An "Ideal" Bioisoster of the *para*-substituted Phenyl Ring

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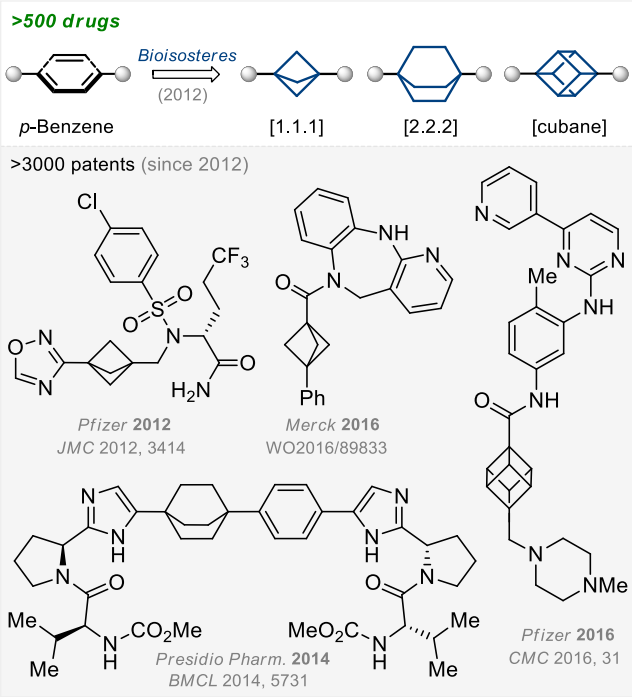
Dedicated to the brave people of Ukraine

Abstract. The phenyl ring is a basic structural element in chemistry, and we learn about it already in school. We have developed an "ideal" saturated bioisoster of the *para*-substituted phenyl ring, - 2-oxabicyclo[2.2.2]octane. Its incorporation into Imatinib drug led to dramatic improvement of all physicochemical properties. This study opens new horizons in science, given the commonplace of the phenyl ring everywhere.

Introduction. The phenyl ring is a basic structural element in chemistry, and we learn about it already in school in a general chemistry class. It is one of the most popular structural motifs in natural products and bioactive compounds.[1] Moreover, more than five hundred drugs contain a fragment of *para*-disubstituted benzene,[2] including the well-known to everyone *Paracetamol*. However, organic compounds with more than two phenyl rings often suffer from poor solubility and low metabolic stability.[3,4]



Scheme 1. Bicyclo[1.1.1]pentanes, bicyclo[2.2.2]octanes, and cubane as saturated bioisosteres of the *para*-substituted phenyl ring.

In 2012, however, Stepan and colleagues showed that a replacement of the central phenyl ring in a γ-secretase inhibitor with the bicyclo[1.1.1]pentane improved its physicochemical properties and retained bioactivity (Scheme 1).[5,6] Later, analogous replacements were undertaken with cubane[7,8] and bicyclo[2.2.2]octane.[9] Therefore, during the past decade, these scaffolds proved to be useful in drug discovery, medicinal chemistry, and supramolecular chemistry.[10,11] Recent studies, however, showed that all three bioisosteres had drawbacks. In bicyclo[1.1.1]pentane, the most popular among them today,[12,13] the distance between two bridgehead carbon atoms (C-C) is 1.8 Å, which is ca. 35% shorter than that in the *para*-substituted phenyl ring (2.8 Å). Bicyclo[2.2.2]octane has a similar C-C distance (2.6 Å), but is much more lipophilic.[14] Cubane, in turn, was recently shown to be unstable in the presence of transition metals,[15] mechanochemistry, or heating.[16]

In this work, we have rationally designed, synthesized, and characterized the ideal bioisoster of the *para*-substituted phenyl ring – 2-oxabicyclo[2.2.2]octane (Figure 1).

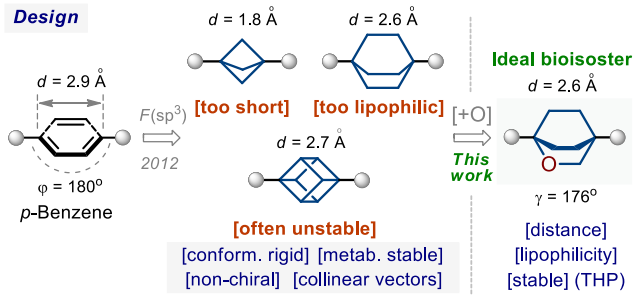
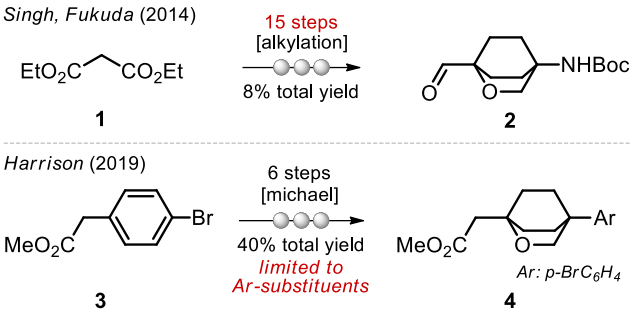


Figure 1. Design of the ideal bioisoster of the *para*-substituted phenyl ring.

Design. In the design of the ideal phenyl bioisoster, we first needed to keep the advantages of the previously used cores: their conformational rigidity,[17] metabolic stability,[18] non-chirality,[19] and collinearity of vectors (φ = 180º).[20] At the same time, we needed to address their drawbacks: C-C distance, and lipophilicity. After thinking for a while (please, see SI for the details of the design),[21] we decided to stick to the stable bicyclo[2.2.2]octane structure, because of its appropriate C-C distance, and decorate it with an oxygen atom.[22] In particular, replacing one carbon atom with oxygen[23] would give 2-oxabicyclo[2.2.2]octane with similar geometry and reduced lipophilicity (Figure 1). Also, this structure should be chemically stable because it is a simple derivative of tetrahydropyran.[24]

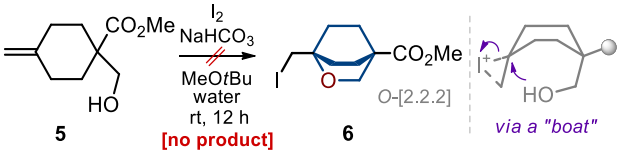
Optimization. Interestingly, 2-oxabicyclo[2.2.2]octane core was known in the literature before. Chemists used it as a starting material in organic synthesis,[25] and even in medicinal chemistry[26] as an analogue of 4-aminopiperidine[27] or cyclohexane.[28] Preparation of 2-oxabicyclo[2.2.2]octane was also reported. In 2014, *Singh* and *Fukuda* obtained compound **2** from diethyl malonate (**1**) in 15 steps using alkylation as a key reaction (Scheme 2).[27a] In 2019, *Harrison* synthesized compound **4** from ester **3** already in six steps employing an intramolecular Michael addition.[28a] The latter approach was limited only to aromatic substituents. We, however, needed a general modular method that would give 2-oxabicyclo[2.2.2]octanes with two functional groups that could be subsequently modified to obtain a wide variety of derivatives - bioisosteres of *para*-substituted benzenes.

Previously, we showed that smaller 2-oxabicyclo[2.1.1]hexane could be assembled via the iodocyclization reaction of the corresponding cyclobutane alkenyl alcohols.[29] The reaction proceeded with I_2/$NaHCO_3$ in the mixture of water and MeO*t*Bu at room temperature. In the beginning, we were confident that



Scheme 2. Previous entries to 2-oxabicyclo[2.2.2]octanes.

similar cyclization would also easily take place with cyclohexane **5** (please, see its preparation further). Therefore, we set the reaction overnight under analogous conditions. Sadly, in the morning we realized that the expected product **6** was not formed at all (Table 1, entry 1). We repeated the synthesis several times varying the time and the temperature, however, with the same negative outcome (entries 2-4). The addition of the iodine molecule to the double C=C bond did take place, but the cyclization did not happen. Subsequently, we realized that in contrast to the already conformationally preorganized small cyclobutane, the flexible larger cyclohexane ring should adopt first the highly energetic boat conformation (Table 1). And this entropic penalty seems to prevent cyclization to occur. We also tried other combinations of solvents still with no success, however (entries 5-8). Being already in a depression, we finally tried pure dipolar aprotic solvents. Indeed, in dimethyl formamide, formation the traces of the needed product was finally seen (entry 9). A similar situation was observed in dimethyl sulfoxide and *N*-methyl pyrrolidone (entries 10, 11). Analogously, in acetonitrile the reaction proceeded much better, and the needed iodide **6** was isolated in a 56% yield (entry 12). Increasing the reaction temperature or using bromine instead of iodine did not increase the yield (entries 13, 14).

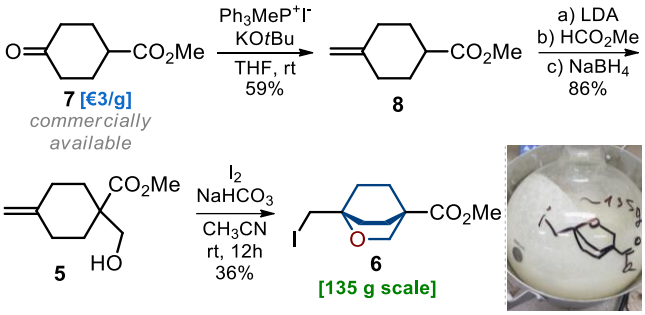


entry	conditions	yield (%)[a]
1	I_2, $NaHCO_3$, MeO*t*Bu, H_2O, rt, 12h	*n.d.*
2	---------- *same* ----------, rt, 48h	*n.d.*
3	---------- *same* ----------, rt, 1h	*n.d.*
4	---------- *same* ----------, reflux, 12h	*n.d.*
5	I_2, $NaHCO_3$, Et_2O, H_2O, rt	*n.d.*
6	I_2, $NaHCO_3$, dioxane, H_2O, rt	*n.d.*
7	--- *same* ---, dioxane, rt	*n.d.*
8	--- *same* ---, MeO*t*Bu, rt	*n.d.*
9	--- *same* ---, DMF, rt	<10
10	--- *same* ---, DMSO, rt	<10
11	--- *same* ---, NMP, rt	<10
12	I_2, $NaHCO_3$, CH_3CN, rt, 12h	56
13	I_2, $NaHCO_3$, CH_3CN, reflux	45
14	Br_2, $NaHCO_3$, CH_3CN, rt	30

[a] Isolated yield.

Table 1. Optimization of synthesis of 2-oxabicyclo[2.2.2]octane **6**.

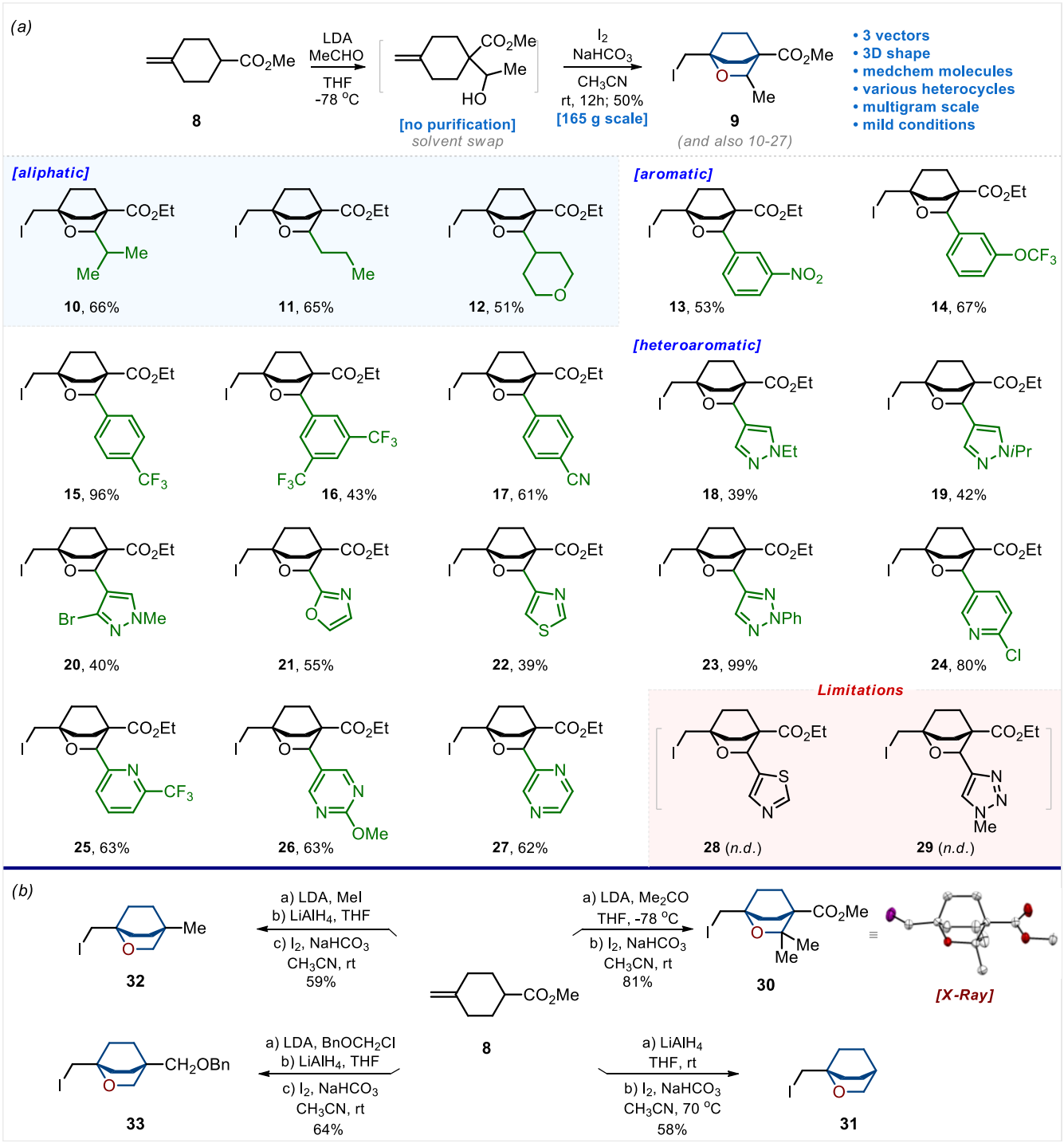
Synthesis. Having a working procedure in hand, we studied its scalability. The whole synthesis scheme commenced from the commercially available ketoester **7** (ca. 3€/g, Scheme 3). Wittig reaction gave alkene **8** in 82% yield. Treatment of the latter with LDA/methyl formate followed by the reduction of the intermediate aldehyde with $NaBH_4$ gave alcohol **5** in 86% combined yield. Finally, the key cyclization was attempted on a multigram scale. Pure iodide **6** was obtained as a white crystalline solid after column chromatography with a 36% yield. Despite the lower yield, this protocol allowed us to obtain 135 g of the product in a single run.



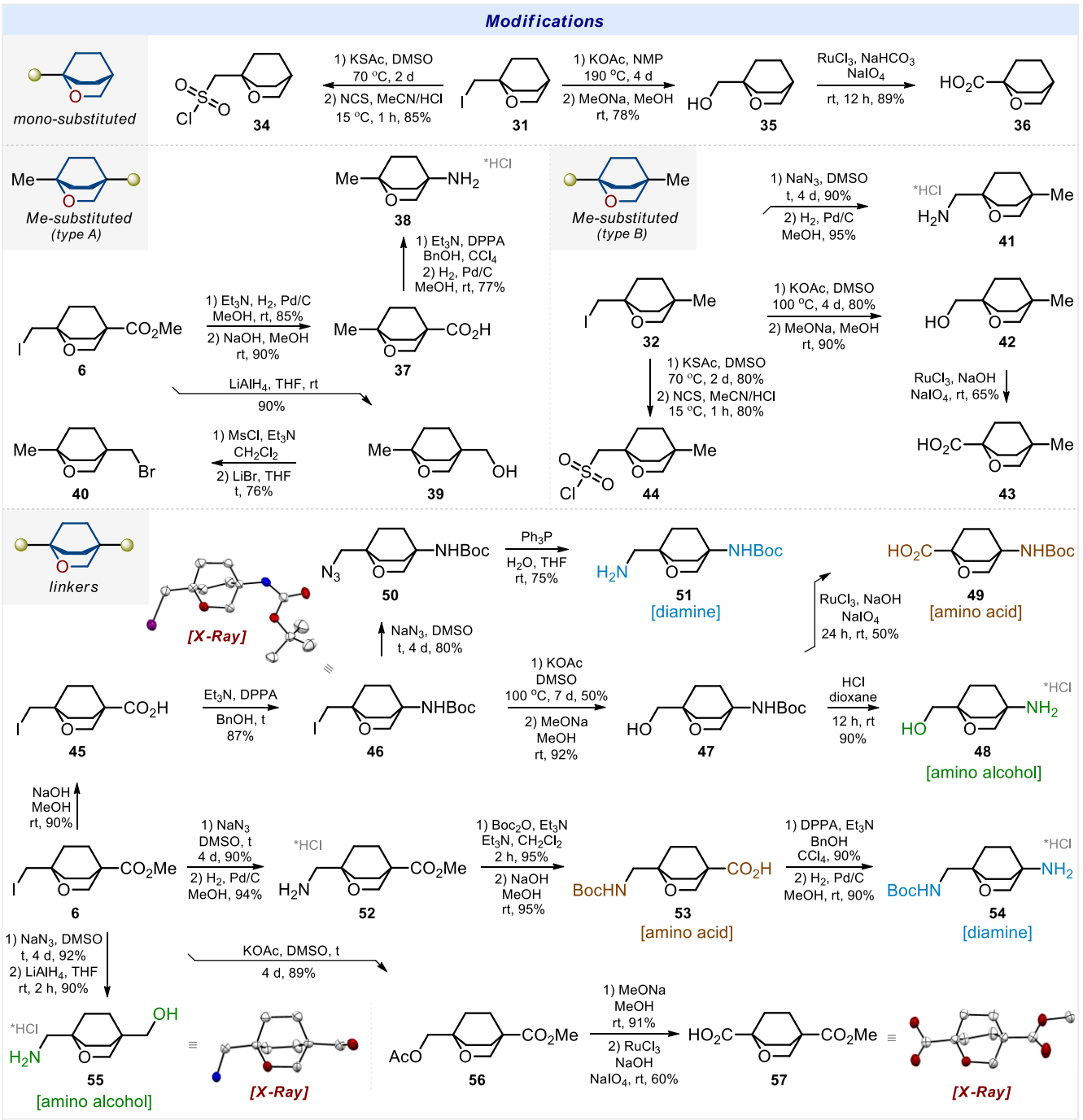
Scheme 3. Scalable synthesis of 2-oxabicyclo[2.2.2]octane **6**.

Scope. Next, we studied the generality of the developed protocol. Treatment of alkene **8** with LDA/acetaldehyde gave the intermediate alcohol that was used in the subsequent cyclization under the developed conditions. The expected iodide **9** with three exit vectors was isolated in 50% yield after column chromatography (Scheme 4). Initially, we isolated the transition alcohol, but subsequently, we understood that performing the two-step procedure with a simple solvent swap ensured a better yield of the final product.

An analogous reaction with aliphatic (**10**-**12**), aromatic (**13**-**17**), and even heteroaromatic (**18**-**27**) aldehydes gave the needed 3D-shaped iodides in moderate to excellent yields. Various functional groups, - nitro, trifluoromethoxy, trifluoromethyl, nitrile, halogens, - were compatible with the reaction conditions. The protocol was not without limitations, however. We could not obtain products **28**, and **29** with thiazole and triazole heterocycles, due to the formation of complex mixtures. Ketones could also be used as electrophiles instead of aldehydes. As a representative example, the reaction of alkene **8** with LDA/acetone followed by cyclization gave dimethyl-substituted product **30** in 81% yield. The structure of **30** was confirmed by X-Ray crystallographic analysis (Scheme 4).[30] A reduction of **8** followed by cyclization gave iodide **31** in 58% yield. Interestingly, the cyclization did not take place at room temperature, and the reaction was performed under heating. Alkylation of **8** with MeI or $BnOCH_2Cl$ followed by reduction and cyclization gave disubstituted products **32**, **33** in 59-64% yield (Scheme 4).



Scheme 4. (a) Synthesis of 2-oxabicyclo[2.2.2]octanes with three exit vectors (for products 10-29, ethyl ester analogue of alkene 8 was used). (b) Synthesis of 2-oxabicyclo[2.2.2]octanes with one and two exit vectors. X-Ray crystal structure of compound **30b** (carbon – white, oxygen – red, iodine - violet). Hydrogen atoms are omitted for clarity.



Scheme 5. Synthesis of functionalized 2-oxabicyclo[2.2.2]octanes for medicinal chemistry. X-Ray crystal structure of compounds **46**, **55**, and **57** (carbon – white, oxygen – red, nitrogen – blue, iodine - violet). Hydrogen and chlorine atoms are omitted for clarity.

Modifications. Several representative modifications of the obtained iodides were undertaken to obtain various mono- and bifunctional 2-oxabicyclo[2.2.2]octanes ready for direct use in medicinal chemistry projects. Treatment of iodide **31** with potassium thioacetate followed by oxidation with NCS gave aliphatic sulfonyl chloride **34** in 85% yield. The reaction of **31** with potassium acetate and the subsequent alkali hydrolysis provided valuable alcohol **35**. Oxidation of the latter afforded carboxylic acid **36** in 89% yield (Scheme 5).

Hydrogenative reduction of the C-I bond in iodide **6** followed by saponification of the ester group gave methyl acid **37**. Curtius reaction of the latter resulted in amine **38**. The reaction of iodide **6** with $LiAlH_4$ gave alcohol **39** in 90% yield. *O*-Mesylation and the subsequent reaction with LiBr provided bromide **40**. Isomeric methyl-substituted 2-oxabicyclo[2.2.2]octanes were obtained from iodide **32**. Its reaction with sodium azide followed by the reduction formed amine **41**. The reaction of iodide **32** with potassium acetate and hydrolysis gave alcohol **42** - isomer of alcohol **39**. Oxidation of **42** formed carboxylic acid **43** - isomer of acid **37**. Sulfonyl chloride **44** was also obtained from iodide **32** via a two-step procedure (Scheme 5).

From iodide **6** we also synthesized various bifunctional linkers for incorporation into bioactive compounds instead of the *para*-disubstituted phenyl ring. Saponification of ester **6** provided

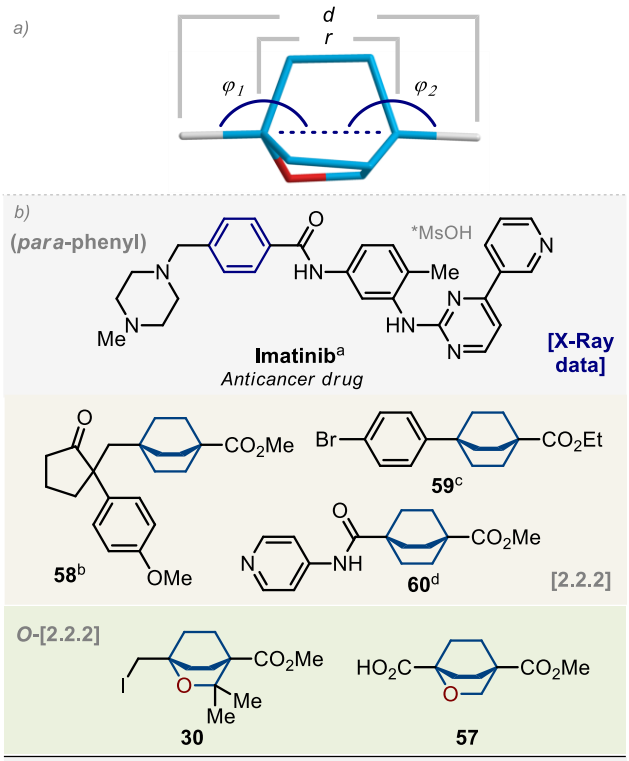
carboxylic acid **45** in 90% yield. The subsequent Curtius reaction afforded *N*-Boc iodide **46** in 87% yield. The structure of **46** was confirmed by X-Ray crystallographic analysis.[30] Reaction of the latter with potassium acetate, followed by hydrolysis (via **47**) and *N*-Boc acidic deprotection gave amino alcohol **48**. Oxidation of the alcohol group in **47** gave *N*-Boc protected amino acid **49** – a saturated analogue of the *para*-aminobenzoic acid. The reaction of iodide **46** with NaN_3 (via **50**) followed by reduction of the azide group formed diamine **51**. The reaction of iodide **6** with NaN_3, the subsequent reduction (via **52**), *N*-Boc protection and saponification gave another *N*-Boc protected amino acid **53**. Curtius reaction of the latter provided *N*-Boc diamine **54** – isomer of diamine **51**. The reaction of iodide **6** with sodium azide followed by extensive reduction of the intermediate azide with $LiAlH_4$ gave amino alcohol **55**. The structure of **55** was confirmed by X-Ray crystallographic analysis.[30] Reaction of iodide **6** with potassium acetate (via **56**) followed by saponification of the ester group and oxidation gave linker **57**. Its structure was also confirmed by X-Ray crystallographic analysis.[30] Worth noting that all syntheses depicted in Scheme 5 were realized on a multigram scale.

Chemical stability. We also checked the thermal and chemical stability of the synthesized 2-oxabicyclo[2.2.2]octanes. As representative examples, we selected three molecules: isomeric acids **37**, **43**, and amine **41**. All compounds were crystalline white solids. They were air-stable and moisture-stable. We stored them at room temperature in closed vials on the shelf for one year and observed no decomposition according to ^{1}H NMR. Under heating at 100 °C for five minutes, all compounds remained stable. Treatment of compounds with aq. 1M hydrochloric acid, or aq. 1M sodium hydroxide at room temperature for one hour and the subsequent control by ^{1}H NMR showed no decomposition either.

Crystallographic analysis. Next, we compared the geometric properties of 2-oxabicyclo[2.2.2]octanes with those of the *para*-substituted phenyl ring, and the previously used bioisosteres - bicyclo[2.2.2]octanes. For that, we measured two C-C distances *r* and *d* to see the overall similarity of cores; and two angles φ_1 and φ_2 to estimate the collinearity of exit vectors (Figure 2).

We calculated the values of *r*, *d*, φ_1, and φ_2 of 2-oxabicyclo[2.2.2]octanes from the X-ray data of compounds **30**, **57**. The related parameters for bicyclo[2.2.2]octanes **58**,[31] **59**,[32] and **60**[33] were calculated from their X-ray data published in the literature. The corresponding parameters for the *para*-substituted phenyl ring were calculated from the reported crystal structure of the anticancer drug *Imatinib* (Figure 2).[34] Analysis of this data revealed that the geometric properties of 2-oxabicyclo[2.2.2]octanes were indeed very similar to those of the *para*-substituted phenyl ring. The distance *r* in 2-oxabicyclo[2.2.2]octanes was ca. 0.3 Å shorter than that in the *para*-phenyl ring: 2.54-2.56 Å *vs* 2.88-2.89 Å (*para*-phenyl). The distance *d* between substituents in 2-oxabicyclo[2.2.2]octanes was also ca. 0.3 Å shorter than that in the *para*-phenyl ring: 5.56-5.58 Å *vs* 5.90-5.93 Å (*para*-phenyl). The difference in collinearity of vectors was insignificant, as angles φ_1 and φ_2 were almost identical in both scaffolds: 176-177° *vs* 178-179° (*para*-phenyl). Interestingly, even in the *para*-substituted phenyl ring (*Imatinib*) in the crystal phase the observed angles φ_1 and φ_2 deviated from the ideal value of 180°. It must be noted, that all parameters, - *r*, *d*, φ_1 and φ_2, - were also almost identical in both bicyclo[2.2.2]octanes (**58**-**60**) and 2-oxabicyclo[2.2.2]octanes (**30**, **57**) (Figure 2).

In short summary, the replacement of the methylene group for an oxygen atom in the bicyclo[2.2.2]octane core did not affect its three-dimensional geometry. Moreover, the formed 2-oxabicyclo[2.2.2]octane core resembled well the *para*-substituted phenyl ring, as the geometric parameters *r*, *d*, φ_1, and φ_2 remained very similar. The key characteristics of both cores and their superposition are shown in Figure 3.



Compound	r (Å)	d (Å)	φ_1 (°)	φ_2 (°)
Imatinib (*A*)[e]	2.893(0)	5.925(0)	176.4(8)	178.5(9)
Imatinib (*B*)	2.883(2)	5.906(0)	176.7(3)	178.7(5)
58 [2.2.2]	2.606(6)	5.62(1)	175.3(2)	177.1(2)
59 [2.2.2]	2.624(2)	5.656(2)	177.2(1)	177.0(1)
60 [2.2.2]	2.615(2)	5.665(2)	178.8(6)	178.7(1)
30 *O*-[2.2.2]	2.555(5)	5.582(5)	174.5(2)	177.3(2)
57 *O*-[2.2.2]	2.539(3)	5.563(3)	176.0(5)	176.4(1)

Figure 2. a) Definition of distances *r*, *d* and angles φ_1, φ_2 (2-oxabicyclo[2.2.2]octane core is shown as example). b) Geometric parameters *r*, *d* and φ_1, φ_2 for *para*-substituted phenyl ring (*Imatinib* drug), its literature saturated bioisosteres **58**-**60** ([2.2.2]) and ideal saturated bioisosteres **30**, **57** (*O*-[2.2.2]). [a]Data is taken from Ref. 34. [b]Data is taken from Ref. 31. [c]Data is taken from Ref. 32. [d]Data is taken from Ref. 33. [e]Two individual molecules of *Imatinib* (A and B) are present in the crystal lattice.

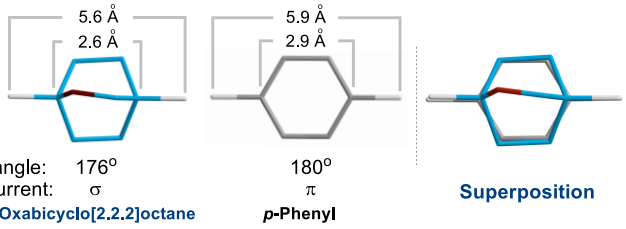


Figure 3. Visualized comparison of 2-oxabicyclo[2.2.2]octane and *para*-disubstituted phenyl ring. The ideal angle (180°) for the *para*-disubstituted phenyl ring is given (the observed angle in Imatinib is 177-178°).

The acidity of functional groups. We also studied the influence of the replacement of the methylene group for oxygen atom in the bicyclo[2.2.2]octane skeleton on the electronic properties. For that, we experimentally measured pK_a values of isomeric 2-oxabicyclo[2.2.2]octane carboxylic acids **37** and **43**, bicyclo[2.2.2]octane carboxylic acid **62**, and *para*-methyl benzoic acid (**61**) as a reference (Figure 4). Replacement of the methylene group in **62** for the oxygen atom at the distal γ-position dramatically increased its acidity from pK_a=5.6 to 4.4 (**37**). However, analogous replacement at the β-position increased the acidity even more to pK_a=4.1 (**43**).

Important to mention that the acidity of aromatic carboxylic acid **61** and 2-oxabicyclo[2.2.2]octane **37** were almost identical (Figure 4). Indeed, the replacement of the phenyl ring in acid **61** with the bicyclo[2.2.2]octane core reduced the acidity: pK_a=4.5 (**61**) *vs* 5.6 (**62**). However, incorporation of the β-oxygen atom into the latter ideally restored it: pK_a=4.4 (**37**). Because the acidity/basicity of functional groups is often responsible for the potency, selectivity, and toxicity of bioactive compounds,[35] the fine-tuning of the pK_a by replacing the phenyl ring with isomeric 2-oxabicyclo[2.2.2]octanes could be a solution here.

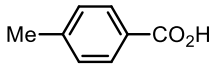
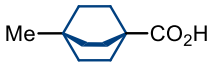
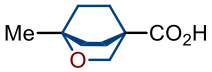
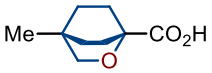
	Carboxylic acid	*pK_a (exp.)*
61		4.5 ± 0.1
62		5.6 ± 0.1
37		4.4 ± 0.1
43		4.1 ± 0.1

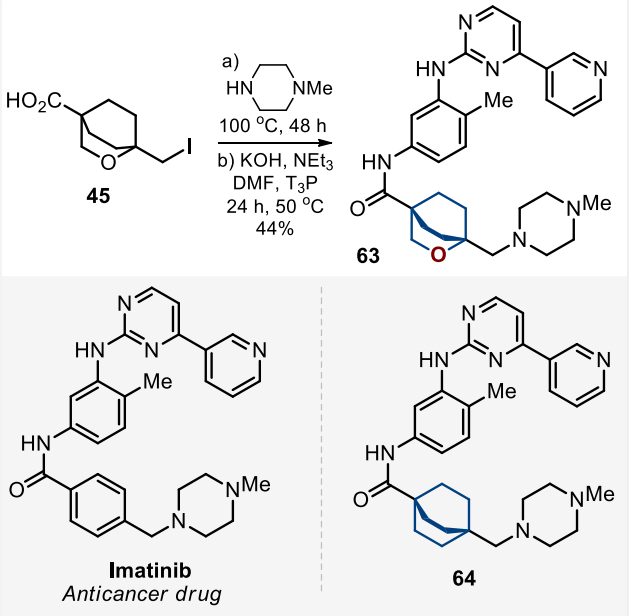
Figure 4. Experimental pK_a values of carboxylic acids **37**, **43**, **61**, and **62**.

Incorporation into bioactive compound. To demonstrate the practical utility of the 2-oxabicyclo[2.2.2]octane scaffold, we incorporated it into the structure of the anticancer drug *Imatinib*, instead of the phenyl ring (Scheme 6). The reaction of iodide **45** with *N*-methyl piperazine, followed by acylation with the substituted aniline gave compound **63** – a saturated analogue of *Imatinib*. For comparison, we also synthesized compound **64** with bicyclo[2.2.2]octane core (please, see SI for details). The commercialized drug *Imatinib* is used in practice as a mesylate salt. However, to estimate the impact of the replacement of the phenyl ring with bioisosteres on the physicochemical properties, we prepared and studied all three compounds, - **63**, **64**, *Imatinib*, - as free bases.

Physicochemical properties. Replacement of the *para*-substituted phenyl ring in *Imatinib* by bicyclo[2.2.2]octane (**64**) decreased the water solubility by more than three times (Scheme 6). However, the incorporation of the 2-oxabicyclo[2.2.2]octane (**63**) in *Imatinib* slightly increased the solubility: 351 μM (*Imatinib*) *vs* 113 μM (**64**) *vs* 389 μM (**63**).

To estimate the influence of the replacement of the phenyl ring with saturated bioisosteres on lipophilicity, we used two parameters: calculated (clogP)[36] and experimental (logD)

Imatinib analogues



Compound	*Sol.*	*clogP*	*logD (7.4)*	*Cl_{int}*	*$t_{1/2}$*
Imatinib	351±2	4.5	2.6±0.1	28	60
64 [2.2.2]	113±1	3.6	2.7±0.1	16	107
63 *O*-[2.2.2]	389±1	2.6	1.8±0.1	19	87

Scheme 6. Synthesis of compounds **63** and **64** (saturated bioisosteres of *Imatinib*). Solubility (*Sol.*): experimental kinetic solubility in phosphate-buffered saline, pH 7.4 (μM). *clogP*: calculated lipophilicity. *logD* (7.4): experimental distribution coefficient in *n*-octanol/phosphate-buffered saline, pH 7.4. Reliable *logD* measured were obtained within a range of 1.0-4.5. *Cl_{int}*: experimental metabolic stability in human liver microsomes (μl/min/mg). *$t_{1/2}$* (min): experimental half-time of a metabolic decomposition.

lipophilicities. Replacement of the phenyl ring with bicyclo[2.2.2]octane led to a decrease of clogP: 4.5 (*Imatinib*) *vs* 3.6 (**64**). The incorporation of 2-oxabicyclo[2.2.2]octane led to an even further decrease of clogP: 2.6 (**63**). A somewhat similar trend was observed with the experimental lipophilicity, logD. While the incorporation of the bicyclo[2.2.2]octane core into *Imatinib* did not significantly affect it; incorporation of the 2-oxabicyclo[2.2.2]octane core reduced it by ca. one unit, logD: 2.6 (*Imatinib*) *vs* 2.7 (**64**) *vs* 1.8 (**63**).

The effect of saturated bioisosteres on metabolic stability was studied next. The incorporation of both bicyclo[2.2.2]octane (**64**) and 2-oxabicyclo[2.2.2]octane (**63**) into *Imatinib*, increased the metabolic stability in human liver microsomes: Cl_{int} (mg/(min•μL))=60 (*Imatinib*) *vs* 107 (**64**) *vs* 87 (**63**) (Scheme 6). Moreover, incorporation of the 2-oxabicyclo[2.2.2]octane core (**63**) into *Imatinib* increased the life half time by almost 50%: $t_{1/2}$ (min)=60 (*Imatinib*) *vs* 87 (**63**).

In summary, the replacement of the *para*-substituted phenyl ring in *Imatinib* with common bicyclo[2.2.2]octane core (**64**) led to an undesired three-times decrease in water solubility. At the same time, analogous replacement with 2-oxabicyclo[2.2.2]octane (**63**) resulted in an improvement of all measured physicochemical parameters: solubility, metabolic stability, and lipophilicity.

Summary. The phenyl ring is a key structural element in chemistry. We have designed, synthesized, and characterized the “ideal” saturated bioisoster of the *para*-substituted phenyl ring: 2-oxabicyclo[2.2.2]octane. In the design of the structure, we kept all advantages of the previously used cores, - conformational rigidity, metabolic stability, non-chirality, collinearity of the exit vectors, - and addressed their drawbacks, - C-C distance and lipophilicity. The 2-oxabicyclo[2.2.2]octane scaffold was synthesized from available starting materials on a multigram scale. Crystallographic analysis revealed its high similarity with the *para*-substituted phenyl ring. Its incorporation into *Imatinib* drug instead of the phenyl ring led to improvement of all physicochemical parameters: solubility, metabolic stability, and lipophilicity.

This study opens new horizons in chemistry, given the commonplace of the phenyl ring everywhere.

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Keywords: 2-oxabicyclo[2.2.2]octane • bicyclo[1.1.1]pentane • bicyclo[2.2.2]octane • phenyl • bioisosteres

Data availability: The authors declare that data supporting the findings of this study are available within the paper and its supplementary information files.

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[17] that excluded the conformationally labile 1,4-disubstituted cycloxetane (please, see SI).

[18] that excluded the metabolically labile alkyne bond (please, see SI).

[19] that excluded adding additional substituents at the bridge position of bicyclo[1.1.1]pentane, bicyclo[2.2.2]octane and cubane (please, see SI).

[20] that excluded smaller less lipophilic bicycloalkanes: bicyclo[2.2.1]heptanes and bicyclo[2.1.1]hexanes. In these structures, C-C vectors are not collinear. The angle □ between vectors is ca. 150º (please, see SI).

[21] A poll on the design of the "ideal" bioisoster of the *para*-substituted phenyl ring was posted previously online (https://twitter.com/MykhailiukChem/status/1554728190362456064). This question initiated a lot of discussions, and we received many suggestions. Analysis of the of the benefits and drawbacks of every suggested structure is given in the SI.

[22] Decoration with SO_2-group is also conceptually interesting.

[23] Insertion of the oxygen atom, instead, would give 3-oxabicyclo[3.2.2]nonane with non-collinear C-C vectors (please, see SI).

[24] Analogous replacement of the carbon atom with oxygen in bicyclo[1.1.1]pentane would give the substituted strained oxetane (2-oxabicyclo[1.1.1]pentane), that is expected to be chemically labile (please, see SI).

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Abstract

An “Ideal” Bioisoster of the *para*-substituted Phenyl Ring

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The phenyl ring is a basic structural element in chemistry, and we learn about it already in school. We have developed an “ideal” saturated bioisoster of the *para*-substituted phenyl ring, -2-oxabicyclo[2.2.2]octane. Its incorporation into Imatinib drug led to dramatic improvement of all physicochemical properties. This study opens new horizons in science, given the commonplace of the phenyl ring everywhere.