Water-soluble Bioisosteres of *meta*-Benzenes

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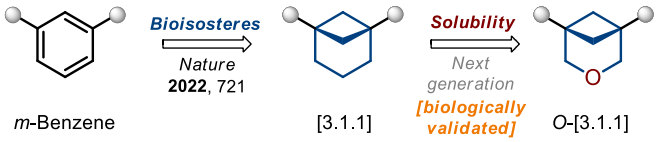
Water-soluble bioisosteres of *meta*-benzenes have been synthesized, characterized, and validated biologically.

Introduction

Benzene is the most popular ring in chemistry.[1] In 2022, scientists showed that bicyclo[3.1.1]heptane could mimic the fragment of *meta*-benzene in a biologically active compound.[2] Both cores had a similar distance between substituents (4.8-5.0 Å), similar angles between exit vectors (119-120º), and similar physicochemical properties (Scheme 1). As a result, bicyclo[3.1.1]heptane was proposed to be a saturated bioisostere of *meta*-benzene.[3]

In this work, we have developed a new generation of these structures - water-soluble bioisosteres of *meta*-benzenes (Figure 1).



Scheme 1. Bicyclo[3.1.1]heptanes as bioisosteres of benzenes. This work: 3-oxabicyclo[3.1.1]heptanes as a new generation of benzene bioisosteres.

Results and discussion

Design. The methylene for oxygen replacement in saturated scaffolds leads to a dramatic improvement in solubility.[4] An analogous maneuver in bicyclo[3.1.1]heptane could potentially give three isomers A, B, and C (Figure 2). Isomer A is a strained oxetaine and therefore is expected to be chemically labile.[5] Isomer B is less symmetric than the original core, as it only has one plane of symmetry.[6] Isomer C, on the other hand, should be (a) chemically stable, and (b) has two plains of symmetry similar to the original bicyclo[3.1.1]heptane. In this context, we decided to focus our attention on the latter isomer, - 3-oxabicyclo[3.1.1]heptane, - as a potential *meta*-benzene bioisostere.

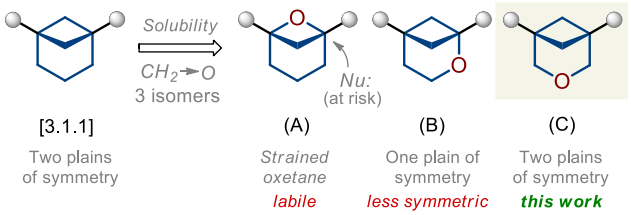
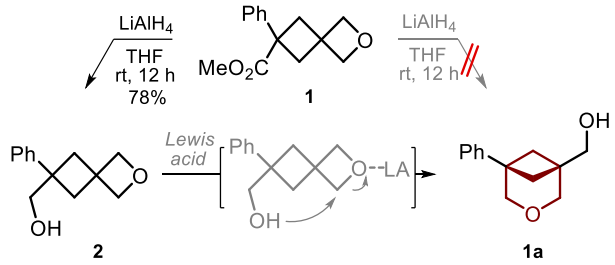


Figure 1. Design of water-soluble bioisosteres of *meta*-substituted benzenes.

Synthesis. *Poly*-substituted 3-oxabicyclo[3.1.1]heptanes were known in the literature.[7,8] We needed, however, a modular approach that would provide compounds with only *two* substituents at the bridgehead positions of the core (to mimic *meta*-disubstituted benzene) without additional (poly)substitution at other positions.[9]

Previously, we showed that the reduction of spirocyclic oxetanyl nitriles with lithium aluminium hydride led to the direct formation of 3-azabicyclo[3.1.1]heptanes.[10] Here, we naively hoped that the alternative reaction under identical conditions would also work for the corresponding esters. As it often happens in life, the reality happened to be a bit different. The reduction of ester **1** with $LiAlH_4$ gave only alcohol **2** (Scheme 2). Formation of the desired 3-oxabicyclo[3.1.1]heptane **1a** was not observed at all. Alcohol **2** did not isomerize into compound **1a** neither at room temperature (Scheme 2, entry 1) nor under heating (entry 2). In a last desperate move with no particular hope, we tried to perform the isomerization under the Lewis acid catalysis. Blessingly, the isomerization indeed proceeded quite smoothly with boron trifluoride etherate, aqueous hydrochloric acid, and phosphoric acid at room temperature (entries 3-7), leading to the formation of the desired compound **1a**. In the experiment with boron trifluoride etherate, product **1a** was isolated in 97% yield.

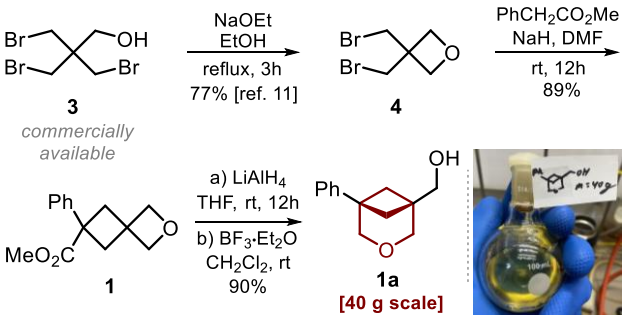


entry	conditions (*Lewis acid*)	conversion.[a]
1	THF, rt, 24 h	0% (SM)
2	THF, reflux, 1 h	0% (SM)
3	$BF_3{\cdot}Et_2O$ (10% mol.), CH_2Cl_2, rt, 2 h	100% (97%)[b]
4	10N HCl (5 eq.), rt, 2 h	95%
5	10N HCl (5 eq.), rt, 8 h	100%
6	H_3PO_4 (20% mol.), dioxane, rt, 2 h	95%
7	H_3PO_4 (20% mol.), dioxane, rt, 8 h	100%

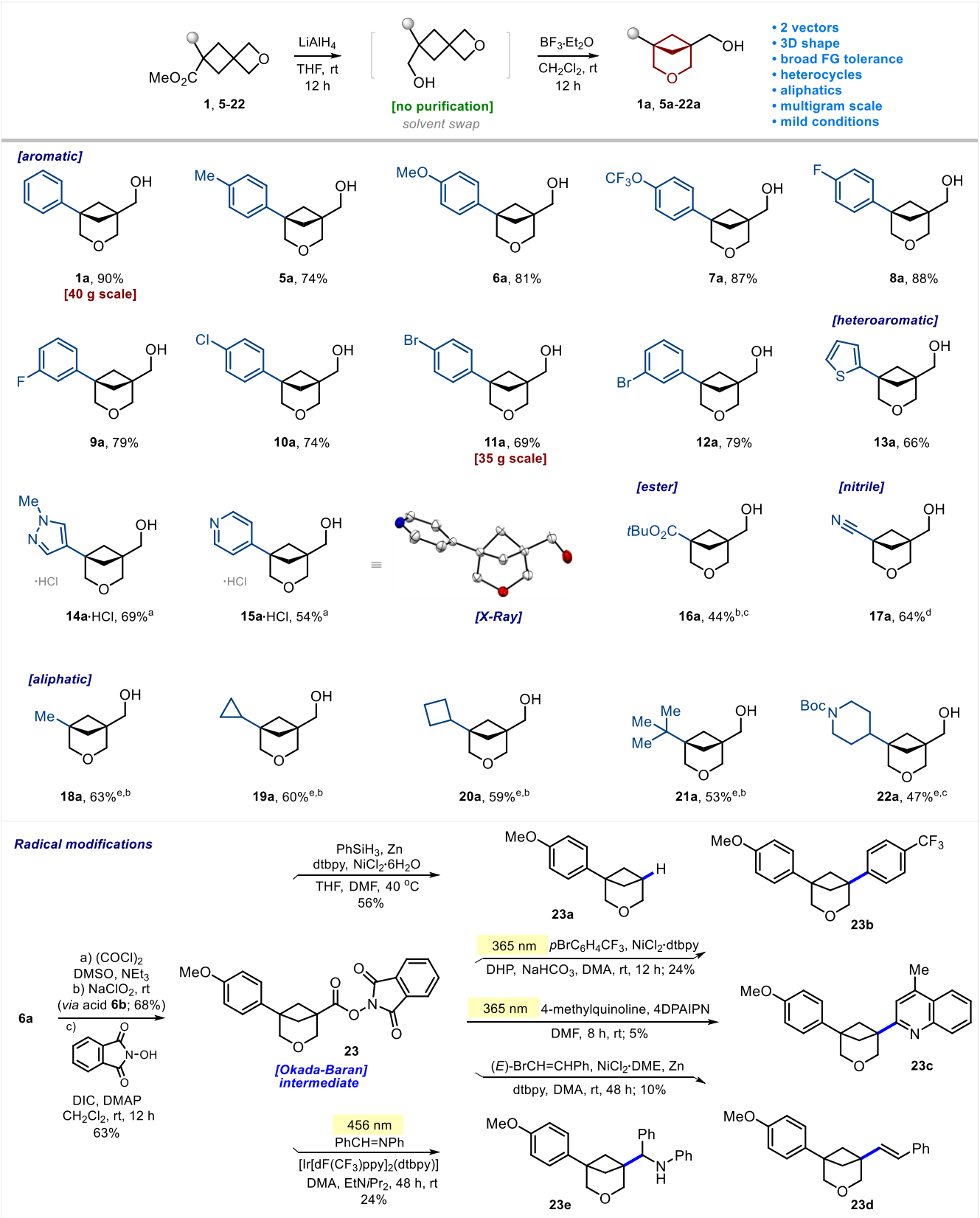
[a] Reaction conversion analyzed by ^{1}H-NMR. SM: starting material. [b] Isolated yield.

Scheme 2. Attempted synthesis of compound **1a** from oxetane **1**. Isomerization of alcohol **2** into 3-oxabicyclo[3.1.1]heptane **1a**.

Scalable synthesis. Having developed conditions for the isomerization of alcohol **2**, we next elaborated the multigram scale synthesis of compound **1a**. The optimized procedure commenced from the commercially available alcohol **1** (ca. 0.5 €/g, Scheme 3). Treatment of the latter with NaOEt in ethanol under reflux led to the formation of oxetane **4** following the literature protocol.[11]



Scheme 3. Scalable synthesis of compound **1a**.



Scheme 4. Synthesis and radical modifications of 3-oxabicyclo[3.1.1]heptanes. [a]Products were isolated as hydrochloride salts. 10M HCl was used instead of BF_3•Et_2O at the recyclization step. [b] Stepwise combination of DIBAL and $NaBH_4$ was used instead of $LiAlH_4$. [c]H_3PO_4 in dioxane was used instead of BF_3•Et_2O. [d]$NaBH_4$ was used instead of $LiAlH_4$. [e] Starting materials **18**-**22** had the nitrile group (-CN) instead of the ester group (-CO_2Me). X-ray crystal structure of compound **15a**•HCl (carbon – grey, oxygen – red, nitrogen - blue). Ellipsoids are shown at a 30% probability level. Hydrogen and chlorine atoms are omitted for clarity. 4DPAIPN: 2,4,5-tris(diphenylamino)isophthalonitrile. Dtbpy: 4,4'-di-tert-butyl-2,2'-bipyridine. DHP: 1,4-dihydropyridine Hantzsch ester. DME: dimethoxyethane. DMA: dimethylacetamide. DMF: dimethylformamide.

Alkylation of $PhCH_2CO_2Me$ with bromide **4** in the presence of sodium hydride in DMF cleanly proceeded at room temperature to provide spirocyclic compound **1** with an 89% yield. Reduction of the ester group with $LiAlH_4$ provided alcohol **2** with ca. 90% purity. Importantly, to ensure a higher overall yield of the synthesis, we did not purify product **2** at this point but used the crude material directly in the subsequent isomerization step with BF_3•Et_2O in dichloromethane. As a result, the desired product **1a** was obtained in 90% yield over two steps from oxetane **1**.

It is worth noting, that this optimized sequence allowed us to prepare 40 g of the target 3-oxabicyclo[3.1.1]heptane **1a** in one run (Scheme 3).

Scope. Moving forward, we studied the generality of the developed method. The reduction-isomerization sequence tolerated various substituents on the aromatic core (Scheme 4). Among them were the alkyl group (**5a**), methoxy group (**6a**), trifluoromethoxy group (**7a**), fluorine (**8a**, **9a**), chlorine (**10a**), and bromine atoms (**11a**, **12a**). The reaction was also compatible with the medicinal chemistry-relevant heterocyclic cores - thiophene (**13a**), pyrazole (**14a**), and pyridine (**15a**). Worth special noting that even the $-CO_2tBu$ (**16a**) and the -CN (**17a**) groups performed well in the reaction, in this case, however, the reduction step was realized with diisobutylaluminium hydride (DIBAL)/$NaBH_4$ (**16a**) and $NaBH_4$ (**17a**), correspondingly.

Aliphatic substituents (**18a**-**21a**) could also be used in this strategy. The corresponding starting materials contained, however, the nitrile group (-CN) instead of the ester group (-CO_2Me), and the reaction step was undertaken with the consecutive combination of DIBAL and $NaBH_4$. Following this modified tactic, the *N*-Boc piperidine containing linker **22a** was obtained in 47% yield. Most compounds were isolated as free bases, however, in some cases (**14a**, **15a**), we converted them into crystalline hydrochloride salts. All syntheses were performed on milligram and gram scales, but products **1a** and **11a** were also synthesized in 35-40 gram amounts. The structure of compound **15a**•HCl was confirmed by X-ray analysis (Scheme 4).[12]

Radical modifications of the 3-oxabicyclo[3.1.1]heptane core at the bridgehead position were also possible (Scheme 4). Oxidation of alcohol **6a** gave the carboxylic acid **6b** in 68%. The reaction of the latter with *N*-hydroxyphtalimide in the presence of *N,N'*-diisopropylcarbodiimide (DIC) / 4-dimethylaminopyridine (DMAP) in dichloromethane at room temperature provided the *Okada-Baran* [13] intermediate **23**. The [Ni]-catalyzed decarboxylative reduction of the latter with $PhSiH_3/Zn$ [14] was performed at 40 °C with no irradiation, producing product **23a** in 56% yield. The photochemical [Ni]-catalyzed $C(sp^3)$-$C(sp^2)$ cross-coupling of the redox-active ester **23** with *p*-$BrC_6H_4CF_3$ in the presence of the Hantzsch ester provided product **23b** in 24% yield. The photochemical Miniscki-type reaction of ester **23** with 4-methylquinoline gave compound **23c**. The [Ni]-catalyzed coupling of **23** with BrCH=CHPh in the presence of zinc resulted in the formation of alkene **23d**. Finally, the reaction of **23** with PhCH=NPh under the reductive "photo-redox" conditions, - $EtNiPr_2$, [Ir], 456 nm, - gave amine **23e**.

Modifications. Modifications of some representative 3-oxabicyclo[3.1.1]heptanes into the building blocks (compounds with one or two functional groups) for medicinal chemistry were undertaken in the next step.

The standard Swern oxidation of alcohol **1a** gave aldehyde **24** in 85% yield (Scheme 5). The subsequent oxidation of the latter with $NaClO_2$ provided the carboxylic acid **1b**. The Curtious reaction of **1a** followed by the acidic *N*-Boc deprotection resulted in the formation of amine **25** as a hydrochloride salt in 74% yield. The Strecker reaction of aldehyde **24** afforded the unique α-amino acid **26**. The Appel reaction of alcohol **1a** with *N*-bromosuccinimide (NBS) and triphenylphosphine smoothly provided alkyl bromide **27** in 94% yield. The reaction of the latter with potassium cyanide in DMF under heating and the subsequent alkali hydrolysis of the nitrile group provided carboxylic acid **28** – a homologue of the previously synthesized acid **1b**. The reaction of bromide **27** with NaN_3 followed by the Staudinger reaction of the intermediate azide led to the formation of amine **29** in 63% yield.

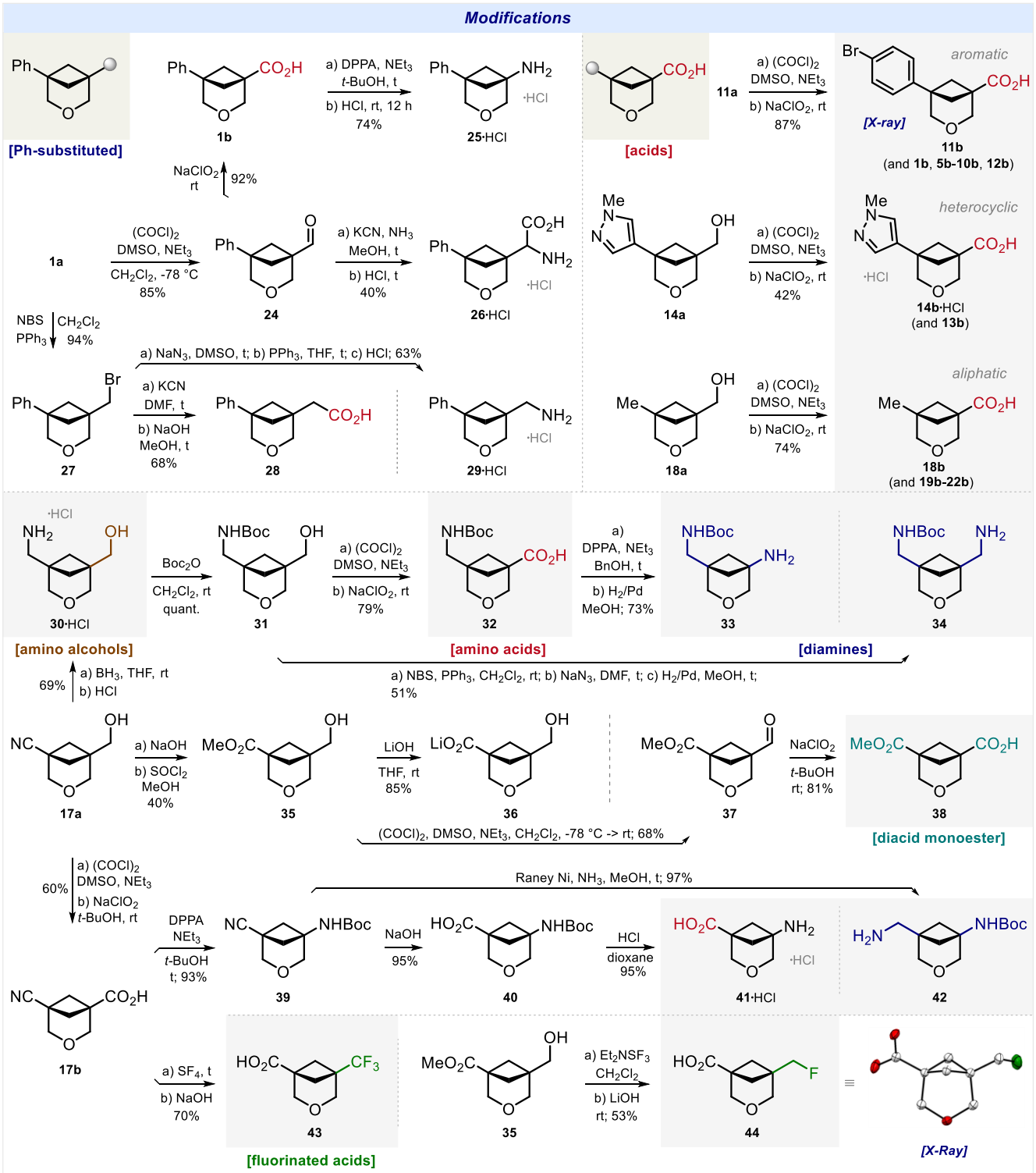
The stepwise oxidation of alcohol **11a** using the Swern protocol and sodium chlorite provided the carboxylic acid **11b** in an 87% yield. The structure of compound **11b** was confirmed by X-ray analysis.[12] Following this tactic, aromatic carboxylic acids **5b**-**10b**, **12b**; heterocyclic carboxylic acids **13b**, **14b**; and even aliphatic carboxylic acids **18b**-**22b** were also easily synthesized from the corresponding alcohols (Scheme 5).

Reduction of the nitrile group in compound **17a** with the BH_3•THF complex afforded amino alcohol **30** in 69% yield (Scheme 5). The *N*-Boc protection (via **31**) and the subsequent full oxidation of the alcohol group gave the *N*-Boc amino acid **32**. The Curtious reaction of the latter and the *N*-Cbz cleavage with H_2/Pd in methanol gave the *N*-Boc diamine **33** in 73% yield. The Appel reaction of alcohol **31** with NBS/PPh_3, treatment with sodium azide in DMF under heating, and the reduction of the intermediate nitrile provided the *N*-Boc diamine **34** – a homologue of the previously obtained compound **33**.

Alkali hydrolysis of the nitrile group in compound **17a** and the subsequent acidic esterification gave methyl ester **35** (Scheme 5). Hydrolysis of the ester group afforded the hydroxy acid **36** in the form of a lithium salt in 85% yield. The Swern oxidation of the alcohol group in **35** gave aldehyde **37**. The subsequent oxidation of the latter with sodium chlorite gave valuable diacid monoester **38** in 81% yield.

Oxidation of the alcohol group in compound **17a** gave carboxylic acid **17b** in 60% yield. The Curtious reaction and the hydrolysis of the nitrile group in the formed compound **39** gave an interesting *N*-Boc amino acid **40**. The acidic *N*-Boc deprotection provided amino acid **41** in the form of a hydrochloride salt. In addition, the reduction of the nitrile group in **40** with Raney nickel resulted in the formation of the *N*-Boc diamine **42** – and isomer of the previously obtained *N*-Boc diamine **33**.

The reaction of carboxylic acid **17b** with sulfur tetrafluoride[15] and the alkali hydrolysis of the nitrile group gave the CF_3-substituted carboxylic acid **43**. The reaction of alcohol **35** with Et_2NSF_3 in dichloromethane at room temperature followed by the hydrolysis of the ester group provided the mono-fluoro-substituted carboxylic acid **44**. The structure of the latter was confirmed by X-ray analysis (Scheme 5).[12]



Scheme 5. Synthesis of functionalized 3-oxabicyclo[3.1.1]heptanes for medicinal chemistry. X-ray crystal structure of compound **44** (carbon – white, oxygen – red, fluorine – green). Hydrogen and chlorine atoms are omitted for clarity. Ellipsoids are shown at a 30% probability level. DPPA: diphenylphosphoryl azide. NBS: N-bromosuccinimide.

Stability. Because of the strained structure of all 3-oxabicyclo[3.1.1]heptanes (Schemes 4, 5), and the existing "strain-release" effect,[16] we also monitored the stability of the obtained products. All compounds were kept on the shelf at room temperature in closed vials. Their regular ^{1}H NMR and LC-MS inspection every three months revealed no detectable decomposition in any of them after at least six months of storage.

In addition, we checked the preliminary thermal stability of several representative 3-oxabicyclo[3.1.1]heptanes: carboxylic acid **11b**, amine hydrochloride **25**•HCl, and *N*-Boc amino acid **40**. The compounds indeed remained stable under heating at 100 °C for five minutes, as monitored by ^{1}H NMR and LC-MS.

Steric volume. To estimate the size of the 3-oxabicyclo[3.1.1]heptane scaffold compared to the benzene ring, we calculated[17] and compared their steric volumes (Figure 2). The bicyclo[3.1.1]heptane scaffold was also included for comparison representing an already established isosteric benzene replacement.[2]

The obtained data show that the volume of the bicyclo[3.1.1]heptane scaffold is bigger than that of the benzene ring: 109 Å^3 (O-311) *vs* 84 Å^3 (benzene). At the same time, the replacement of the methylene group for the oxygen atom led to a significant reduction of the volume making the formed 3-oxabicyclo[3.1.1]heptane core more similar to the benzene ring: 101 Å^3 (311) *vs* 84 Å^3 (benzene).

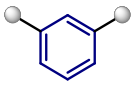
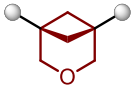
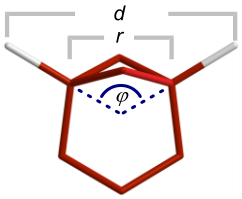
Scaffold	*Structure*	*Volume* (Å^3)
Benzene		84
Bicyclo[3.1.1]peptane		109
3-Oxabicyclo[3.1.1]heptane		101

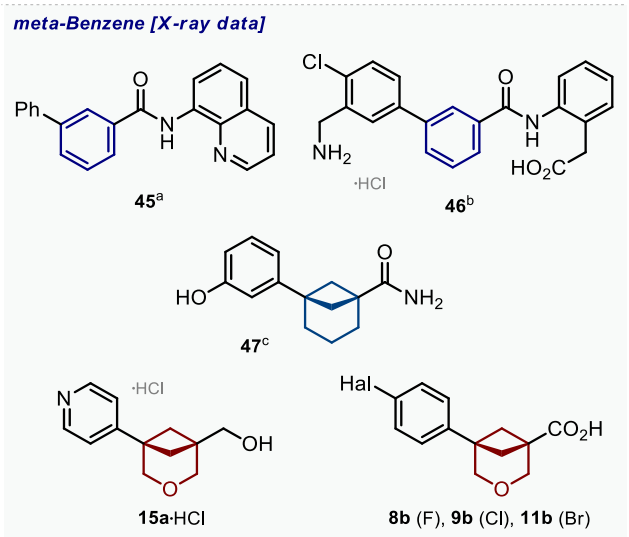
Figure 2. Calculated molecular volume (Å^3) of benzene, bicyclo[3.1.1]heptane, and 3-oxabicyclo[3.1.1]heptane.

Crystallographic analysis. Next, we compared the geometric properties of 3-oxabicyclo[3.1.1]heptanes with those of *meta*-benzenes. We also included the bicyclo[3.1.1]heptane scaffold for comparison.[2] For that, we measured two C-C distances *r* and *d* to see the overall similarity of cores; and angle *φ* between two exit vectors to see the similarity of angular models (Figure 3).

We obtained the values of *r*, *d*, and *φ* of 3-oxabicyclo[3.1.1]heptanes from the X-ray data of compounds **15a**•HCl, **8b**, **9b**, and **11b**. The corresponding parameters for the *meta*-substituted benzenes **45**,[18] **46**;[19] and bicyclo[3.1.1]heptane **47**[2] were calculated from the X-ray data published in the literature.

The distance *r* in 3-oxabicyclo[3.1.1]heptanes was ca. 0.3 Å shorter than that in *meta*-benzene: 2.10-2.12 Å *vs* 2.42-2.43 Å (*meta*-benzene). The distance *d* between substituents in 3-oxabicyclo[3.1.1]heptanes was also ca. 0.2 Å shorter than that in *meta*-benzene: 4.75-4.77 Å *vs* 4.93-5.05 Å (*meta*-benzene). However, angle *φ* was similar in both scaffolds and was very close to the ideal value of 120°: 120-124° *vs* 116-122° (*meta*-benzene). It must be also noted, that both saturated scaffolds, - bicyclo[3.1.1]heptane and 3-oxabicyclo[3.1.1]heptane, - were almost identical according to the measured parameters.





Compound	*r* (Å)	*d* (Å)	*φ* (°)
45	2.416(9)	4.926(9)	116.0(3)
46	2.427(3)	5.051(4)	122.0(1)
47 (A)	2.119(2)	4.770(2)	123.69(5)
47 (B)	2.124(2)	4.752(2)	121.35(5)
15a·HCl	2.101(3)	4.754(3)	124.59(9)
8b	2.121(4)	4.732(4)	120.5(1)
9b	2.116(3)	4.772(3)	125.2(1)
11b	2.102(5)	4.746(5)	124.3(2)

Figure 3. Definition of distances *r*, *d*, and angle *γ* (the 3-oxabicyclo[3.1.1]heptane core is shown as an example). Geometric parameters *r*, *d*, and *γ* for the *meta*-substituted benzene ring (**45**, **46**); bicyclo[3.1.1]heptane **47**, and 3-oxabicyclo[3.1.1]heptanes **15a**•HCl, **8b**, **9b**, **11b**. [a] The data is taken from ref. 18. [b] The data is taken from ref. 19. [c] The data is taken from ref. 2.

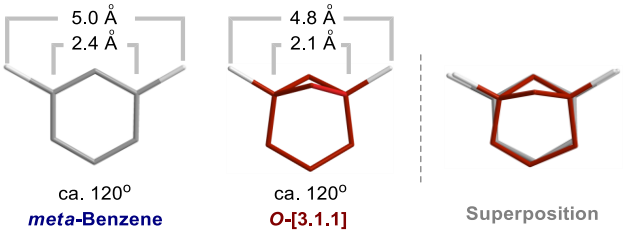


Figure 4. A visual comparison of *meta*-substituted benzene and 3-oxabicyclo[3.1.1]heptane.

In short summary, the 3-oxabicyclo[3.1.1]heptane core resembled closely the *meta*-benzene ring, as the geometric characteristics *r*, *d*, *φ* remained very similar. The superposition of both scaffolds visualizes their perfect match (Figure 4).

The acidity of functional groups. We also studied the influence of the replacement of the methylene group for the oxygen atom in the bicyclo[3.1.1]heptane skeleton on the electronic properties. For that, we experimentally measured pK_a values of the bicyclo[3.1.1]heptane carboxylic acid **49**, the 3-oxabicyclo[3.1.1]heptane carboxylic acid **18b**, and *meta*-methyl benzoic acid (**48**) as a reference (Figure 5).[20]

It is important to mention that the acidity of *meta*-methyl benzoic acid (**48**) and 3-oxabicyclo[3.1.1]heptane **18b** were almost identical (Figure 5). Indeed, the replacement of the benzene ring with the saturated bicyclo[3.1.1]heptane core reduced the acidity by ca. 0.7 pK_a units. However, incorporation of the oxygen atom into the latter almost ideally restored it: pK_a = 4.3 (**48**) *vs* 5.0 (**49**) *vs* 4.2 (**18b**). Because the acidity/basicity of functional groups is often responsible for the potency, selectivity, and toxicity of bioactive compounds,[21] the fine-tuning of the pK_a value by replacing the benzene ring with 3-oxabicyclo[3.1.1]heptane could be a useful solution in this case.

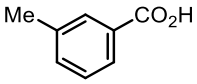
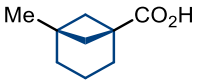
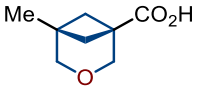
	Carboxylic acid	*pK_a (exp.)*
48		4.27[a]
49		5.03
18b		4.23

Figure 5. Experimental pK_a values of carboxylic acids **49** and **18b**. [a] For compound **48**, the data is taken from ref. 20.

Incorporation into a drug. Having developed a general practical approach towards 3-oxabicyclo[3.1.1]heptanes (Scheme 4) and their functionalized derivatives (Scheme 5), we wanted to study the effects of the replacement of *meta*-benzene on physicochemical, and biological properties of bioactive compounds. Toward this goal, we synthesized the 3-oxabicyclo[3.1.1]heptane analogue **51** of the FDA-approved anticancer drug *Sonidegib* from carboxylic acid **7b** (for details, please see SI page S47). For comparison, we also included the previously reported bicyclo[3.1.1]heptane-containing compound **50** (Figure 6).[2]

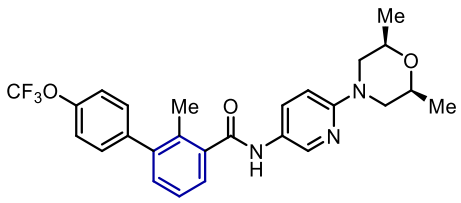
Physicochemical properties. First, we studied experimental physicochemical properties - water solubility, lipophilicity (see SI p. S224-S232), - and metabolic stability (see SI p. S233-239); - of *Sonidegib* and its saturated analogues **50**, **51**.

Replacement of the benzene ring in *Sonidegib* with bicyclo[3.1.1]heptane decreased the water solubility: 6 μM (*Sonidegib*) *vs* 4 μM (**50**). At the same time, the analogous replacement with 3-oxabicyclo[3.1.1]heptane led to a dramatic five times increase (!) in the solubility: 6 μM (*Sonidegib*) *vs* 34 μM (**51**).

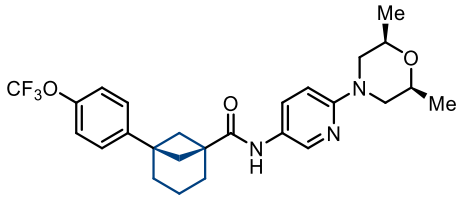
An effect of the replacement of the benzene ring in *Sonidegib* with saturated scaffolds on the experimental lipophilicity (logD, 7.4) was not observed due to too high lipophilicity of all three compounds, outside of the sensitivity range of the experimental method. Therefore, we used the calculated lipophilicity index (clogD, 7.4). [22] Replacement of the benzene ring with bicyclo[3.1.1]heptane slightly decreased clogD: 6.8 (*Sonidegib*) *vs* 6.2 (**50**). However, the effect of such replacement with the 3-oxabicyclo[3.1.1]heptane core was more than significant - the clogD index decreased by two units: 6.8 (*Sonidegib*) *vs* 4.8 (**51**).

The replacement of the benzene ring in *Sonidegib* with saturated scaffolds either tolerated the metabolic stability or slightly reduced it: CL_{int} (μL min^{-1} mg^{-1}) = 16 (*Sonidegib*) *vs* 14 (**50**) *vs* 28 (**51**).

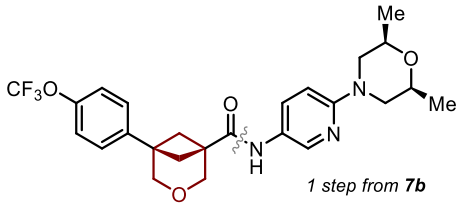
Sonidegib
Anticancer drug



50



51



*1 step from **7b***

Physico-chemical properties	**Sonidegib**	**50**	**51**
Solubility (μM)	6	4	34
logD (7.4)	□ 4.5	□ 4.5	□ 4.5
clogD (7.4)	6.8	6.2	4.8
Metabolic stability			
CL_{int} (μL min^{-1} mg^{-1})	16	14	28
$t_{1/2}$ (min)	104	120	61
Biological activity			
IC_{50} (HH signal) (nM)	1	616	96

Figure 6. Properties of *Sonidegib*, and its saturated analogues **50**, **51**. *Solubility.*: the experimental kinetic solubility in phosphate-buffered saline, pH 7.4 (μM). *clogD (7.4)*: the calculated lipophilicity at pH 7.4. *logD* (7.4): the experimental distribution coefficient in *n*-octanol/phosphate-buffered saline, pH 7.4. Reliable *logD* values could be obtained within a range of 1.0-4.5. CL_{int}: the experimental metabolic stability in human liver microsomes (μL min^{-1} mg^{-1}). $t_{1/2}$ (min): the experimental half-time of a metabolic decomposition. The experimental inhibition, IC_{50} (nM), of the Hedgehog signaling pathway by *Sonidegib* and saturated analogues **50**, **51** in the Gli reporter NIH3T3 cell line.

In summary, the replacement of the benzene ring in *Sonidegib* with 3-oxabicyclo[3.1.1]heptane (**51**) led to a slight decrease in metabolic stability (within a normal range), dramatic

improvement of solubility (>500%) and significant beneficial reduction of lipophilicity (2 clogD units).

Biological activity. Finally, we wanted to answer the key question, - if 3-oxabicyclo[3.1.1]heptane could indeed mimic *meta*-benzene in bioactive compounds? Towards this goal, we measured the biological activity of the marketed drug *Sonidegib* and its saturated analogues **50**, **51**.

The mechanism of action of the anticancer drug *Sonidegib* involves inhibiting the Hedgehog signaling pathway. Thus, we measured the inhibition of this signaling pathway caused by *Sonidegib*[23] versus its saturated analogues **50** and **51** in Gli-Luc reporter NIH3T3 cells (Figure 6; see also SI, p. S240-S243). On one hand, the *O*-[3.1.1]-containing analogue **51** was two orders of magnitude less potent than the original drug. On the other hand, the patent-free compound **51** demonstrated a level of inhibition in a nanomolar range and was six times more active than the known saturated analogue **50**, IC_{50} (nM): 6 (*Sonidegib*) *vs* 616 (**50**) *vs* 96 (**51**) (Figure 6).

Conclusions. In 2022, bicyclo[3.1.1]heptanes were proposed to mimic *meta*-benzenes in biologically active compounds.[2] In this work, we designed, synthesized, and biologically validated a new generation of saturated bioisosteres of *meta*-benzene - 3-oxabicyclo[3.1.1]heptanes. The patent-free analogue **51** of the anticancer drug *Sonidehib* had a nanomolar potency, exhibited reduced lipophilicity, and improved solubility (>500%) compared to the original drug.

Given the commonplace of the *meta*-benzene ring in chemistry, we expect that after this publication its saturated bioisostere, - 3-oxabicyclo[3.1.1]heptanes, - will find immediate practical application by other academic/industrial research groups.[24]

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Conflict of Interest

DD and PKM are employees of a chemical supplier Enamine.

Data Availability Statement

The data that support the findings of this study are available in the Supporting Information of this article.

Keywords: bicyclo[3.1.1]heptane • 3-oxabicyclo[3.1.1]heptane • *meta*-benzene • bioisosteres • medicinal chemistry

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Graphical Abstract

Water-soluble Bioisosteres of *meta*-Benzenes

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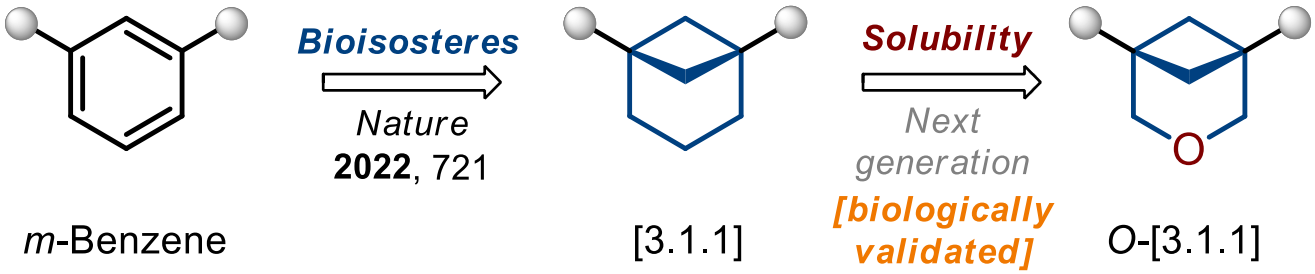

Water-soluble bioisosteres of *meta*-benzenes have been synthesized, characterized, and validated biologically.