1,2-Disubstituted Bicyclo[2.1.1]hexanes as Bioisosteres of the *ortho*-substituted Benzene

Aleksandr Denisenko,[a] Pavel Garbuz,[a] Yelyzaveta Makovetska,[a] Oleh Shablykin,[a,b] Dmytro Lesyk,[c] Galeb Al-Maali,[a,d] Rodion Korzh,[a] Iryna V. Sadkova,[a] Pavel K. Mykhailiuk[a]*

[a] A. Denisenko, P. Garbuz, Y. Makovetska, O. Shablykin, G. Al-Maali, Radion Korzh, I. V. Sadkova, P. K. Mykhailiuk. Enamine Ltd; Winston Churchill st. 78, 02094 Kyiv (Ukraine), www.mykhailiukchem.org, E-mail: Pavel.Mykhailiuk@gmail.com

[b] O. Shablykin. V.P. Kukhar Institute of Bioorganic Chemistry and Petrochemistry NAS of Ukraine, 02094 Kyiv (Ukraine).

[c] Bienta. Winston Churchill st. 78, 02094 Kyiv (Ukraine).

[d] G. Al-Maali. M. G. Kholodny. Institute of Botany of the National Academy of Sciences of Ukraine, Kyiv (Ukraine).

Dedicated to the people of Ukraine

Abstract: 1,2-Disubstituted bicyclo[2.1.1]hexanes have been designed, synthesized, and validated as a new generation of saturated bioisosteres of *ortho*-substituted benzenes. Incorporation of the bicyclo[2.1.1]hexane core into the structure of agrochemicals *Boskalid* (BASF), *Bixafen* (Bayer CS), and *Fluxapyroxad* (BASF) gave saturated analogs that exhibited a high antifungal activity.

Introduction. In 2020, we discovered that 1,5-disubstituted bicyclo[2.1.1]hexanes are bioisosteres of the *ortho*-substituted benzenes (Figure 1). [1] These scaffolds were obtained photochemically as a mixture of two diastereomers. They were separated by crystallization or column chromatography, and incorporated into bioactive compounds. In many cases, however, the separation of diastereomers was problematic and failed to produce the needed products.

Pleasingly, our discovery was appreciated by the scientific community, and later the groups of *Glorius*,[2] *Brown*,[3] *Procter*,[4] *Li*,[5] *Wang*,[6] and *Studer*[7] developed alternative approaches to *di*- and *poly*-substituted bicyclo[2.1.1]hexanes based on the functionalization of bicyclo[1.1.0]butanes.[8,9]

In this work, we have synthesized, characterized, and validated 1,2-disubstituted bicyclo[2.1.1]hexanes as a new generation of bioisosteres of the *ortho*-substituted benzenes. These cores exist as only one stereoisomer;[10] and are more similar geometrically to the aromatic counterparts than the previous scaffolds.

Synthesis. Despite the numerous studies on the topic,[2-9] we needed a practical modular approach to bicyclo[2.1.1]hexanes with only two substituents (two exit vectors) at the 1- and 2-positions of the core (Scheme 1) without additional (poly)substitution at other positions. Moreover, one substituent should be (hetero)aromatic, and another one a carboxylic group, needed for the subsequent modifications of the core.[11,12]

The photochemical [2+2]-cycloaddition between alkenes proved to be a powerful strategy to construct cyclobutanes.[13] In this context, we wondered if diene **1** (easily obtained from acetophenone, please see Scheme 1) would undergo an intramolecular cyclization into the desired bicyclo[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 broad wavelength mercury lamp gave

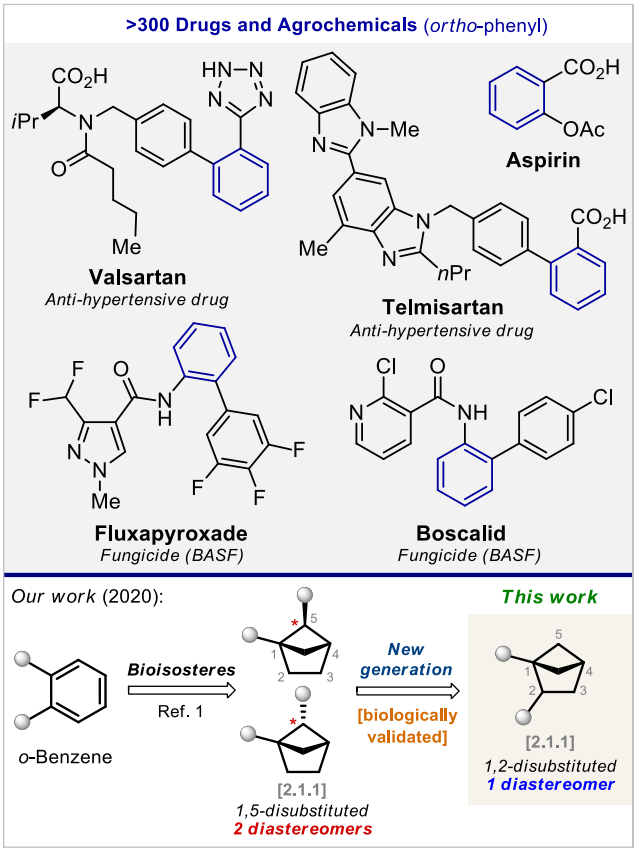
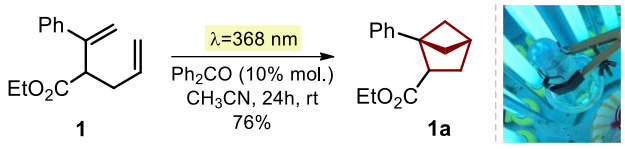


Figure 1. Bicyclo[2.1.1]hexanes as saturated bioisosteres of the *ortho*-substituted phenyl ring: state of the art.

the needed product in 35% yield along with the formation of unidentified side products (entry 5). Next, we tried available organic ketones for the triplet sensitization of the styrene moiety. Cleaner formation of the needed bicyclo[2.1.1]hexane **1a** was observed (entries 6-10). The best yield of 76% was obtained with benzophenone (entry 8), whereas thioxantone also worked well (entry 7). Among all tested solvents (entries 11-14), the best outcome was obtained in acetonitrile. Without irradiation, the reaction did not take took place (entry 15).

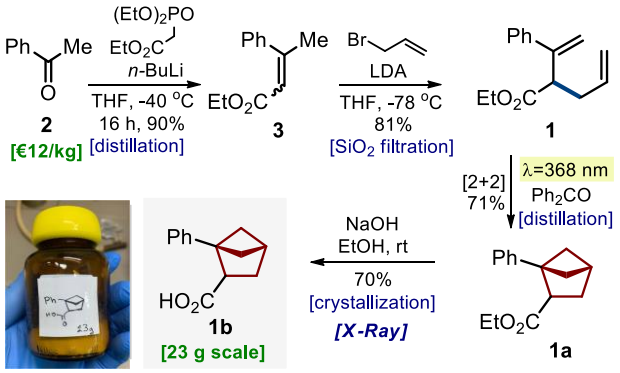


entry	Conditions	yield (%)[b]
1	419 nm, CH_3CN	*n.r.*
2	365 nm, CH_3CN	<10
3	313 nm, CH_3CN	<10
4	254 nm, CH_3CN	<20
5	broad wavelenght Hg lamp, CH_3CN	35
6	365 nm, CH_3CN, acetophenone	43
7	365 nm, CH_3CN, thioxanthone	54
8	365 nm, CH_3CN, benzophenone	(82)76[c]
9	365 nm, CH_3CN, $(p\text{-}NO_2C_6H_4)_2CO$	31
10	365 nm, CH_3CN, $(p\text{-}MeOC_6H_4)_2CO$	62
11	365 nm, CH_2Cl_2, Ph_2CO	47
12	365 nm, Me_2CO, Ph_2CO	45
13	365 nm, PhMe, Ph_2CO	31
14	365 nm, EtOAc, Ph_2CO	43
15	in the dark, rt	*n.r.*

[a] 100 mmol scale. [b] ^1H NMR yield (CH_2Br_2 as an internal standard). [c]Isolated yield after column chromatography. See SI for details. *n.r.*: no reaction.

Table 1. Optimization of the synthesis of bicyclo[2.1.1]hexane **1a**.

Scalable synthesis. The whole optimized synthetic protocol is shown in Scheme 1. It was important for us to elaborate on a modular method that would provide bicyclo[2.1.1]hexanes employing only available and cheap starting materials. The synthesis started with acetophenone (**2**). The Horner–Wadsworth–Emmons reaction of acetophenone smoothly gave diene **3** in 90% yield after distillation. Treatment of the latter with LDA in THF under -78 °C followed by the addition of allyl bromide gave diene **1** in 81% yield after filtration of the crude product through a plug of silica gel. An intramolecular photocyclization of diene **1** proceeded smoothly on scale to provide the desired bicyclo[2.1.1]hexane **1a** in 71% yield after distillation. Saponification of the ester group in **1a** followed by crystallization from hexane-*t*BuOMe gave carboxylic acid **1b** as a white crystalline solid in 70% yield. The structure of acid **1b** was confirmed by X-ray crystallographic analysis (Scheme 2).[14]



Scheme 1. Gram-scale synthesis of compound **1b** from acetophenone (**2**).

Important to note, that following this optimized sequence, we could easily synthesize 23 g of product **1b** in one run. No column chromatography was involved at any step.

Scope. Next, we studied the scope of the developed method. The photocyclization method tolerated various substituents on the aromatic core (Scheme 2). Among them were alkyl groups (**7a**), fluorine (**4a**, **14a**, **15a**) and chlorine (**5a**, **13a**) and bromine atoms (**6a**, **11a**), methoxy groups (**9a**, **10a**) and trifluoromethyl groups (**8a**, **12a**). All three substitution patterns of the phenyl ring, - *para* (**1a**-**10a**), *meta* (**11a**-**14a**), and *ortho* (**15a**), - were compatible with the reaction conditions. The reaction was also compatible with the fluorine atom directly attached to the diene structure (**3a**, **10a**). Various small medicinal chemistry-related heterocycles, - pyrazole (**16a**, **17a**), imidazole (**18a**), thiophene (**19a**), furane (**20a**), and pyridine (**21a**-**23a**), - also gave the desired bicyclo[2.1.1]hexanes in good yields. Products **3a**-**23a** were purified by distillation. Saponification of the ester group in **3a**-**23a** gave crystalline carboxylic acids **3b**-**23b** in 63-76% yield. All products were synthesized in gram quantities. The structure of bicyclo[2.1.1]hexanes **1b**, **3b**, **4b**, **10b**, and **12b** was confirmed by X-ray crystallographic analysis (Scheme 2).[14]

Modifications. Compounds **1b**, (**3**-**23**)**b** bear one functional group (-CO_2H). We next aimed to perform the representative modifications of these bicyclo[2.1.1]hexanes to obtain linkers for medicinal chemistry – compounds with two functional groups.

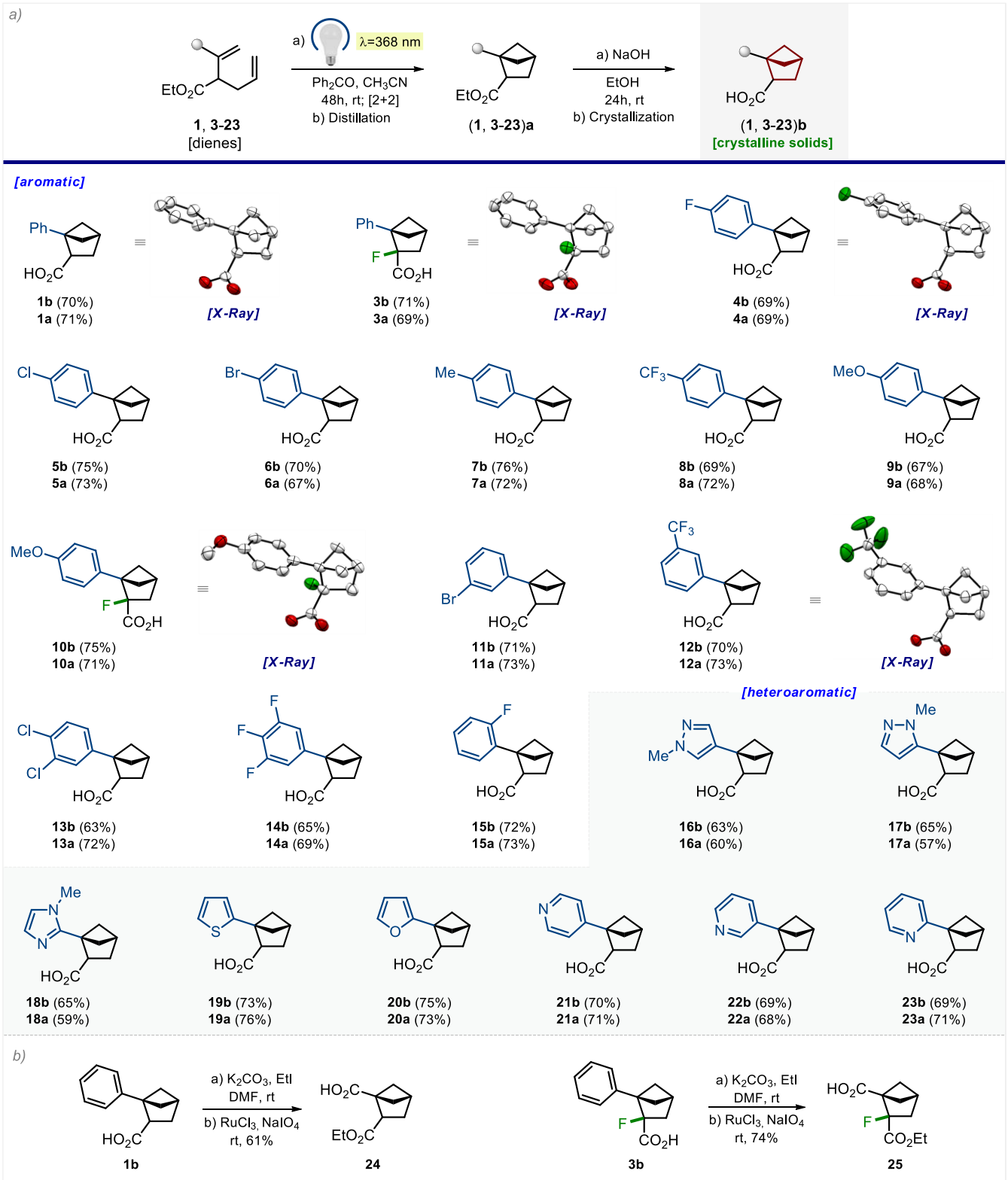
Esterification of carboxylic acid **1b**, followed by oxidation of the phenyl ring with $NaIO_4/RuCl_3$ gave monoacid ester **24** (Scheme 2). Fluorine-substituted monoacid **25** was synthesized analogously from compound **3b**. Both linkers **24** and **25** open up a way to synthesize various 1,2-disubstituted bicyclo[2.1.1]hexanes by stepwise modifications of carboxylic groups (amide synthesis, heterocyclizations, radical couplings, *etc*).[15]

Crystallographic analysis. Next, we compared the geometric parameters of 1,2-disubstituted bicyclo[2.1.1]hexanes with those of the previously used 1,5-disubstituted isomers and the *ortho*-substituted phenyl ring. For that, we employed the exit vector plots tool. In this method, substituents at the disubstituted scaffold were simulated by two exit vectors n_1 and n_2 (Figure 2). 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, *C*-*C* and n_2. An additional representative parameter - distance *d* between two carbon substituents (Figure 2) - was also measured.

We calculated the values of *d*, *r*, φ_1, φ_2, and θ of 1,2-disubstituted bicyclo[2.1.1]hexanes from the X-ray data of compounds **1b**, **4b**, and **12b**.[14] The related parameters for 1,5-disubstituted bicyclo[2.1.1]hexanes **26**-**28**[1] were calculated from their X-ray data published in the literature.

The corresponding parameters for *ortho*-substituted phenyl rings were obtained from the reported crystal data of two antihypertensive drugs - *Valsartan* and *Telmisartan* (Figure 2).[16] Analysis of this data revealed that the geometric properties of 1,2-disubstituted bicyclo[2.1.1]hexanes in general were similar to those of the *ortho*-substituted phenyl ring. In particular, distance *d* in 1,2-isomers was only 0.1 Å longer than that in the *ortho*-phenyl ring. The corresponding distance *d* in the previously used 1,2-isomers was already ca. 0.4 Å longer: 3.05-3.19 Å (**1b**, **4b**, **12b**) *vs* 3.43-3.50 Å (**26**-**28**) *vs* 3.04-3.10 Å (*ortho*-phenyl).

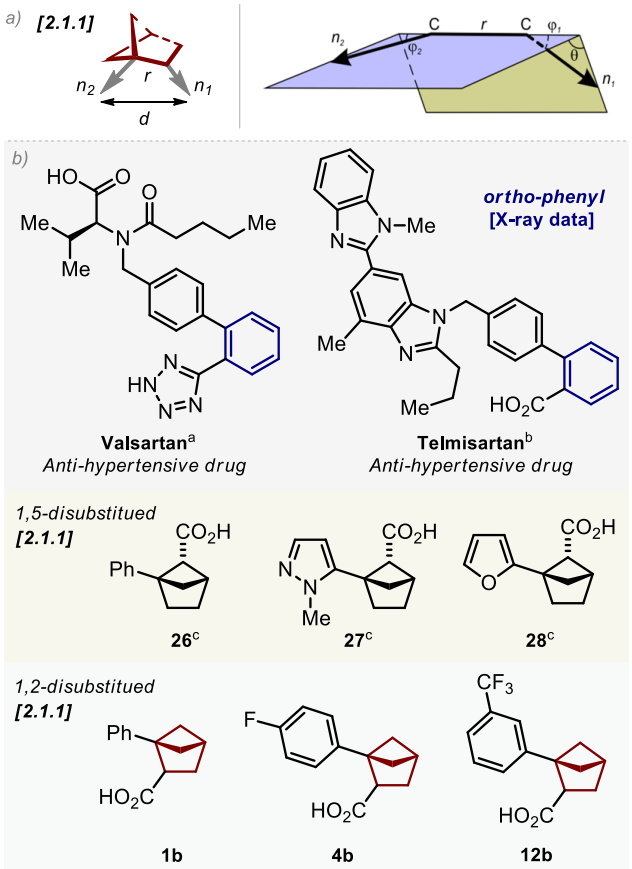
Distance *r* in both saturated scaffolds was identical and was 0.1-0.2 Å longer than that in the *ortho*-phenyl ring: 1.56 Å (**1b**, **4b**, **12b**) *vs* 1.56-1.57 Å (**26**-**28**) *vs* 1.39-1.44 Å (*ortho*-phenyl).



Scheme 2. Scope of the reaction. X-ray crystal structure of compounds **1b**, **3b**, **4b**, **10b**, and **12b** (carbon – white, oxygen – red, fluorine - green). Hydrogen and chlorine atoms are omitted for clarity. Ellipsoids are shown at a 50% probability level.

Angles φ_1 and φ_2 were similar in all three scaffolds: 61-65º (**1b**, **4b**, **12b**) *vs* 55-60º (**26**-**28**) *vs* 55-57º (*ortho*-phenyl). The difference in planarity, however, between both saturated scaffolds and the phenyl ring was significant: while *ortho*-phenyl was almost flattened, both bicyclo[2.1.1]hexanes had a significant three-dimensional character: /θ/ = 56-59º Å (**1b**, **4b**, **12b**) *vs* 75-78º (**26**-**28**) *vs* 7-8º (*ortho*-phenyl).

In general, vector characteristics (distance *d*, angles φ_1 and φ_2) of 1,2-disubstituted bicyclo[2.1.1]hexanes were similar to those of the *ortho*-substituted phenyl ring.



Compound	*d* (Å)	*r* (Å)	φ_1 (º)	φ_2 (º)	/θ/ (º)
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)
26	3.502(2)	1.556(3)	59.9(2)	57.3(1)	77.9(2)
27	3.439(6)	1.574(6)	60.3(3)	60.3(4)	75.8(5)
28	3.486(2)	1.555(2)	54.5(2)	59.6(2)	74.7(2)
1b	3.190(4)	1.557(3)	65.1(2)	61.3(2)	58.6(3)
4b	3.178(3)	1.560(3)	64.9(2)	62.2(2)	58.8(2)
12b	3.048(3)	1.557(3)	69.0(2)	64.0(2)	55.5(3)

Figure 2. a) Definition of vectors n_1 and n_2, and geometric parameters *d*, *r*, φ_1, φ_2 and θ. 1,2-Disubstitued bicyclo[2.1.1]hexane is shown as an example. b) Geometric parameters *d*, *r*, φ_1, φ_2, and $|\theta|$ for *ortho*-substituted benzenes (*Valsartan*, *Telmisartan*); 1,5-disubstitued bicyclo[2.1.1]hexanes **26**-**28**; and 1,2-disubstitued bicyclo[2.1.1]hexanes **1b**, **4b**, **12b**. [a]Data is taken from ref. 16a. [b]Data is taken from ref. 16b. [c]Data is taken from ref. 1.

Incorporation into bioactive compounds. The incorporation of bicyclo[2.1.1]hexane scaffold into bioactive compounds was realized next. We chose five bioactive products with the *ortho*-substituted phenyl ring: agent for hyponatremia treatment *Conivaptan*, lipid-lowering agent *Lomitapide* (Scheme 3); agrochemical fungicides *Boscalid*, *Bixafen,* and *Fluxapyroxad* (Scheme 4).

Synthesis of the saturated analog of *Conivaptan* was performed from carboxylic acid **1b** (Scheme 3). The standard amide synthesis with the corresponding *para*-substituted aniline gave the needed compound **29**. Using an analogous amide synthesis, compound **30**, - a saturated analog of *Lomitapide*, - was also obtained from carboxylic acid **8b** (Scheme 3).

Synthesis of the saturated analog of *Boskalid* was performed from carboxylic acid **5b** (Scheme 4). The Curtius reaction followed by acylation of the intermediate amine with the substituted pyridine carboxylic acid gave the needed compound **31**. Using an analogous strategy, compound **32**, - a saturated analog of *Bixafen*, - was obtained from carboxylic acid **13b** (Scheme 4). The saturated analog of *Fluxapyroxad*, compound **33**, was obtained analogously from carboxylic acid **14b**.

The structure of bicyclo[2.1.1]hexanes **31** and **32** was confirmed by X-ray crystallographic analysis.[14]

Physico-chemical parameters. In the next step, we studied the effect of the replacement of the *ortho*-phenyl ring by bicyclo[2.1.1]hexanes on the physicochemical properties of all five bioactive compounds (Schemes 3, 4).

Water solubility. Replacement of the *ortho*-phenyl ring in *Conivaptan* by bicyclo[2.1.1]hexane (**29**) increased its solubility by three times: 5 μM (*Conivaptan*) *vs* 14 μM (**29**) (Scheme 3). An analogous trend was also seen with *Lomitapide*. Replacement of the phenyl ring in *Lomitapide* with bicyclo[2.1.1]hexane (**30**) led to a six-time increase in solubility: 3 μM (*Lomitapide*) vs 18 μM (**30**).

Replacement of the *ortho*-phenyl ring by bicyclo[2.1.1]hexane in agrochemicals *Boscalid*, *Bixafen*, and *Fluxapyroxad* was controversial. In *Boskalid*, such replacement led to a three-time increase in solubility: 11 μM (*Boskalid*) vs 35 μM (**31**). In *Bixafen*, an opposite effect was observed, and the solubility was reduced: 30 μM (*Bixafen*) vs 4 μM (**32**). [17] In *Fluxapyroxad*, such replacement resulted in a slight increase of solubility: 25 μM (*Fluxapyroxad*) vs 27 μM (**33**).

In a short summary, in four out of five bioactive compounds, the replacement of the *ortho*-phenyl ring by bicyclo[2.1.1]hexane led to an increase in water solubility.

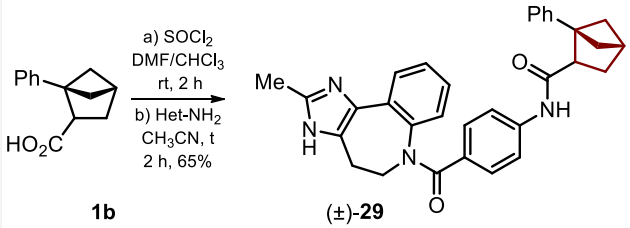
Lipophilicity. To estimate the influence of the replacement of the *ortho*-phenyl ring with bicyclo[2.1.1]hexane on lipophilicity, we used two parameters: calculated (clogP)[18] and experimental (logD) lipophilicity.

Replacement of the *ortho*-phenyl ring in four bioactive compounds (*Conivaptan*, *Boskalid*, *Bixafen*, *Fluxapyroxad*) with bicyclo[2.1.1]hexane (**29**, **31**-**33**) led to an increase of clogP by 0.4-0.7 units. In *Lomitapide*, however, such replacement resulted in a slight decrease of clogP: 7.0 (*Lomitapide*) vs 6.9 (**30**).

The replacement of the *ortho*-phenyl ring with bicyclo[2.1.1]hexane had only a small effect on the logD index. In four bioactive compounds (*Conivaptan*, *Boskalid*, *Bixafen*, *Fluxapyroxad*) such replacement almost did not affect logD. Only in *Lomitapide*, the saturated analog **30** had a significantly lower logD: >4.5 (*Lomitapide*) vs 3.9 μM (**30**).

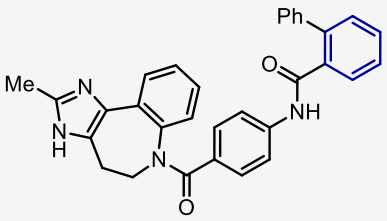
In summary, in four out of five bioactive compounds, replacement of the *ortho*-phenyl ring by bicyclo[2.1.1]hexane led to an increase of calculated lipophilicity (clogP) by 0.4-0.7 units; and almost did not affect the experimental lipophilicity (logD).

Saturated analogues of drugs

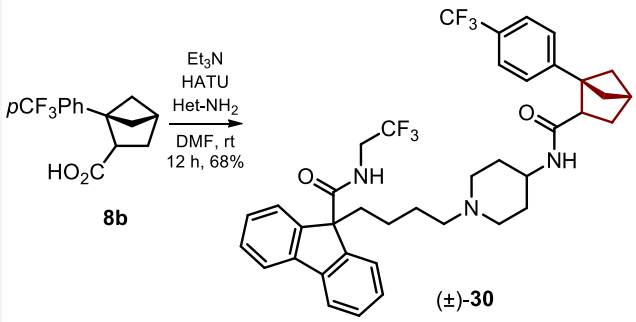


1b (±)-**29**

Conivaptan
Hyponatremia treatment

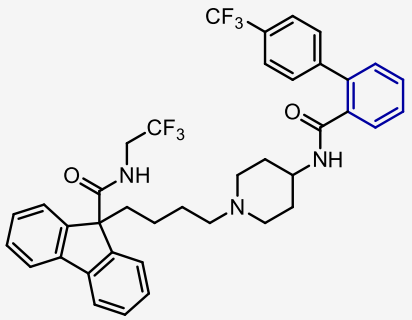


Compound	*Sol.*	*clogP*	*logD (7.4)*	CL_{int}	$t_{1/2}$
Conivaptan	5	5.0	4.3	31	54
(±)-**29**	14	5.4	4.1	12	135



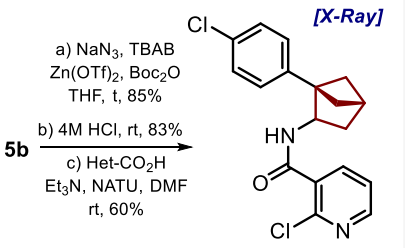
8b (±)-**30**

Lomitapide
Lipid-lowering drug



Compound	*Sol.*	*clogP*	*logD (7.4)*	CL_{int}	$t_{1/2}$
Lomitapide	3	7.0	>4.5	55	30
(±)-**30**	18	6.9	3.9	186	9

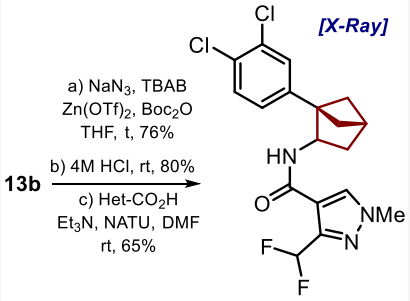
Saturated analogues of agrochemicals



(±)-**31**

Boscalid
Fungicide (BASF)

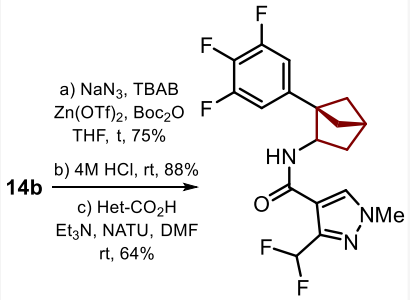
Compound	*Sol.*	*clogP*	*logD (7.4)*	CL_{int}	$t_{1/2}$
Boscalid	11	3.4	3.6	26	64
(±)-**31**	35	4.1	3.6	29	58



(±)-**32**

Bixafen
Fungicide (Bayer CS)

Compound	*Sol.*	*clogP*	*logD (7.4)*	CL_{int}	$t_{1/2}$
Bixafen	30	3.4	4.2	10	161
(±)-**32**	4	3.9	4.2	35	47



(±)-**33**

Fluxapyroxad
Fungicide (BASF)

Compound	*Sol.*	*clogP*	*logD (7.4)*	CL_{int}	$t_{1/2}$
Fluxapyroxad	25	2.2	3.5	28	59
(±)-**33**	27	2.9	3.6	61	27

Scheme 3. Synthesis and properties of compounds **29**, **30** - saturated analogs of drugs *Conivaptan* and *Lomitapide*, correspondingly. *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 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.

Scheme 4. Synthesis and properties of compounds **31**-**33** - saturated analogs of agrochemicals *Boscalid*, *Bixafen* and *Fluxapyroxad*, correspondingly. *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 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.

Metabolic stability. The effect of bicyclo[2.1.1]hexane on the metabolic stability of bioactive compounds was more complex and depended on the chemical structure. In *Conivaptan*, incorporation of bicyclo[2.1.1]hexane (**29**) increased the metabolic stability: Cl_{int} (mg/(min•μL)) = 31 (*Conivaptan*) *vs* 12 (**29**). In *Lomitapide*, *Bixafen,* and *Fluxapyroxad* an incorporation of bicyclo[2.1.1]hexane (**30**, **32**, **33**) dramatically decreased the metabolic stability by two (**33**) to three (**30**, **32**) times, as measured by $t_{1/2}$ (min). In *Boscalid*, such replacement led to only a slight decrease in metabolic stability: Cl_{int} (mg/(min•μL)) = 26 (*Boskalid*) *vs* 29 (**31**) (Schemes 3, 4).

In brief summary, in four out of five bioactive compounds, the replacement of the *ortho*-phenyl ring with bicyclo[2.1.1]hexane decreased the metabolic stability.

Bioactivity. Finally, we wanted to answer a key question, - if 1,2-disubstituted bicyclo[2.1.1]hexanes could indeed act as bioisosteres of the *ortho*-phenyl ring in bioactive compounds? Therefore, we measured the antifungal activity of the marketed fungicides *Boskalid* (BASF), *Bixafen* (Bayer CS), *Fluxapyroxad* (BASF) and their saturated analogs **31**-**33**. In strict contrast to medicinal chemistry, the use of racemic mixtures in agrochemistry is common;[19] therefore for the validation of the proof-of-concept, we directly studied the biological activity of the available racemic compounds **31**-**33** (Figure 3).

Compound	*Penicillium polonicum* MIC (mg/mL)	*Aspergillus niger* MIC (mg/mL)
Boskalid	0.016	0.004
(±)-**31**	-*	0.06
Bixafen	0.03	0.004
(±)-**32**	1	0.03
Fluxapyroxad	0.008	0.004
(±)-**33**	2	0.06

Figure 3. Experimental minimal inhibitory concentration (MIC, mg/mL) for *Boskalid*, *Bixafen*, *Fluxapyroxad,* and its analogs **31-33** of *Penicillium polonicum* (strain VURV-F 823) and *Aspergillus niger* (strain VURV-F 822). *Absence of antifungal activity.

We measured the antifungal activity of all six compounds against two fungal strains, - *Penicillium polonicum* and *Aspergillus niger*, - using the disk diffusion method (SI, p. S320-332). As a comparison characteristic, we used a minimal inhibitory concentration (MIC) (Figure 3).

In strict contrast to the launched agrochemicals, - *Boskalid*, *Bixafen,* and *Fluxapyroxad*, - the saturated analogs **31**-**33** had only a small effect at inhibition of the growth of *Penicillium polonicum* (Figure 3). However, all three analogs **31**-**33** showed a high inhibition of the growth of *Aspergillus niger*: MIC (mg/mL) = 0.03-0.06. The original agrochemicals, however, were slightly more potent (Figure 3; and SI, p. S320-332).

Summary. The *ortho*-substituted phenyl ring is a basic structural element in chemistry. It is found in the structure of >300 drugs and agrochemicals (Figure 1). In this work, we have designed, synthesized, and validated 1,2-disubstituted bicyclo[2.1.1]hexanes as improved saturated bioisosteres of the *ortho*-substituted benzenes. In strict contrast to the previously used 1,5-isomers, these scaffolds exist as only one diastereomer (Figure 1). The structures were synthesized photochemically from available starting materials (acetophenone) on a multigram scale (Schemes 1, 2). Physicochemical and geometric properties of bicyclo[2.1.1]hexanes were measured and compared to those of the *ortho*-substituted benzenes (Figure 2). Moreover, the replacement of the *ortho*-substituted phenyl ring in two drugs *Conivaptan*, *Lomitapide*; and three agrochemicals *Boskalid*, *Bixafen*, *Fluxapyroxad* with bicyclo[2.1.1]hexanes was realized (Schemes 3, 4). The saturated analogs **31**-**33** showed a high inhibition of the growth of fungi strain *Aspergillus niger* (Figure 3, and SI, p. S320-332).

We believe that given the commonplace of the *ortho*-phenyl ring in chemistry, its saturated bioisosteres developed here, - 1,2-disubstituted bicyclo[2.1.1]hexanes, - will soon become popular in chemistry, and scientists will use them routinely.

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Keywords: Bicyclo[2.1.1]hexanes • *ortho*-substituted benzenes • conformational restriction • bioisosteres • bicyclo[1.1.1]pentanes.

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Abstract

Aleksandr Denisenko, Pavel Garbuz, Yelyzaveta Makovetska, Oleh Shablykin, Dmytro Lesyk, Galeb Al-Maali, Rodion Korzh, Iryna V. Sadkova, Pavel K. Mykhailiuk

1,2-Disubstituted Bicyclo[2.1.1]hexanes as Bioisosteres of the *ortho*-substituted Benzene

1,2-Disubstitued bicyclo[2.1.1]hexanes have been designed, synthesized, and validated as a new generation of saturated bioisosteres of *ortho*-substituted benzenes. Incorporation of the bicyclo[2.1.1]hexane core into the structure of agrochemicals *Boskalid* (BASF), *Bixafen* (Bayer CS), and *Fluxapyroxad* (BASF) gave saturated analogs that exhibited a high antifungal activity.