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Saturated mimetics for *ortho*-substituted benzenes

Aleksandr Denisenko,[a] Pavel Garbuz,[a] Svetlana V. Shishkina,[b] Nataliya M. Voloshchuk,[c] and Pavel K. Mykhailiuk[a,d]*

Abstract: Saturated mimetics for *ortho*-disubstituted benzenes - bicyclo[2.1.1]hexanes, - were synthesized, characterized and validated. These cores were incorporated into bioactive compounds *Valsartan, Boskalid* and *Fluxapyroxad* instead of the benzene ring. The saturated analogues showed a similar level of antifungal activity compared to that of *Boskalid* and *Fluxapyroxad*.

Introduction and Aim. The fragment of benzene is the most popular ring in bioactive compounds.[1] In fact, more than 500 drugs and agrochemicals are benzene-containing molecules.[2] During the last decade, however, the concept "*escape from flatland*",[3] has already changed the way how medicinal chemists think – these days small compact F(sp^3)-rich structures are especially prevalent in drug discovery projects.[4,5] In particular, the replacement of benzene rings with saturated bioisosteres has become an important strategy to obtain novel patent-free molecules with improved biological activity and physico-chemical profile.[6] In 2012, *Stepan* and colleagues from *Pfizer* replaced the substituted phenyl fragment in a ɣ-secretase inhibitor *Avagacestat* with the bicyclo[1.1.1]pentyl skeleton (Figure 1).[7] The obtained analogue showed higher activity, solubility and metabolic stability. Since then, bicyclo[1.1.1]pentyl-containing derivatives have been playing an important role in both academic and industrial research - they have already been mentioned in more than one hundred patents.[8,9] Moreover, cubane and bicyclo[2.2.2]octane have also been validated as saturated bioisosteres for *para*-substituted benzenes in bioactive compounds.[10]

It is important to mention, that the replacement of the phenyl ring with saturated mimetics is only possible when the phenyl ring in a bioactive compound is not involved in specific π-protein interactions (cation-π, π-π, dipole-π),[11] and acts purely as a rigid linker to hold two substituents in a well-defined distance.

An idea of replacing *ortho*- and *meta*-substituted benzenes in bioactive compounds has been coming up over the years. Such compounds will be of great importance for academic and industrial scientists, but so far still nothing is known in the open literature. Presumably, the lack of the rational design and synthetic methods has been slowing down the progress in this area.

Only recently, water-soluble 2-oxabicyclo[2.1.1]hexanes, that have similar geometric properties to *meta*-substituted benzenes, were synthesized employing the iodocyclization reaction.[12]

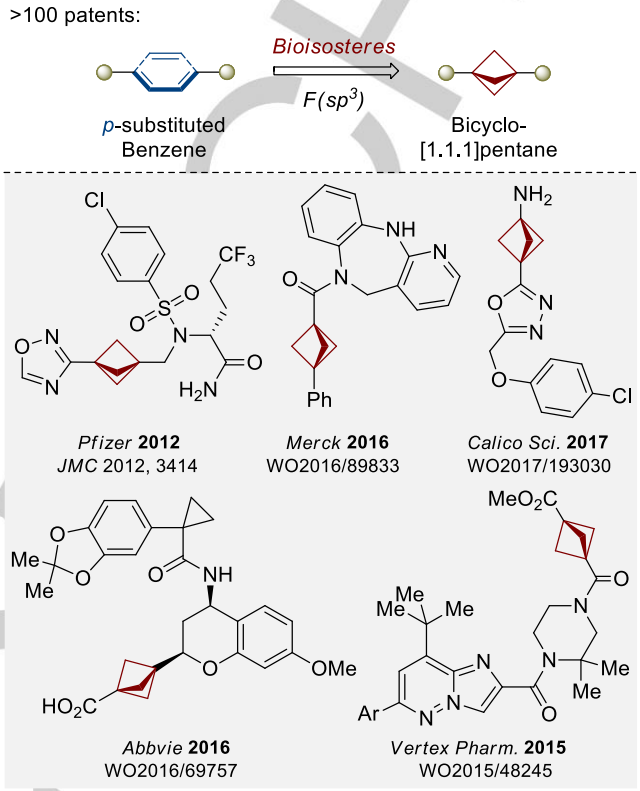
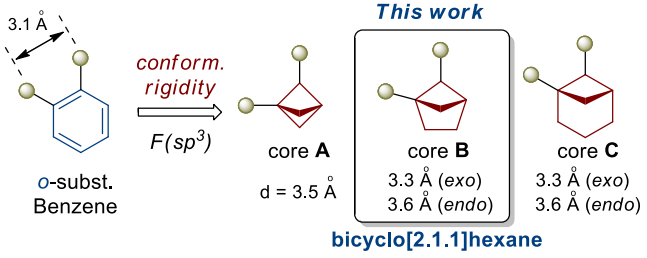


Figure 1. Bicyclo[1.1.1]pentanes as saturated mimics for *para*-substituted phenyl ring in medicinal chemistry.

In this context, herein we report on the preparation of the first saturated mimetics for *ortho*-substituted benzenes, their incorporation into bioactive compounds, and biological validation.

Design. In the design of a saturated core that would mimic *ortho*-substituted benzene, we followed the principles based on the advantages of the known bioisostere for the *para*-substituted benzene – bicyclo[1.1.1]pentane. (a) First, the linker must structurally closely resemble the residue of benzene. (b) Second, it must be conformationally rigid - bicyclic - to fix the positions of the substituents in space. (c) Finally, the distance between the substituents must be similar to that in the disubstituted benzenes. Structures **A**-**C** (Scheme 1) seem to fulfill all criteria highlighted



Scheme 1. Designed saturated bioisosteres **A**-**C** *ortho*-substituted benzenes. DTF-calculated distance (d) between the *C*-substituents is shown.

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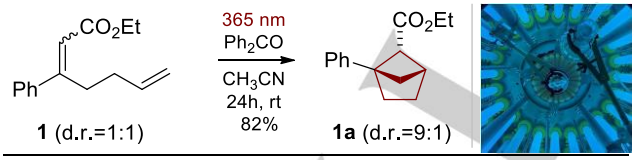
above. In contrast to the 2D-shaped benzene, they are 3D-shaped, but their size is similar to that of the benzene (criterion a). Moreover, these small bicyclic cores with one substituent at the bridgehead position are intrinsically conformationally restricted (criterion b). Finally, DFT-calculations show that C-C distances in compounds **A**-**C** (R=Me, 3.3-3.6 Å) are close to that in *ortho*-dimethyl benzene (3.1 Å).[13]

All three cores **A**-**C** seem to be appropriate for the replacement of *ortho*-substituted benzenes in bioactive compounds (where phenyl ring is not involved in specific π-protein interactions), and in this work we report on the development of the first core in this series - core **B** (Figure 2).[14]

Synthesis. Mono- and poly-substituted core **B** is known in the literature, and several research groups contributed to its synthesis.[15] However, we needed a synthetic approach that would give core **B** with only two substituents at the specific bridgehead and side-chain positions. Moreover, at least one substituent must be a functional group that can be further modified during incorporation into bioactive compounds. In this context, it is worth mentioning a recent work of *Matsuo* and coworkers, who developed an approach to substituted ketones **B**.[16] However, further modification of the ketone group was not elaborated.

Based on our previous results on photochemical synthesis of azaheterocycles,[17] we became interested if compound **1** (easily obtained as a mixture of *E*/*Z* isomers from benzoic acid) could undergo photochemical cyclization into the bicyclic structure **1a** (Table 1). Indeed, after some experimentation, we found that this reaction can be performed in acetonitrile under irradiation with 365 nm using benzophenone as a triplet sensitizer (Table 1). Product **1a** was obtained in 82% yield as a mixture of two stereoisomers (9:1). Irradiation with other standard wavelengths (254 nm, 313 nm, 419 nm) or broad wavelength mercury lamp gave lower yields of the product (Table 1, entries 2-5). Other triplet sensitizers, - acetophenone or *para*-disubstituted benzophenones, - also showed a lower efficacy (entries 6-8). Importantly, the reaction did not proceed without light at room temperature, or under heating (Table 1, entries 13, 14).[18]



1 (d.r.=1:1) **1a** (d.r.=9:1)

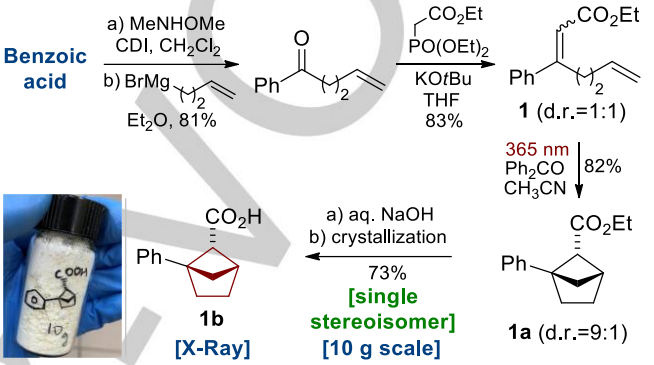
entry	deviation from above	yield (%)[b]
1	None	86 (82)[c]
2	419 nm	23
3	313 nm	17
4	254 nm	51
5	broad wavelenght Hg lamp	61
6	PhCOMe instead of Ph_2CO	33
7	$(p\text{-}MeOC_6H_4)_2CO$ instead of Ph_2CO	47
8	$(p\text{-}FC_6H_4)_2CO$ instead of Ph_2CO	55
9	CH_2Cl_2	68
10	acetone	19
11	toluene	31
12	EtOAc	54
13	no light, rt	0
14	no light, reflux	0

[a] 1 mmol. [b] Yield determined by ^1H NMR with CH_2Br_2 as an internal standard. [c] Isolated yield. See Supporting Information for details.

Table 1. Optimization of the synthesis of compound **1a** (core B).

The separation of two stereoisomers of the oily product **1a** by column chromatography was problematic. Therefore, we performed an alkali hydrolysis of the ester group in **1a**. The formed solid acid, still as a mixture of two isomers 9:1, was easily recrystallized from hexane to obtain product **1b** as a single stereoisomer in 73% yield (Scheme 2). Structure of compound **1b** was determined by X-Ray analysis.

The developed sequence was easily scalable, and, importantly, the photochemical cyclization of diene **1** was not significantly affected during the scale up. In particular, we could synthesize 10 g of product **1b** from benzoic acid in one run (Scheme 2).



Scheme 2. Gram-scale synthesis of compound **1b** from benzoic acid.

Scope. Next, we studied scope of the reaction, paying attention to diverse aromatic and especially heteroaromatic substituents prevalent in bioactive compounds.[19] All syntheses were started from the corresponding (hetero)aromatic acids that are commercially available. The photochemical step was tolerated by the presence of methoxy (**2a**), fluorine (**3a**), trifluoromethyl (**4a**), chlorine (**5a**) and bromine substituents (**6a**, **7a**) (Scheme 3). More importantly, the photochemical step worked also with diverse heterocycles: three isomeric pyridines (**8**-**10**), oxazole (**11**), thiophene (**12**), pyrazoles (**13**, **15**), thiazoles (**14**, **16**), and furan (**17**) gave the desired products **2a**-**17a** in good yields. A mixture of isomers was obtained in each case. After none-selective alkali hydrolysis, diastereomeric ratio of the obtained acids remained the same. A single crystallization from hexane allowed isolating the major components **1b**-**17b** as single stereoisomers. All products were synthesized on a gram scale. Structures of acids **13b**, **15b** and **16b** were confirmed by X-Ray analysis (Scheme 3).[20]

From nitrile-substituted substrates **18-20**, the corresponding photochemical cyclization also worked well to give products **18a-20a** (Scheme 3). Compounds **18a-20a** were isolated as individual major isomers by column chromatography.

Chemical stability. We next checked a chemical stability of three representative compounds – acids **1b**, **10b** and **15b** (Scheme 3). Treatment of them with aq. 1M hydrochloric acid, or aq. 1M aq. sodium hydroxide at room temperature for 24 hours did not lead to any decomposition of the starting materials. Also, these compounds were stored on the shelf at room temperature, and we did not observe any decomposition after at least three months. These experiments indicate that products containing core **B** possess sufficient chemical stability to be used as building blocks in chemical synthesis.

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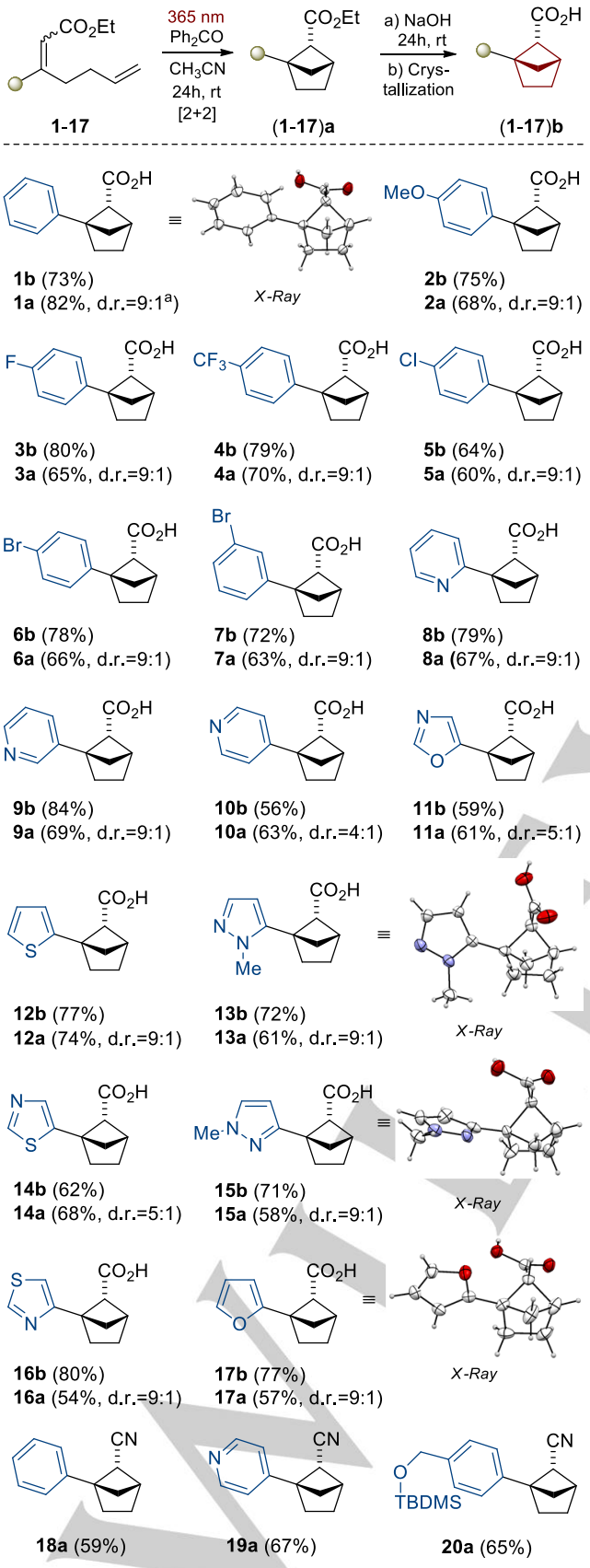
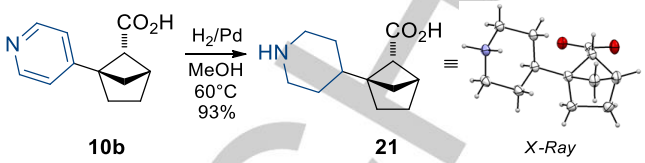


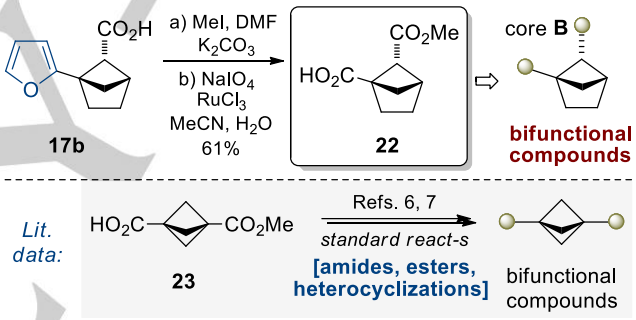
Scheme 3. Scope of the reaction. [a]Diastereomeric ratio was determined by ^{1}H NMR.

Chemical modifications. We also performed a reductive hydrogenation of the pyridine ring in compound **10b** to obtain aliphatic amino acid **21** in 81% yield. Structure of product **21** was confirmed by X-Ray analysis (Scheme 4).



Scheme 4. Synthesis of amino acid **21**.

Next, we synthesized the saturated bifunctional linker **22** (Scheme 5). First, acid **17b** was converted into the methyl ester, followed by oxidation of the furane ring with $NaIO_4$ and a catalytic amount of $RuCl_3$. Compound **22** opens up a way to synthesize various bifunctional derivatives of core **B**, - amino acids, amines, diamines, *etc* - by simple stepwise modifications of carboxylic groups using the standard reactions (synthesis of amides, esters, heterocyclizations). This tactic is being used routinely these days to prepare bifunctional bicyclo[1.1.1]pentanes from acid **23**.[6,7]



Scheme 5. Synthesis of linker **22**, from which various bifunctional derivatives of core B are available.

Crystallographic analysis. We next wanted to compare the geometric parameters of core **B** with those of *ortho*-substituted benzenes. To do that, we used an exit vector plots tool, introduced recently by our colleagues.[21] In this approach, the substituents mounted onto the disubstituted scaffold were simulated by two exit vectors n_1 and n_2 (Figure 2). Relative spatial arrangement of these vectors can be described by four geometric parameters: the distance between *C*-variation points *r*, the plane angles φ_1 (between vectors n_1 and **C**) and φ_2 (between n_2 and **C**), and the dihedral angle θ defined by vectors n_1, **CC** and n_2. Additionally, the final key parameter - distance *d* between two substituents (Scheme 1) - was also measured.

We calculated the values of *d*, *r*, φ_1, φ_2, and θ from the *X*-Ray data for compounds **1b**, **13b**, **15b**, **17b** and **21b**. As reference models for *ortho*-substituted benzenes, we chose molecules of two antihypertensive drugs - *Valsartan* and *Telmisartan*, - crystal data of which are available (Fifure 2).[22] Analysis of the data showed that core **B** was indeed similar to *ortho*-substituted benzenes. In particular, distance *r* was ca. 0.2 Å longer than that in *ortho*-benzenes: 1.56-1.58 Å (core **B**) *vs* 1.38-1.44 Å (*ortho*-benzene). Angles φ_1 and φ_2 were similar in both cores: 54-64° (core **B**) *vs* 55-57° (*ortho*-benzene). The key difference was in planarity of both cores: while *ortho*-benzene is almost flatten (θ =

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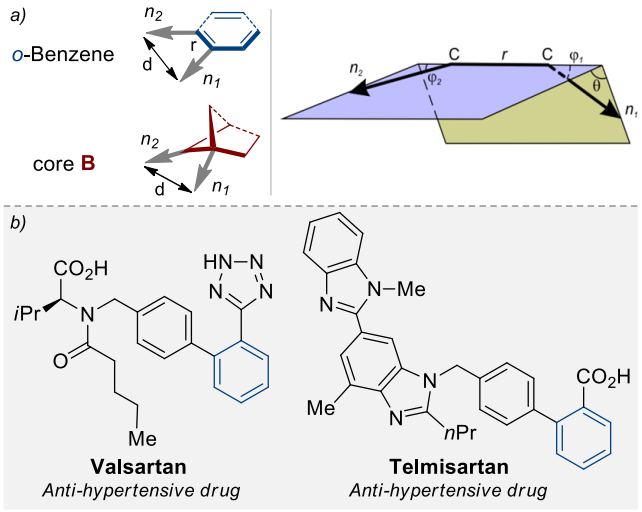
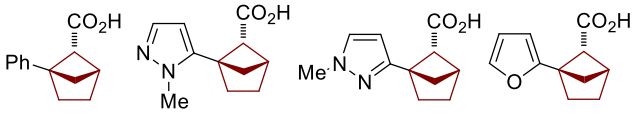
7-8°), core **B** is three-dimentional (two vectors are not planar, θ = 45-78°). Nonplanarity is also expected for other saturated linkers - cores **A** and **C** (Scheme 1).





Compound	d (Å)	r (Å)	φ_1 (°)	φ_2 (°)	θ (°)
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)
1b	3.221(4)	1.583(4)	56.5(2)	63.6(2)	44.9(4)
13b	3.439(6)	1.574(6)	60.3(3)	60.3(4)	75.8(5)
15b	3.526(6)	1.556(5)	56.3(3)	59.4(3)	77.8(5)
17b	3.486(2)	1.555(2)	54.5(2)	59.6(2)	74.7(2)
21	3.550(2)	1.562(3)	57.3(1)	59.1(1)	78.0(2)

Figure 2. a) Definition of vectors n_1, n_2 (1,2-disubstituted *ortho*-benzene, and core **B** 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 θ for *ortho*-substituted benzenes (*Valsartan*, *Telmisartan*) and core **B** (**1b**, **13b**, **15b**, **17b**, **21**).

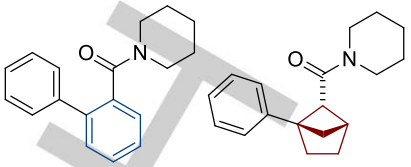
It is important to mention that although core **B** (3D-shaped) and *ortho*-substituted benzene (2D-shaped) are different in terms of planarity (angle θ), the similarity of other characteristics - *r*, φ_1, and φ_2, makes them overall alike. The key distance between the substituents (*d*) differs by up to 0.6 Å in both cores: 3.2-3.6 Å (core **B**) *vs* 3.0-3.1 Å (*ortho*-benzene).

Physico-chemical properties. In the next step, we wanted to experimentally study an effect of the replacement of the benzene fragment by core **B** onto physico-chemical properties of organic compounds. Therefore, we first synthesized two models - amides of piperidine **24** and **25** – from *ortho*-phenyl benzoic acid and acid **1b**, correspondingly (Table 2).

Water solubility (Sol.). Indeed, replacement of the phenyl ring in compound **24** by core B (**25**) increased the water solubility in agreement with the literature data:[7] 397 μM (**24**, *Ph*) *vs* 492 μM (**25**, *core B*).

Lipophilicity (logD$_{7.4}$). Replacement of the phenyl ring by core **B** did not have any significant impact on the compound lipophilicity. Lipophilicity indexes (logD) of models **24**, **25** were similar:[7] 3.5 (**24**, *Ph*) *vs* 3.7 (**25**, *core B*).

Table 2. Experimental data on water solubility (Sol.) and lipophilicity (logD) for model compounds **24**, **25**.

Model compound		
	24	**25**
Water solubility (7.4)[a]	397	492
Lipophilicity, logD(7.4)[b]	3.5	3.7

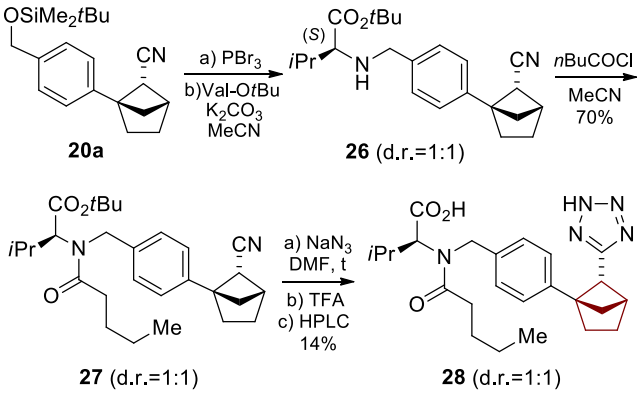
[a]Experimental kinetic aqueous solubility (μM) in 50 mM phosphate buffer (pH 7.4). [b]Experimental *n*-octanol/water distribution coefficient (log) at pH 7.4.

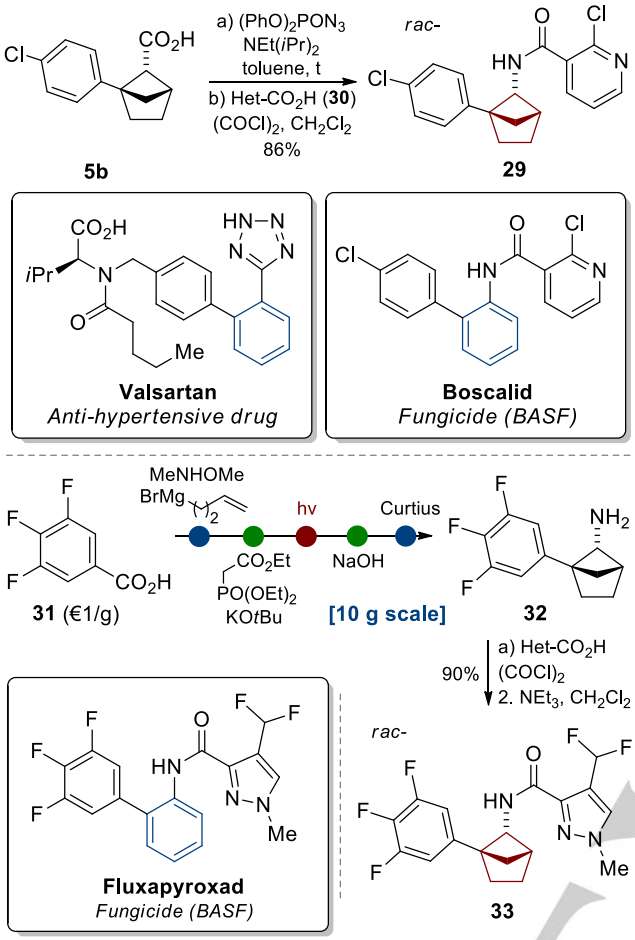
In a brief summary, replacing the benzene fragment by core **B** in organic compounds increases their water solubility, but does not have any significant impact on the overall lipophilicity.

Incorporation into bioactive compounds. An incorporation of core **B** into bioactive compounds was undertaken next. We selected three bioactive products with the fragment of *ortho*-substituted benzene: antihypertensive drug *Valsartan*; and fungicides *Boscalid*, *Fluxapyroxad*.

We started the synthesis of the saturated analogue of *Valsartan* by treatment of compound **20a** with phosphorus tribromide (Scheme 6). The intermediate bromide was reacted with *L*-Valine ester to form compound **26**. The product was obtained as a mixture of two stereoisomers that we could not separate. Acylation of the amino group in **26** with pentanoyl chloride gave amide **27**. Treatment with sodium azide in dimethyl formamide under heating, followed by an acidic cleavage of the *tert*-butyl group gave the desired tetrazole **28**, as an equimolar mixture of two stereoisomers.

The saturated analogue of *Boscalid* - racemic compound **29** - was easily synthesized by Curtius reaction from acid **5b** followed by a standard acylation reaction with 2-chloropyridine-3-carboxylic acid (**30**) (Scheme 6). The synthesis of a saturated analogue of another fungicide - *Fluxapyroxad,* - was undertaken from the commercially available 3,4,5-trifluorobenzoic acid (**31**, 1€/g). The above developed five steps sequence gave amine **32** on a gram scale. Simple amide synthesis accomplished the preparation of a racemic compound **33** (Scheme 6).





Scheme 6. Syntheses of compounds **28**, **29** and **33** – saturated analogues of antihypertensive drug **Valsartan** and fungicides **Boscalid**, **Fluxapyroxad**, correspondingly.

Biological activity. Finally, we experimentally studied a biological activity of compounds **29**, **33** and compared the data to that of the parent agrochemicals. In fact, *Boscalid* and its analogue **29**; *Fluxapyroxad* and its analogue **33** indeed showed a similar inhibition of a growth of *Fusarium oxysporum* Schltdl.

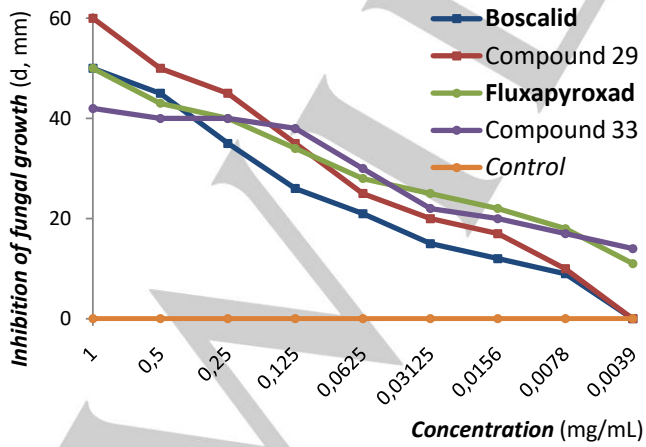


Figure 3. Inhibition of a growth of *Fusarium oxysporum* (measured as a diameter of inhibition zone, mm) by *Boscalid*, *Fluxapyroxad* and compounds **29**, **32** at different concentrations after 48 h of incubation.

after incubation during 48 h at different concentrations (Figure 3). These results experimentally prove that core **B** could mimic the fragment of *ortho*-substituted benzene in bioactive compounds.[23]

Summary. Over the past decade, cubane, bicyclo[2.2.2]octane, and bicyclo[1.1.1]pentane were validated as saturated bioisosteres for *para*-substituted benzenes in medicinal chemistry projects.[6-10] It was shown that such replacement increases the water solubility, lowers lipophilicity and retains bioactivity of compounds. On the other hand, so far nothing is known on the saturated bioisosteres for *ortho*-substituted benzenes.

Herein, we designed, synthesized and practically validated the first saturated mimetics of *ortho*-substituted benzenes - core **B** (bicyclo[2.1.1]hexanes). Crystallographic analysis of both scaffolds revealed their overall high similarity. The obtained structures were chemically stable, and could be stored on the shelf for at least several months. Replacing the benzene fragment by core **B** in model compounds increased their water solubility, but did not have any significant effect on their lipophilicity. We also synthetically incorporated core **B** into antihypertensive drug *Valsartan*, fungicides *Boscalid* and *Fluxapyroxad* instead of the fragment of the benzene ring. Moreover, *Boscalid* and its analogue **29**; *Fluxapyroxad* and its analogue **33** showed a similar antifungal activitiy against *F. oxysporum.* We believe that the results described in this work will be useful to a broad audience of scientists working in organic synthesis, agrochemistry, and medicinal chemistry.

Acknowledgements

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Keywords: bicyclo[1.1.1]pentanes • *ortho*-substituted benzenes • benzene mimetics • conformational restriction • bioisosterism

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Benzene bioisosteres. Saturated mimetics for *ortho*-disubstituted benzenes - bicyclo[2.1.1]hexanes, - were synthesized, characterized and validated. These cores were incorporated into bioactive compounds *Valsartan, Boskalid* and *Fluxapyroxad* instead of the benzene ring. The saturated analogues showed a similar level of antifungal activity compared to that of *Boskalid, Fluxapyroxad*.

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Saturated mimetics for *ortho*-substituted benzenes