). The photoredox-catalyzed variant ($Ir(ppy)_3$) proved more general and higher yielding, affording iodo-BCHeps from α-iodocarbonyls (**6a**–**6d**) benzyl iodides (**6e**–**6f**), unactivated alkyl iodides (**6g**–**6k**), α-amino acids (**6l**), and heteroaryl iodides (**6m**). In contrast to ATRAs with [1.1.1]propellane (*30*), Et_3B initiation was suitable mainly for electrophilic radicals such as α-iodocarbonyls (**6a**, **6b**) and azetidines (**6h**). Notably, the addition of iodotrifluoromethane to **1** proceeded in the absence of an external initiator to afford **6n**, which could be a valuable building block for the synthesis of bioisosteres of *meta*-CF_3-substituted arenes. Addition to alkyl bromides such as bromomalonate (**6o**, 57%) and bromotrichloromethane (**6p**, 68%) also proved feasible, the latter proceeding without an initiator. The chemistry could further be applied to the late-stage bicycloheptylation of various drug analogues, affording BCHep derivatives of corticosterone (**6q**), nicotinic acid (**6r**), brequinar (**6s**) and indomethacin (**6t**). Notably, in contrast to equivalent ATRA reactions with [1.1.1]propellane, no ‘staffane’ byproducts arising from [3.1.1]propellane oligomerization were observed.

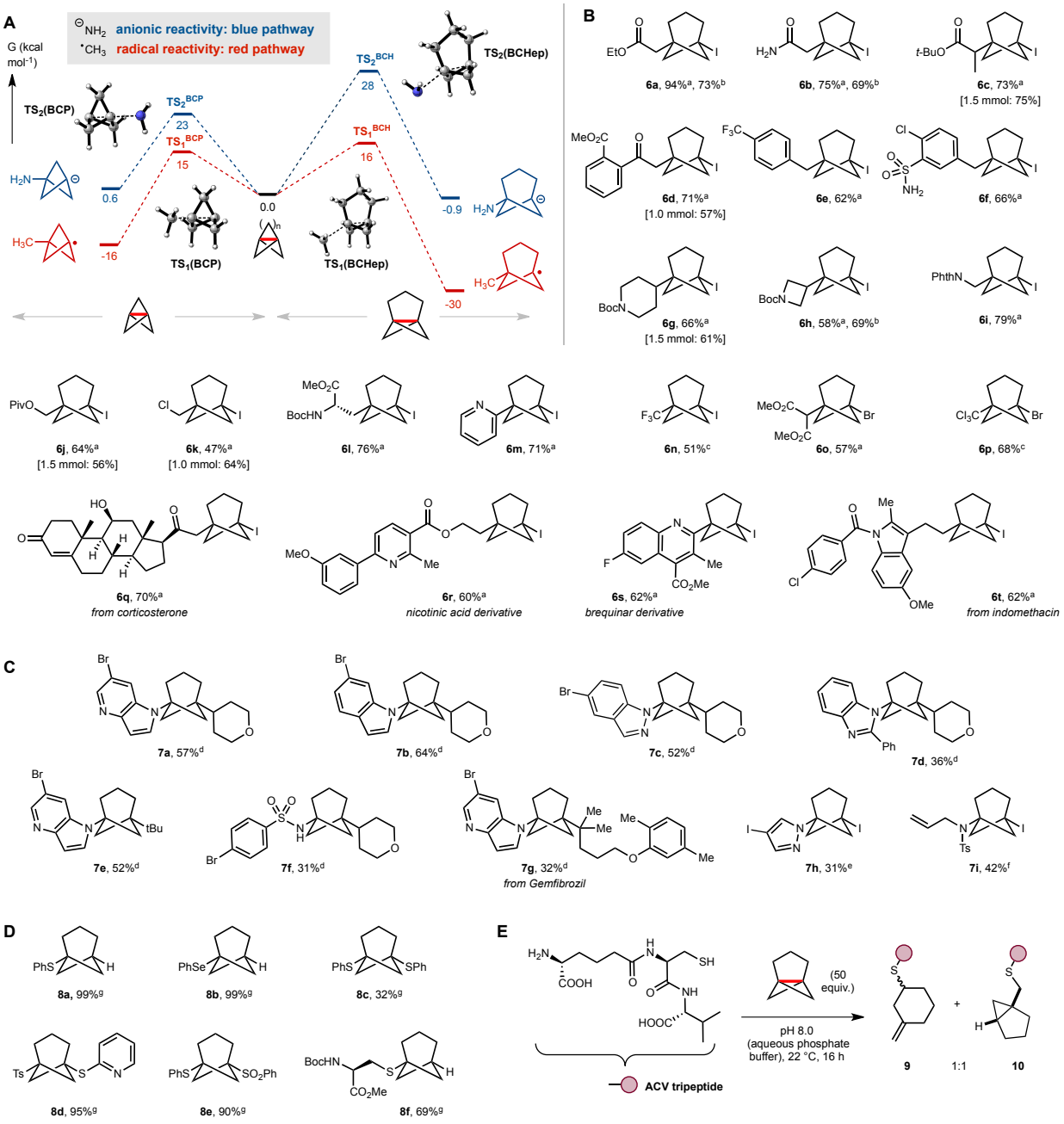


Fig. 2. Theoretical analysis of [1.1.1] and [3.1.1]propellane reactivity and synthesis of BCHeps from [3.1.1]propellane. (**A**) Reactivity profile of **1** calculated at SMD(THF)-DLPNO-CCSD(T)/ma-def2-QZVPP//SMD(THF)-B2PLYP-D3BJ/def2-TZVP (ma-def2-TZVP on N) level of theory, (**B**) Carbon/halogen-substituted BCHeps prepared from organohalides using a) $Ir(ppy)_3$ (2.5 mol%), blue LED irradiation, or b) Et_3B (10 mol%) as initiator, or c) without an initiator, (**C**) Nitrogen-substituted BCHeps prepared using d) dual photoredox / Cu-catalyzed coupling of iodonium dicarboxylates and N-heteroarenes, or e) pyrazole / I_2, or f) α-iodoaziridine, $Ir(ppy)_3$ (2.5 mol%), blue LEDs, (**D**) g) Chalcogen-substituted BCHeps prepared by direct reaction with the chalcogen–X precursor, (**E**) Cysteine-selective conjugation studies using the (L,L,D) δ-(α-aminoadipolyl)-Cys-Val (ACV) tripeptide in aqueous phosphate buffer (50 mM, pH 8.0). Reactions run on 0.1–0.2 mmol scale unless shown otherwise. See the Supplementary Materials for details.

Bridgehead amine substituents are highly attractive as potential *meta*-substituted aniline bioisosteres. We found that the three-component metallaphotoredox catalyzed coupling of iodonium dicarboxylates, [1.1.1]propellane and *N*-heteroarenes described by the Macmillan group (*32*) translated smoothly to [3.1.1]propellane (Fig. 2C), affording azole- and sulfonamide-substituted BCHeps **7a**–**7g** in good yields, including pharmaceutical derivatives (gemfibrozil, **7g**). The synthesis of *N*-substituted iodo-BCHeps was achieved using other methods, such as pyrazole BCHep **7h** by reaction of **1** with pyrazole / I_2 (*33*), and allyl sulfonamide BCHep **7i** from radical fragmentation of an iodoaziridine (*34*). As well as *C*- and *N*-centered radicals, other heteroatoms proved excellent substrates for reactions with **1** (Fig. 2D): Thioether **8a** and selenoether **8b** were formed in quantitative yields at room temperature, sulfonothioate addition (**8c**, **8d**) proceeded efficiently under heating (*35, 36*), and reaction with a disulfide could be achieved under UV irradiation (**8e**) (*37*). The successful bicycloheptylation of protected cysteine (**8f**) in diethyl ether highlights the potential for applications in peptide modification (*38*); unexpectedly, reaction of a

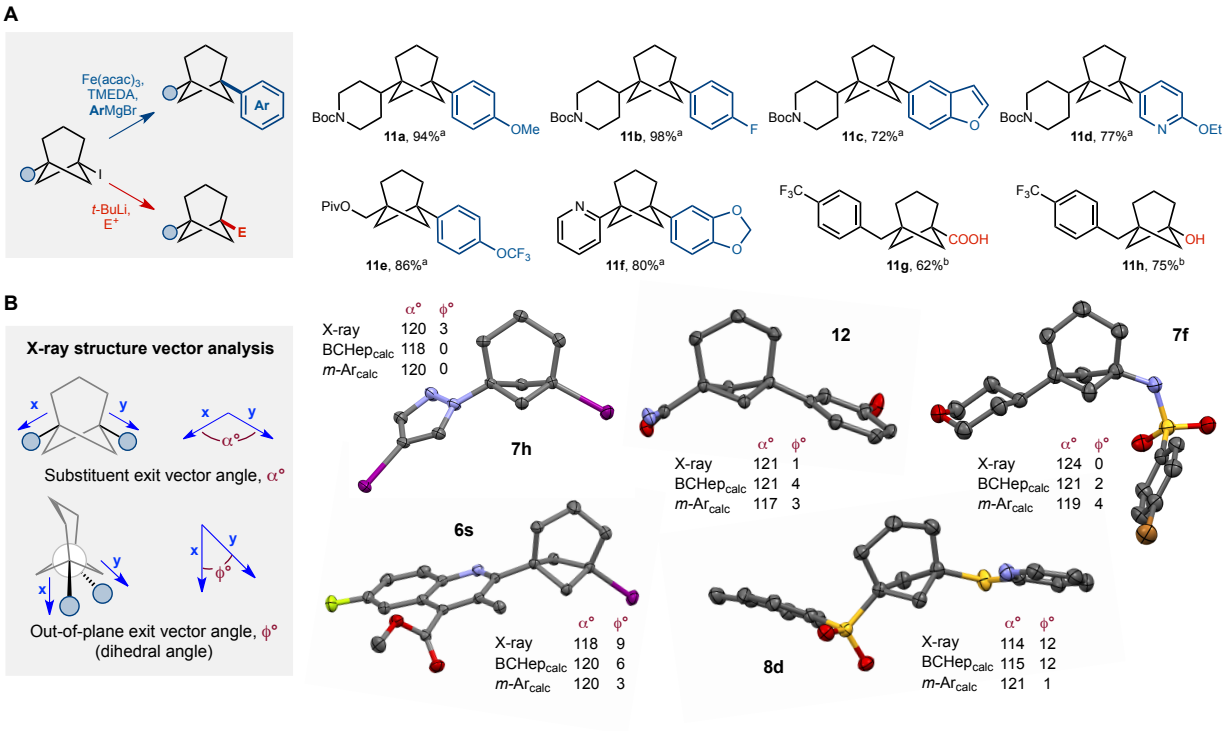


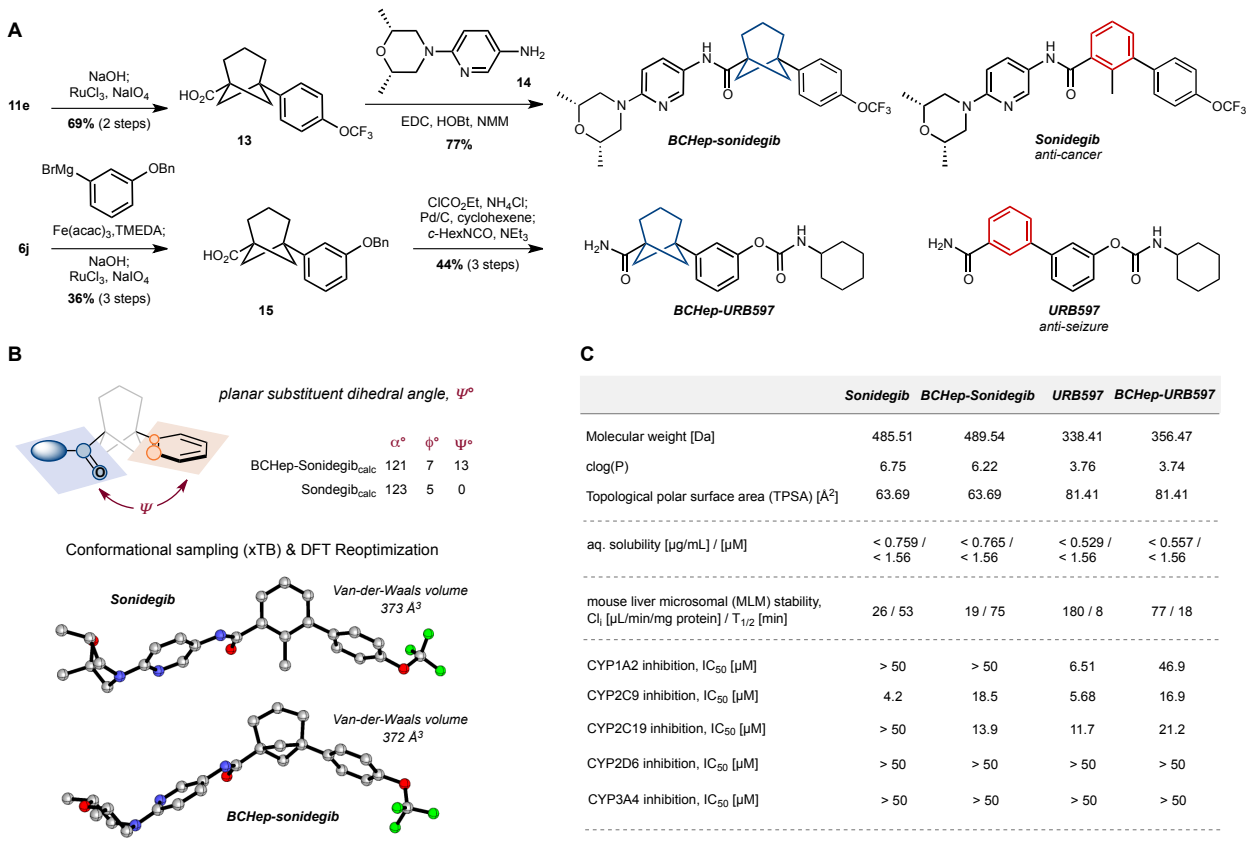
Fig. 3. BCHep functionalization and topological analysis of crystalline derivatives. (**A**) Functionalization of iodo-BHeps through a) iron-catalyzed Kumada coupling, or b) lithiation / electrophilic quench, (**B**) Comparison of angles between substituent vectors from single crystal X-ray structures ('X-ray'), and computed structures for BCHeps and the parent arenes ('BCHep$_{calc}$' and '*m*-Ar$_{calc}$', CPCM(THF)-B2PLYP-D3BJ/def2-TZVP level of theory). See the Supplementary Materials for details.

similar cysteine residue in a tripeptide ((L,L,D) δ-(α-aminoadipolyl)-Cys-Val, ACV) in aqueous buffer afforded the rearranged adducts **9** and **10** (Fig. 2E), which may arise from a cationic reaction pathway. While the reason for this reactivity difference is unknown, it is clear that selective *S*-alkylation of cysteine is possible under physiologically-relevant conditions.

Iodinated BCHeps offer opportunities for C–I functionalization towards medicinally-relevant difunctionalized scaffolds. Investigation of iron-catalyzed Kumada cross-coupling (*39*) revealed efficient reaction of iodo-BCHeps with both aryl and heteroaryl Grignard reagents to afford (hetero)aryl BCHeps in excellent yields (**11a**–**11f**, Fig. 3A). BCHep functionalization was also possible by lithiation of the iodide; reaction of the resulting bridgehead carbanion with CO_2 or *i*-PrOBpin gave carboxylic acid **11g** and hydroxy-BCHep **11h** (after *in situ* oxidation) respectively, the latter of which corresponds to a *meta*-phenol bioisostere.

X-Ray structural determination of several crystalline BCHeps enabled us to study the geometry of the scaffold in more detail (Fig. 3B). Two substituent vector angles were considered: the exit vector angle α (~120° for *m*-arenes), and the out-of-plane vector angle ϕ (the dihedral angle along the BCHep inter-bridgehead axis, ~0° for *m*-arenes). Comparison of the BCHep solid state structures with computed structures of the BCHep and the equivalent *meta*-arene showed excellent agreement for both angles ($\Delta\alpha$ = 0–7°, $\Delta\phi$ = 3–11°), validating our hypothesis that the replacement of *meta*-substituted arenes with a BCHep conserves the critical substituent geometry.

Kumada cross-coupling was deployed to synthesise two BCHep drug analogues (Fig. 4A). The BCHep analogue of the anticancer agent sonidegib was accessed from coupling product **11e** by pivaloate ester hydrolysis, oxidation of the resulting primary alcohol to the carboxylic acid **13**, and amide formation with aminopyridine **14** (53% yield over three steps, 19% from **1**). BCHep-URB597, the parent *meta*-arene of which was developed as a fatty acid amide hydrolase inhibitor, was synthesized from **6j** by a similar cross-coupling / hydrolysis / oxidation sequence, followed by amide formation, debenzylation, and carbamoylation with cyclohexyl isocyanate (16% over 5 steps). Computational conformer sampling once again revealed a similar global topology between BCHep-sonidegib and the parent drug for the vector angles α and ϕ (Fig. 4B). Here, an additional parameter was considered: the rotational orientation of the planes between the two substituent groups as defined by the dihedral angle ψ ($\Delta\psi$ = 13°). The BCHep displayed a shallow potential energy profile



	Sonidegib	BCHep-Sonidegib	URB597	BCHep-URB597
Molecular weight [Da]	485.51	489.54	338.41	356.47
clog(P)	6.75	6.22	3.76	3.74
Topological polar surface area (TPSA) [Å^2]	63.69	63.69	81.41	81.41
aq. solubility [µg/mL] / [µM]	< 0.759 / < 1.56	< 0.765 / < 1.56	< 0.529 / < 1.56	< 0.557 / < 1.56
mouse liver microsomal (MLM) stability, Cl_i [µL/min/mg protein] / $T_{1/2}$ [min]	26 / 53	19 / 75	180 / 8	77 / 18
CYP1A2 inhibition, IC_{50} [µM]	> 50	> 50	6.51	46.9
CYP2C9 inhibition, IC_{50} [µM]	4.2	18.5	5.68	16.9
CYP2C19 inhibition, IC_{50} [µM]	> 50	13.9	11.7	21.2
CYP2D6 inhibition, IC_{50} [µM]	> 50	> 50	> 50	> 50
CYP3A4 inhibition, IC_{50} [µM]	> 50	> 50	> 50	> 50

Fig. 4. Synthesis of BCHep pharmaceutical analogues and comparison of pharmacokinetic profile and metabolic stability. (**A**) Synthesis of BCH analogues of sonidegib and URB597, (**B**) Computational investigation of the topology of BCHep-sonidegib, (**C**) Physicochemical and metabolic profile of BCHep-sonidegib and BCHep-URB597 along with their parent compounds. See the Supplementary Materials for details.

for rotation around the BCHep–substituent C–C bond (ΔG = 1.5 kcal mol^{-1}), reflecting a low conformational preference of the substituents adjacent to the quaternary carbons of the BCHep. This may suggest that BCHeps offer significant flexibility in substituent conformation, which could be a valuable property for drug design by facilitating a more adaptable association with protein targets.

Synthesis of these drug analogues raises the question of how the physicochemical and pharmacological properties of the BCHep compare with the parent arene (Fig. 4C). The cLogP, Topological Polar Surface Area (TPSA) and solubility of each drug / analogue pair are remarkably similar, demonstrating that BCHeps can be readily deployed in drug design as true *meta*-arene bioisosteres. In keeping with their well-established BCP cousins, BCHeps showed reduced clearance rates in mouse liver microsomes compared to their arene equivalents. The BCHep analogues were also tested for CYP inhibition and generally showed an improvement compared to

their corresponding arenes (Fig 4C). URB597 inhibits CYP1A2 and CYP2C9 with IC_{50}'s below 10 μM, but BCH-URB597 is 7- and 3-fold weaker against these two polymorphic enzymes. This further demonstrates the potential for BCHep analogues to address problems with drug-drug interactions.

Summary: Bridgehead-disubstituted bicyclo[3.1.1]heptanes (BCHeps) accurately replicate the geometry of *meta*-substituted arenes, and are readily accessed by radical ring opening of [3.1.1]propellane. This unusual member of the propellane family can now be prepared on multigram scale, but to date has barely been explored as a BCHep precursor. A wide variety of radical-based functionalizations demonstrate the potential of this entry to novel bioisosteres, and application to the synthesis of pharmaceutical analogues provides a first demonstration of BCHep installation for use in sp^3-rich drug design.

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