Water-soluble Bioisosteres of the *ortho*-substituted Phenyl Ring

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Dedicated to the people of Ukraine

Introduction. The phenyl ring is a basic structural element in chemistry. Children learn about three isomers of the disubstituted phenyl ring, - *ortho*, *meta* and *para*, - already at school in a general chemistry class. Moreover, the phenyl ring is one of the most popular rings in bioactive compounds. [1] However, organic compounds that have more than two phenyl rings often have poor solubility and low metabolic stability – undesired effects in medicinal chemistry.[2] In this context, during the last decade, the concept "*escape from flatland*" changed the preferences of medicinal chemists on what kind of building blocks to use in research.[3] Today, chemists prefer modifying small symmetric F(sp^3)-rich structures in drug discovery projects.[4,5] The replacement of the phenyl ring in bioactive compounds with saturated bioisosteres has become a popular tactic to obtain novel structures with an improved physicochemical profile.[6,7] However, most of the research in this area is devoted to the replacement of *mono*-substituted and *para*-disubstituted phenyl rings.[7a,8,9,10]

The *ortho*-disubstituted phenyl ring is a part of more than three hundred drugs and agrochemicals (Figure 1).[11] For example, Aspirine, which is known to everyone, has an *ortho*-disubstituted phenyl ring in the structure. During the past two years, the first saturated bioisosteres of the *ortho*-disubstituted phenyl ring were introduced: 1,2-disubstituted bicyclo[1.1.1]pentanes (A, Figure 1),[12] and bicyclo[2.1.1]heptanes (B, Figure 1).[13,14,15] In this work, we report on the preparation, characterization and application of the next generation of these saturated bioisosteres: water-soluble analogues of the *ortho*-substituted phenyl ring (Figure 1).

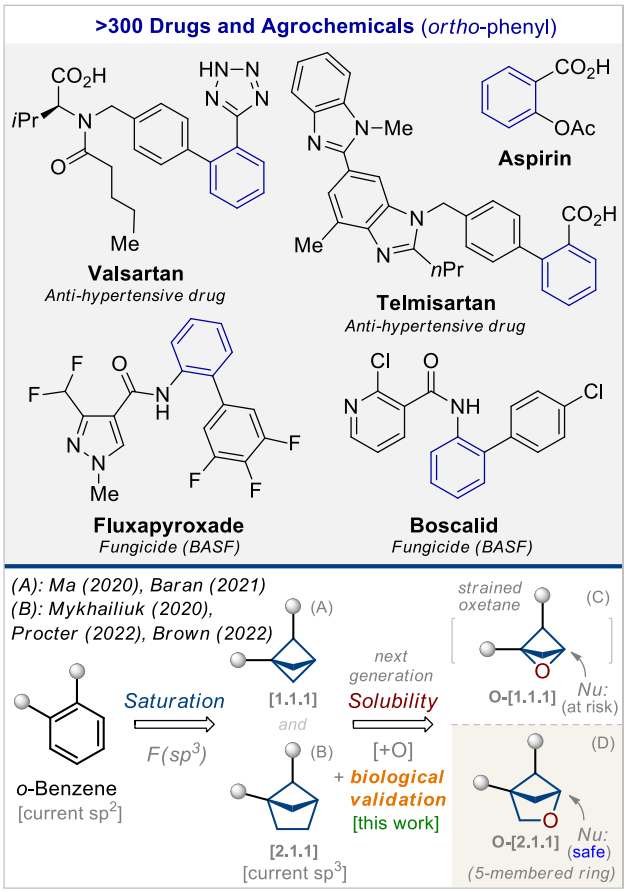

Figure 1. Saturated bioisosteres of *o*-substituted phenyl ring: state of the art.

Design. In the design of a core that would have a similar structure to bicyclo[1.1.1]pentanes and bicyclo[2.1.1]heptanes, but enhanced water solubility, we decided to insert an oxygen atom into it. Replacing the methylene group in bicyclo[1.1.1]pentane with the oxygen atom leads to the strained oxetane structure (C, Figure 1), which could be labile or even unstable due to possible ring-opening with nucleophiles. [16] Analogous replacement in bicyclo[2.1.1]heptanes, however, gives the substituted tetrahydrofuran (D, Figure 1). That core should be chemically stable, but also more water-soluble than the phenyl ring and its carbon-based saturated bioisosteres. From the medicinal chemistry perspective, having the ether oxygen atom in the core is also useful, because it could serve as an additional binding site with a receptor.

Synthesis. The photochemical [2+2]-cycloaddition between alkenes proved to be a powerful strategy to construct cyclobutanes.[17] In this context, we wondered if diene **1** (easily obtained from the commercially available starting materials, please see next paragraph) would undergo an intramolecular cyclization into the needed 2-oxabicyclo[2.1.1]hexane core. Direct irradiation of diene **1** in acetonitrile under different wavelengths gave only traces of products (entries 1-4, Table 1). Irradiation with a Hanovia broad wavelength mercury lamp gave the needed product along with many side products (entry 5). Next, we tried the addition of available organic ketones for the triplet sensitization of the styrene moiety. Indeed, smooth formation of the needed products **1a** was already observed. The best result was obtained with benzophenone (entry 7), whereas acetophenone and substituted benzophenones also worked, but provided the product with lower yields (entries 6, 8, 9). Among all tested solvents (entries 10-13), the best outcome was obtained in acetonitrile. Without irradiation, the reaction did not take took place neither at room temperature nor under heating (entries 14, 15).

Even though under optimized conditions, cyclization of diene **1** led to rather a clean formation of a diastereomeric mixture ofproducts **1a** (d.r.=4:1), the pure major isomer **1a** was isolated by column chromatography in only 56% yield. The separation of isomers by column chromatography was problematic and led to a significant loss of the yield, which needed to be solved

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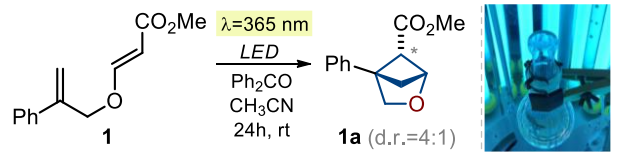
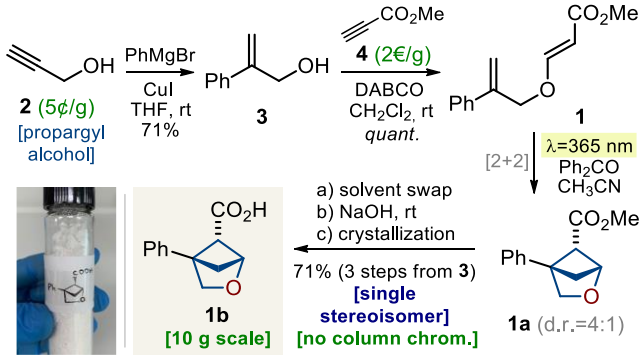


entry	Conditions	yield (%)[b]
1	419 nm, CH_3CN	*n.d.*
2	365 nm, CH_3CN	<5
3	313 nm, CH_3CN	<5
4	254 nm, CH_3CN	<20
5	Hanovia mercury lamp, CH_3CN	39
6	365 nm, CH_3CN, PhC(O)Me	47
7	365 nm, CH_3CN, Ph_2CO	83 (56)[c]
8	365 nm, CH_3CN, $(p\text{-}MeOC_6H_4)_2CO$	61
9	365 nm, CH_3CN, $(p\text{-}NO_2C_6H_4)_2CO$	38
10	365 nm, CH_2Cl_2, Ph_2CO	71
11	365 nm, Me_2CO, Ph_2CO	68
12	365 nm, PhMe, Ph_2CO	42
13	365 nm, EtOAc, Ph_2CO	29
14	no light, rt	*n.d.*
15	no light, reflux	*n.d.*

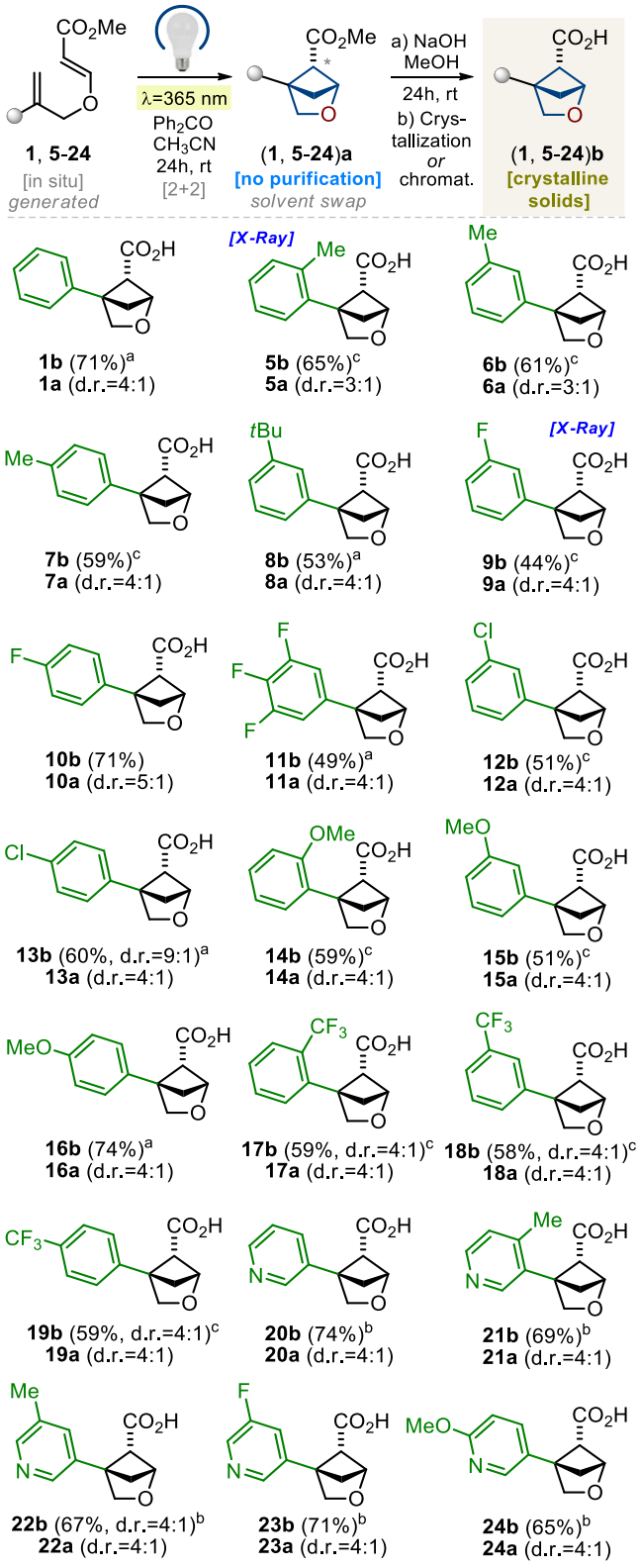
[a] 20 mmol scale. [b] ^1H NMR yield of both isomers (CH_2Br_2 as an internal standard). [c]Isolated yield of major stereoisomer of **1a**. See SI for details.

Table 1. Optimization of the synthesis of compound **1a**.

Scaled-up synthesis. The whole optimized synthetic protocol is shown in Scheme 1. For us, it was important to elaborate on a method that employed only available and cheap starting materials. The synthesis started from propargyl alcohol (**2**). Copper-catalyzed reaction with phenyl magnesium bromide gave alcohol **3** in 71% yield, following the reported procedure.[18] Michael-addition of the latter with methyl propiolate (**4**) in the presence of DABCO afforded the needed diene **1**. We mentioned that compound **1** partially decomposed during column chromatography and even under storage at room temperature. Therefore on the scale, we generated crude diene **1** *in situ* (please, see SI) and used it directly in the photochemical step. A mixture of isomers **1a** was obtained. After extensive experimentation, we found a solution on how to avoid column chromatography, and not lose the yield. The crude reaction mixture after irradiation (isomers **1a** and benzophenone) was saponified with sodium hydroxide. Standard workup (removal of benzophenone) followed by crystallization from hexane-MeO*t*Bu mixture (removal of the minor isomer) allowed isolation of pure major isomer **1b** in 71% yield after three steps from alcohol **3**. Product **1b** was obtained on a ten-gram scale with no column purifications involved.



Scheme 1. Gram-scale synthesis of compound **1b** from propargyl alcohol **2**.



Scheme 2. Scope of the reaction. Isolated yields in three steps from allylic alcohols. [a]Product was isolated by crystallization from hexane-MeO*t*Bu mixture. [b]Product was isolated by crystallization from acetone-water mixture. [c]Product was isolated by column chromatography.

Scope. Next, we studied the scope of the developed method. The photocyclization tolerated well various substituents on the aromatic core (Scheme 2). Among them were the alkyl groups (**5a**-**8a**), fluorine (**9a**-**11a**) and chlorine atoms (**12a**, **13a**), methoxy groups (**14a**-**16a**) and trifluoromethyl groups (**17a**-**19a**). The reaction was also compatible with various substituted pyridines (**20a**-**24a**). In all cases, we isolated analytical quantities of intermediate esters **5a**-**24a** by column chromatography to characterize them. On the gram scale, however, we directly used crude reaction mixtures with **5a**-**24a** after photocyclization in the subsequent saponification step. In half of all cases, we could obtain the final carboxylic acids by simple crystallization of crude reaction mixtures from various solvents (Scheme 2). In another half of the cases, column chromatography was still needed. The structure of carboxylic acids **5b** and **9b** was confirmed by X-ray crystallographic analysis (Figure 2).[19]

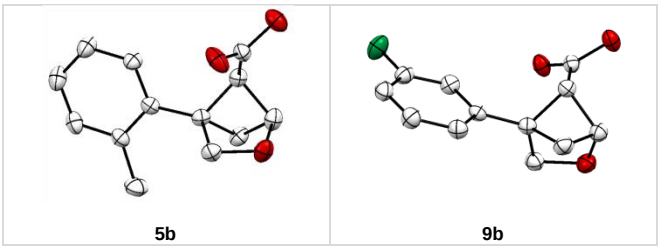
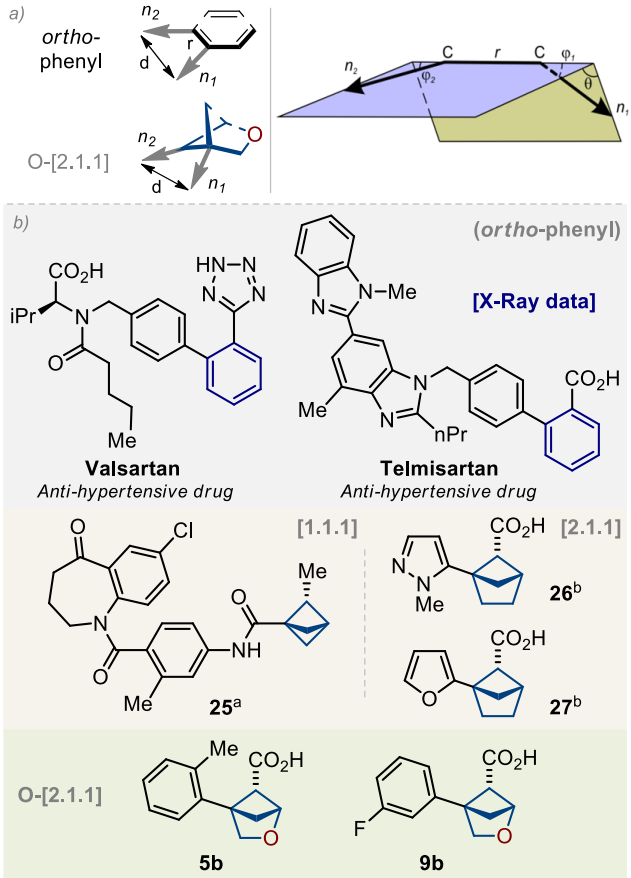


Figure 2. X-ray crystal structures of compounds **5b** and **9b**. Hydrogen atoms are omitted for clarity. Carbon – grey, oxygen – red, fluorine – green.

Chemical stability. We also checked the chemical stability of three representative carboxylic acids **1b**, **19b** and **22b** (Scheme 2), because we suspected that some of them could decompose via a retro-Michael type reaction. Treatment of them with aq. 1M hydrochloric acid, or aq. 1M aq. sodium hydroxide at room temperature for one day did not lead to any decomposition. All products were crystalline solids, and we stored all of them in closed vials at room temperature on the shelf. ^{1}H-NMR, LC-MS inspection after three months did not reveal any decomposition either.

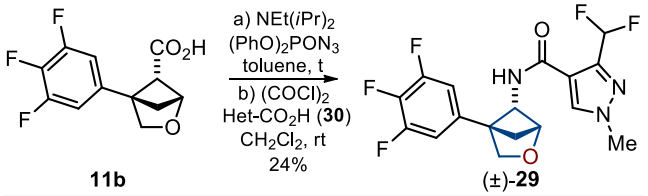
Crystallographic analysis. Next, we compared the geometric parameters of 2-oxabicyclo[2.1.1]hexanes with the *ortho*-substituted phenyl ring and their previously suggested saturated bioisosteres, bicyclo[1.1.1]pentanes and bicyclo[2.1.1]heptanes. For that, we employed the exit vector plots tool.[20] In this method, substituents at the disubstituted scaffold were simulated by two exit vectors n_1 and n_2 (Figure 3). The relative spatial arrangement of vectors is described by four geometric parameters: the distance between *C*-variation atoms *r*, the plane angles φ_1 (between vectors n_1 and C-atom) and φ_2 (between n_2 and C-atom), and the dihedral angle θ defined by vectors n_1, CC and n_2. An additional important parameter - distance *d* between two carbon substituents (Figure 3) - was also measured.

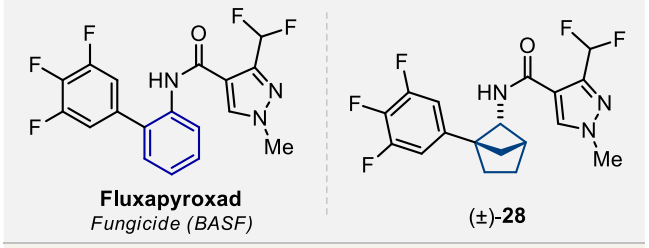
We calculated the values of *d*, *r*, φ_1, φ_2, and θ of 2-oxabicyclo[2.1.1]hexanes from the X-ray data of compounds **5b**, **9b**. The related parameters for bicyclo[1.1.1]pentane **25**[12b] and bicyclo[2.1.1]heptanes **26**, **27**[13a] were calculated from their X-ray data published in the literature. The corresponding parameters for *ortho*-substituted phenyl rings were calculated from the reported crystal data of two antihypertensive drugs - *Valsartan* and *Telmisartan* (Figure 3).[21] Analysis of this data revealed that geometric properties of 2-oxabicyclo[2.1.1]hexanes in general were indeed similar to those of the *ortho*-substituted phenyl ring. In particular, distance *r* in 2-oxabicyclo[2.1.1]hexanes was ca. 0.2 Å longer than that in the *ortho*-phenyl ring: 1.56-1.57 Å *vs* 1.38-1.44 Å (*ortho*-phenyl). The distance *d* between substituents in 2-oxabicyclo[2.1.1]hexanes was also ca. 0.5 A longer than that in the *ortho*-phenyl ring: 3.6 Å *vs* 3.0-3.1 Å (*ortho*-phenyl). Angles φ_1 and φ_2 were almost identical in both scaffolds. Moreover, φ_1 and φ_2 in 2-oxabicyclo[2.1.1]hexanes were much closer to those in the *ortho*-phenyl ring, than to those of the previously used saturated bioisosteres - bicyclo[1.1.1]pentanes and bicyclo[2.1.1]heptanes. The difference in planarity was significant, however: while *ortho*-phenyl was almost flattened ($|\theta|$ = 7-8°), 2-oxabicyclo[2.1.1]hexanes had a significant three-dimensional character: $|\theta|$ = 80°. It must be noted, however, the nonplanarity was also present in bicyclo[1.1.1]pentanes ($|\theta|$ = 58°) and bicyclo[2.1.1]heptanes ($|\theta|$ = *ca.* 75°) (Figure 3).



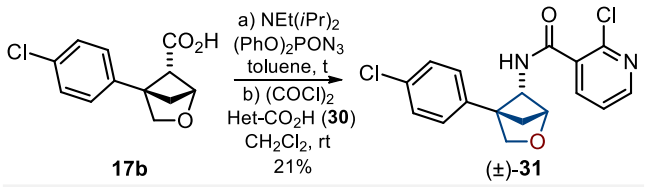
Compound	*d* (Å)	*r* (Å)	φ_1 (°)	φ_2 (°)	$\|\theta\|$ (°)
Valsartan	3.036(2)	1.441(2)	56.6(1)	56.9(1)	8.3(2)
Telmisartan	3.101(7)	1.385(7)	55.3(5)	55.2(5)	7.5(8)
25 [1.1.1]	3.355(6)	1.529(4)	53.7(2)	62.8(3)	57.5(4)
26 [2.1.1]	3.439(6)	1.574(6)	60.3(3)	60.3(4)	75.8(5)
27 [2.1.1]	3.486(2)	1.555(2)	54.5(2)	59.6(2)	74.7(2)
5b O-[2.1.1]	3.557(5)	1.559(5)	58.8(3)	56.0(3)	80.0(4)
9b O-[2.1.1]	3.589(5)	1.568(5)	56.4(2)	56.5(2)	79.6(4)

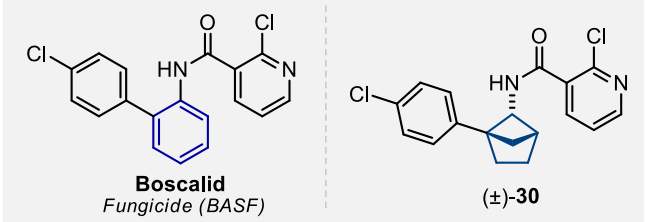
Figure 3 a) Definition of vectors n_1, n_2 (1,2-disubstituted *ortho*-phenyl ring, and core O-[2.1.1] are shown as examples). Definition of geometric parameters *d*, *r*, φ_1, φ_2, and θ. b) Geometric parameters *d*, *r*, φ_1, φ_2, and $|\theta|$ for *ortho*-substituted benzenes (*Valsartan*, *Telmisartan*), its saturated literature bioisosteres **25**-**27** and water-soluble saturated bioisosteres **5b**, **9b**. [a]Data is taken from Ref. 12b. [b]Data is taken from Ref. 13a.



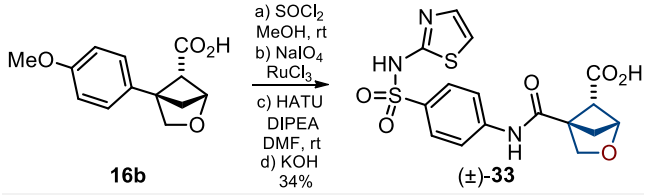


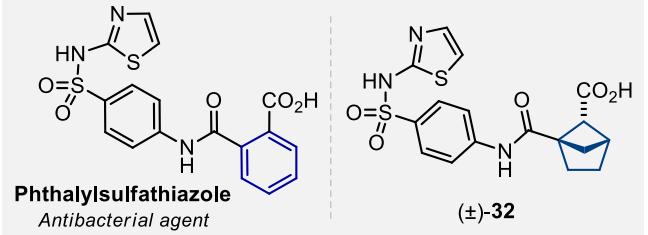
Compound	Solubility	clogP	logD (7.4)	Cl_{int}
Fluxapyroxad	25±1.1	2.2	3.5±0.1	28
28 [2.1.1]	34±0.4	2.9	4.3±0.2	35
29 O-[2.1.1]	155±3.2	1.3	2.8±0.1	23



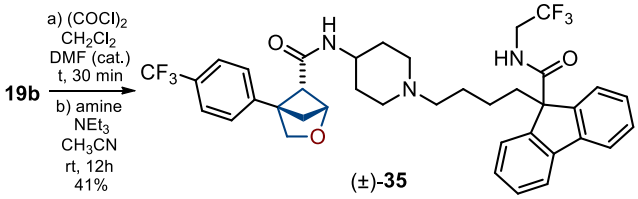


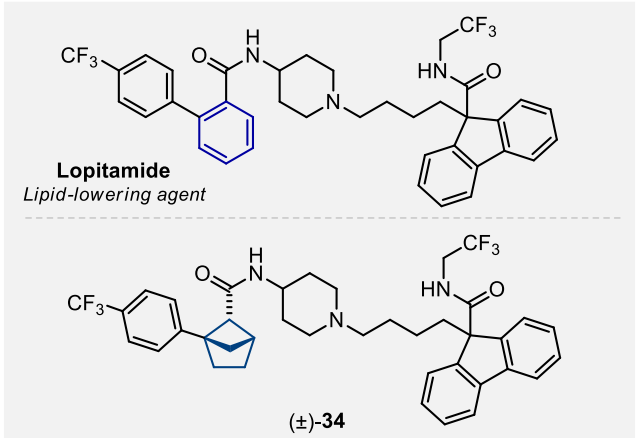
Compound	Solubility	clogP	logD (7.4)	Cl_{int}
Boscalid	11±2.0	3.4	3.6±0.1	26
30 [2.1.1]	17±0.3	4.1	3.5±0.1	12
31 O-[2.1.1]	152±4.4	2.5	2.7±0.2	3





Compound	Solubility	clogP	logD (7.4)	Cl_{int}
Phthalyl-e	170±1.2	1.3	<1	2
32 [2.1.1]	101±0.6	1.3	<1	0
33 O-[2.1.1]	158±6.9	0.8	<1	1





Compound	Solubility	clogP	logD (7.4)	Cl_{int}
Lopitamide	3±0.1	7.0	>4.5	55
34 [2.1.1]	2±0.2	6.9	>4.5	157
35 O-[2.1.1]	3±0.8	5.6	>4.5	87

Scheme 4. Synthesis of compounds **28**, **29** (saturated bioisosteres of analogues of *Fluxapyroxad*); **30**, **31** (saturated bioisosteres of *Boscalid*); **32**, **33** (saturated bioisosteres of *Phthalylsulphathiazole*); **34**, **35** (saturated bioisosteres of *Lopitamide*). clogP: calculated lipophilicity. Solubility: experimental kinetic solubility in phosphate-buffered saline, pH 7.4 (μM). logD (7.4): experimental distribution coefficient in *n*-octanol/phosphate-buffered saline, pH 7.4. Reliable logD measured were obtained within a range 1.0-4.5. Cl_{int}: experimental metabolic stability in human liver microsomes (μl/min/mg).

In general, vector characteristics of 2-oxabicyclo[2.1.1]hexanes were very similar to those of the previously used bioisosteres of the *ortho*-substituted phenyl ring: bicyclo[1.1.1]pentanes and bicyclo[2.1.1]heptanes. Moreover, important angles φ_1 and φ_2 in 2-oxabicyclo[2.1.1]hexanes were even closer to the *ortho*-phenyl ring than to those of bicyclo[1.1.1]pentanes and bicyclo[2.1.1]heptanes.

Incorporation into bioactive compounds. Incorporation of 2-oxabicyclo[2.1.1]hexane scaffold into bioactive compounds was attempted next. We chose four bioactive products with the *ortho*-substituted phenyl ring: agrochemical fungicides *Fluxapyroxad* and *Boscalid*, antibacterial agent *Phthalylsulphathiazole* and lipid-lowering agent *Lopitamide* (Scheme 4).

Synthesis of the saturated analogue of *Fluxapyroxad* was undertaken from carboxylic acid **11b** (Scheme 4). The standard Curtius reaction followed by acylation of the intermediate amine with the substituted pyrazole carboxylic acid gave the needed compound **29**. Using an analogous tactic, compound **31**, - a saturated analogue of *Boscalid*, - was also obtained from carboxylic acid **17b** (Scheme 4). The saturated analogue of *Phtalylsulfathiazole* was obtained by converting carboxylic acid **16b** first into the methyl ester followed by the oxidation of the phenyl ring. Amide coupling of the formed acid with the substituted aniline followed by saponification of the methyl ester gave the final compound **33** (Scheme 4). Amide coupling of carboxylic acid **19b** with the correspondingly *N*-substituted 4-

aminopiperidine gave compound **35** – a saturated analogue of *Lopitamide* (Scheme 4).

In all cases, in addition to bioactive compounds with 2-oxabicyclo[2.1.1]hexane core (**29**, **31**, **33**, **35**), we also synthesized analogous carbocyclic analogues **28**, **30**, **32**, **34** (Scheme 4; please, see SI for details).

Physico-chemical parameters. In the next step, we studied the effect of the replacement of the *ortho*-phenyl ring by 2-oxabicyclo[2.1.1]hexanes on the physicochemical properties of bioactive compounds. For the comparison, we also used the corresponding carbon-based core, - bicyclo[2.1.1]heptane.

Water solubility. Replacement of the *ortho*-substituted phenyl ring in *Fluxapyroxad* by bicyclo[2.1.1]heptane (**28**) slightly increased its solubility (Scheme 4). However, incorporation of the 2-oxabicyclo[2.1.1]hexane in *Fluxapyroxad* (**29**) resulted in a dramatic increase in solubility by six times: 25 μM (*Fluxapyroxad*) *vs* 34 μM (**28**) *vs* 155 μM (**29**). An analogous trend was also seen with *Boscalid* and its analogues **30**, **31**. Replacement of the phenyl ring in *Boscalid* with bicyclo[2.1.1]heptane (**30**) led to the increase of solubility by ca. 50%. However, the corresponding replacement with 2-oxabicyclo[2.1.1]hexane (**31**) increased the solubility by more than ten times: 11 μM (*Boscalid*) *vs* 17 μM (**30**) *vs* 152 μM (**31**). Replacement of the phenyl ring in *Phthalylsulphathiazole* with bicyclo[2.1.1]heptane (**32**) decreased its solubility, while the incorporation of the 2-oxabicyclo[2.1.1]hexane core (**33**) restored it: 170 μM (*Phthalylsulphathiazole*) *vs* 101 μM (**32**) *vs* 158 μM (**33**). *Lopitamide* had poor solubility in water, and replacement of the phenyl ring in *Lopitamide* with saturated bioisosteres (**34**, **35**) did not have a significant impact on the solubility.

In short summary, in two (*Fluxapyroxad*, *Boscalid*) out of four bioactive compounds, replacement of the *ortho*-substituted phenyl ring with 2-oxabicyclo[2.1.1]hexane led to a dramatic increase in water solubility by ca. one order of a magnitude.

Lipophilicity. To estimate the influence of the replacement of the *ortho*-substituted phenyl ring with saturated bioisosteres on lipophilicity, we used two parameters: calculated (clogP)[22] and experimental (logD) lipophilicity.

Replacement of the phenyl ring with bicyclo[2.1.1]heptane led to either increase of clogP (*Fluxapyroxad*, *Boscalid*), or did not affect it significantly (*Phthalylsulphathiazole*, *Lopitamide*) (Scheme 4). However, in all four bioactive compounds incorporation of 2-oxabicyclo[2.1.1]hexane instead of the *ortho*-substituted phenyl ring led to a decrease of clogP index by ca. one unit.

The effect of the replacement of the *ortho*-substituted phenyl ring with saturated bioisosteres on logD index was more complex. In *Fluxapyroxad*, incorporation of bicyclo[2.1.1]heptane core increased logD, while the incorporation of 2-oxabicyclo[2.1.1]hexane slightly decreased it: 3.5 (*Fluxapyroxad*) *vs* 4.3 (**28**) *vs* 2.8 (**29**). In *Boskalid*, incorporation of bicyclo[2.1.1]heptane core did not affect logD significantly, while the incorporation of 2-oxabicyclo[2.1.1]hexane reduced it: 3.6 (*Boskalid*) *vs* 3.5 (**28**) *vs* 2.7 (**29**).

In summary, in all tested bioactive compounds, replacement of the *ortho*-substituted phenyl ring with 2-oxabicyclo[2.1.1]hexane decreased the lipophilicity as measured by both clogP and logD indexes by ca. one unit.

Metabolic stability. The effect of saturated bioisosteres on the metabolic stability of bioactive compounds was complex and depended on the chemical structure. In *Fluxapyroxad*, incorporation of bicyclo[2.1.1]heptane (**28**) decreased the metabolic stability (Scheme 4). However, incorporation of 2-oxabicyclo[2.1.1]hexane (**29**) unexpectedly increased it, Cl_{int} (mg/(min•μL)) = 28 (*Fluxapyroxad*) *vs* 35 (**28**) *vs* 23 (**29**). In *Boscalid*, incorporation of the bicyclo[2.1.1]heptane (**30**) increased the metabolic stability, but the incorporation of 2-oxabicyclo[2.1.1]hexane (**31**) increased it even more, Cl_{int} (mg/(min•μL)) = 26 (*Boskalid*) *vs* 12 (**30**) *vs* 3 (**31**). All three compounds, *Phthalylsulphathiazole* and its two saturated analogues **32** and **33** were metabolically stable. In *Lopitamide*, incorporation of the bicyclo[2.1.1]heptane core (**34**) decreased the metabolic stability, but the incorporation of 2-oxabicyclo[2.1.1]hexane core (**35**) somewhat restored it, Cl_{int} (mg/(min•μL)) = 55 (*Lopitamide*) *vs* 157 (**34**) *vs* 87 (**35**).

In brief summary, among four bioactive compounds, replacement of the *ortho*-substituted phenyl ring with 2-oxabicyclo[2.1.1]hexane improved metabolic stability (Cl_{int}) in two (*Boscalid*, *Fluxapyroxad*), slightly decreased in one (*Lopitamide*) and tolerated it in another one (*Phtalylsulfathiazole*).

Bioactivity. Finally, we wanted to answer a key question, - if 2-oxabicyclo[2.1.1]hexanes could indeed mimic the *ortho*-substituted phenyl ring in real-world bioactive compounds? Therefore, we measured the antifungal activity of the marketed fungicides *Fluxapyroxad* (BASF), *Boscalid* (BASF) and their saturated analogues **28**-**31**. In strict contrast to medicinal chemistry, the use of racemic mixtures in agrochemistry is common;[23] therefore for the primary validation of the proof-of-concept, we directly studied the biological activity of the available racemic compounds **28**-**31** (Scheme 4).

Fluxapyroxad, and its saturated analogues **28**, **29** showed a similar level of activity at inhibition of *Fusarium oxysporum* growth (Figure 4, A). In the inhibition of growth of *Fusarium verticillioides*, the oxygen-containing saturated analogue **29** was almost the same potent as *Fluxapyroxad* at high concentrations but showed a reduced potency at low concentrations (Figure 4, B).

Boscalid and both saturated analogues **30**, **31** also effectively inhibited the growth of *Fusarium oxysporum* (Figure 5, A). Moreover, at low concentrations, the oxygen-containing saturated analogue **31** exhibited a potency identical to that of *Boscalid*. In the inhibition of growth of *Fusarium verticillioides*, compound **31** was still active but exhibited a lower potency compared to *Boscalid* (Figure 5, B).

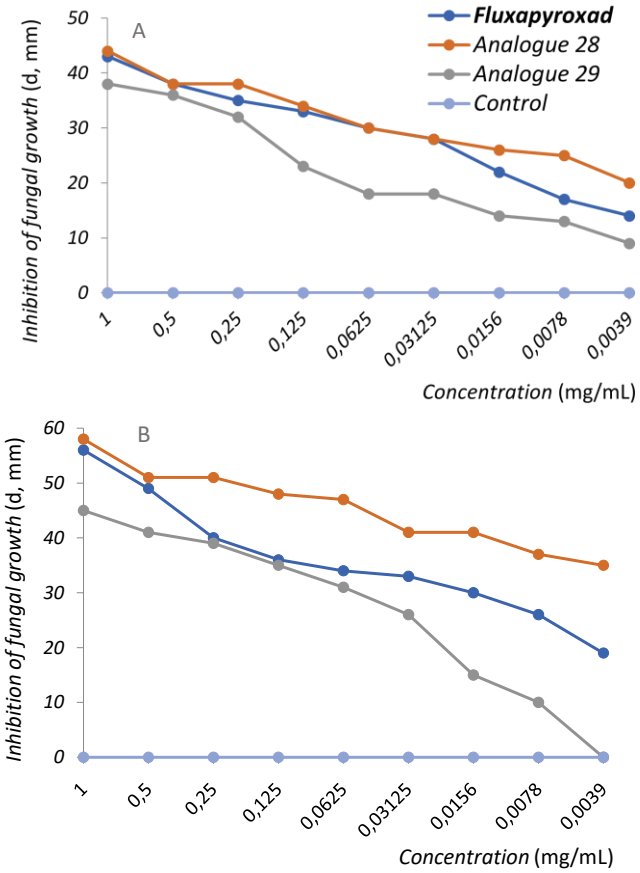


Figure 4. Inhibition of growth of (A) *Fusarium oxysporum*, and (B) *Fusarium verticillioides* (measured as a diameter of inhibition zone, mm) by *Fluxapyroxad* and its saturated analogues **28** [2.1.1] and **29** O-[2.1.1] at different concentrations after 48 h of incubation.

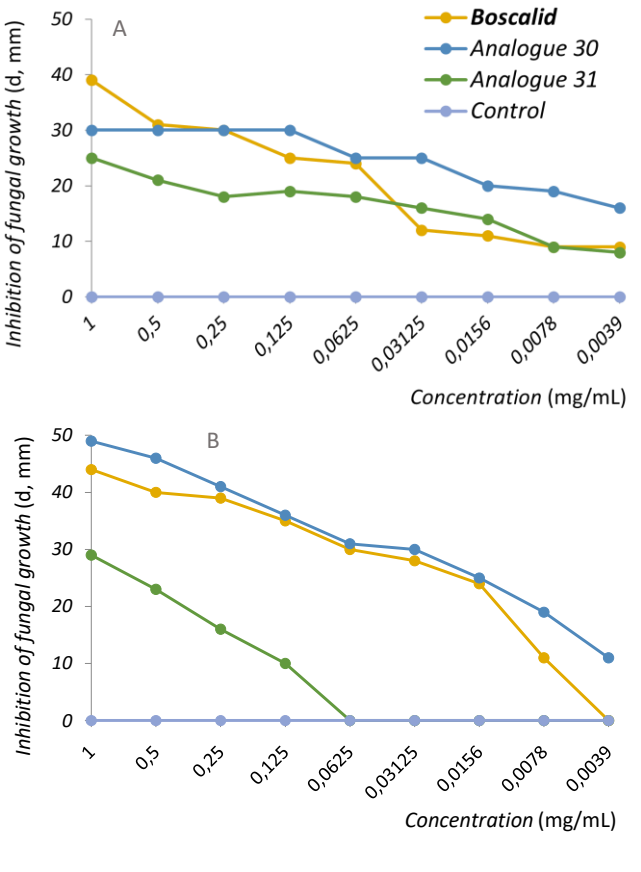


Figure 5. Inhibition of a growth of (A) *Fusarium oxysporum*, and (B) *Fusarium verticillioides* (measured as a diameter of inhibition zone, mm) by *Boscalid* and its saturated analogues **30** [2.1.1] and **31** O-[2.1.1] at different concentrations after 48 h of incubation.

Summary. The *ortho*-substituted phenyl ring (as well as *meta*- and *para*-isomers) is a basic structural element in chemistry, and children learn about it already at school in a general chemistry class. In this work, we developed water-soluble saturated bioisosteres of *ortho*-substituted phenyl ring: 2-oxabicyclo[2.1.1]hexanes (Figure 1). These scaffolds were synthesized from available starting materials on a multigram scale. Crystallographic analysis revealed that these structures and the *ortho*-substituted phenyl ring indeed have similar geometric properties. Moreover, replacement of the *ortho*-substituted phenyl ring in bioactive compounds with 2-oxabicyclo[2.1.1]hexanes, in most cases, improved water solubility (up to more than ten times), reduced lipophilicity, improved metabolic stability and most importantly - retained bioactivity.

Given the commonplace of the *ortho*-substituted phenyl ring in chemistry, we believe that its water-soluble bioisosteres will soon become very popular in practice and scientists will use them routinely.

Acknowledgements. Authors are grateful to Prof. A. A. Tolmachev for the support; to Dr. P. Borysko (Bienta) for the managing help; to Mrs. I. Sadkova for the help with the preparation of the supporting information; to Dr. S Shishkina for X-ray analysis of compounds **5b** and **9b**. This project has received funding from the European Research Council (ERC) under the European Union's Horizon 2020 research and innovation program (grant agreement No. 101000893 - BENOVELTY).

Keywords: 2-oxabicyclo[2.1.1]hexanes • bicyclo[1.1.1]pentanes • bicyclo[2.1.1]hexanes • bioisosteres • *ortho*-substituted benzenes

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Abstract

Water-soluble Bioisosteres of the *ortho*-substituted Phenyl Ring

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Water-soluble analogues of the *ortho*-substituted phenyl ring were developed. Replacement of the phenyl ring in bioactive compounds with 2-oxabicyclo[2.1.1]hexanes in many cases improved solubility, reduced lipophilicity, enhanced metabolic stability, and most importantly – retained bioactivity.