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ARTICLE

Oxa-spirocycles: synthesis, properties and applications

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A general approach to a new generation of spirocyclic molecules - *oxa*-spirocycles - was developed. The key synthetic step was iodocyclization. More than 150 *oxa*-spirocyclic compounds were prepared. Incorporation of oxygen atom into spirocyclic unit dramatically improved water solubility (up to 40-times), and to lowered lipophilicity. More potent *oxa*-spirocyclic analogues of antihypertensive drug *Terazosin* were synthesized and studied *in vivo*.

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Introduction

Saturated monocyclic units, - cyclohexane, cyclopentane, piperidine, *etc*, - dominated in chemistry and in drug discovery for a long time.[1] The situation started switching at the beginning of this century. In 2009, *Lovering* introduced the concept "escape from flatland,"[2] that already changed the way how medicinal chemists think. Today, scientists tend to use small F(sp^3)-rich molecules in their research.[3,4] In 2010, saturated spirocycles were shown to possess improved physico-chemical characteristics over common monocyclic counterparts.[5] Since that time, spirocyclic molecules have been playing an important role in chemistry.[6,7] In fact, more than 10.000 research manuscripts and 50.000 patents on the topic appeared during the last decade (Figure 1).[8]

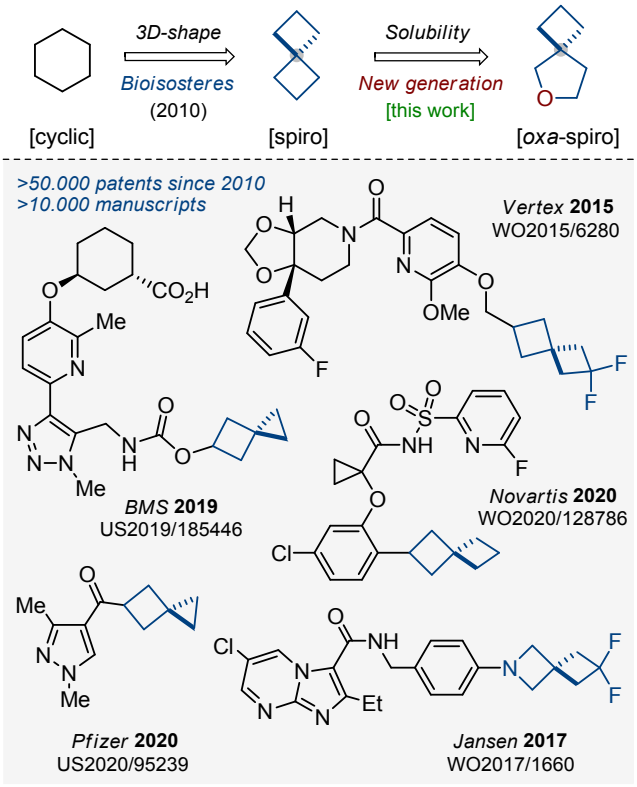

Figure 1. Spirocycles and their application in chemistry.

Earlier, we reported on the preparation of *oxa*-bridged bicycles via iodocyclization of alkenyl alcohols.[9] These compounds were designed as water-soluble analogues of popular bicyclo[1.1.1]pentanes. The work received a positive feedback from both academy and industry, and therefore we decided to expand this tactic onto a new generation of spirocycles - *oxa*-spirocycles (Figures 1). Previously, *oxa*-spirocycles remained mostly in the shadow. For example, while three representative spirocyclic substituents (left, Figure 2) are extremely popular in chemistry, the corresponding *oxa*-spirocyclic counterparts (right, Figure 2) remain almost unknown.[10]

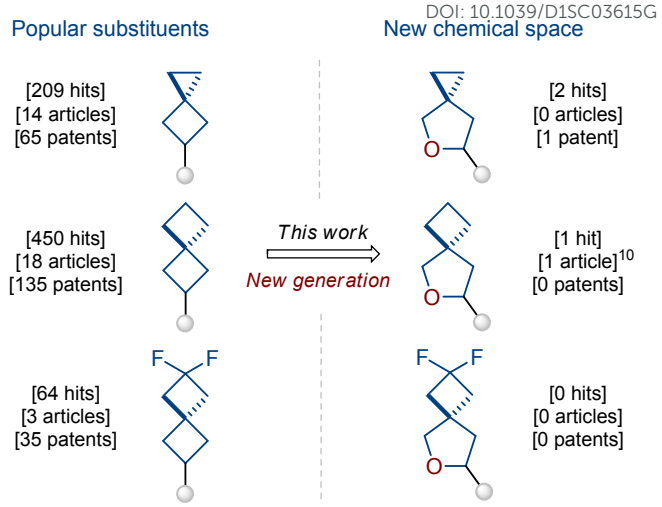

Figure 2. Spirocycles and their unexplored *oxa*-counterparts.

Of course, there was some interest to *oxa*-spirocycles before, but examples reported in the literature were rare and non-systematic.[11] In 1985, *Yohida* synthesized two substituted *oxa*-spirocycles via iodocyclization (Scheme 1).[12] In 2008, *Gouverneur* studied an influence of fluorine atom on diastereoselectivity of the iodocyclization reaction. In this work, one example of the *oxa*-spirocyclic core was shown (Scheme 1).[13] In 2011, *Cernak* and co-workers from Merck employed Grubbs-metathesis reaction to synthesize *oxa*-spiropiperidines with reduced lipophilicity (Scheme 1).[14] Later, *Carreira* used the same approach to prepare *oxa*-spiroazetidines.[15] In 2013, *Santini* elaborated gold-catalyzed oxidative cyclization of propargyl alcohols into *oxa*-spirocyclic amines (Scheme 1).[16] In the same year, *Santini* also developed an alternative approach to *oxa*-spirocyclic amines via oxidative intramolecular hydroxycyclization of alkenes.[17] Subsequently, *Cocotos* realized an organocatalytic version of that method (Scheme 1).[18] In 2018, *Cossy* developed a [Rh]-catalyzed cyclization of unsaturated alkoxyamines.[19] All these reports described different topics and contained one to three examples of the desired *oxa*-spirocyclic molecules. Only recently, *Baik* and *Hong* developed a [Pd]-mediated directed oxidative synthesis of sterically hindered *oxa*-spirocycles (Scheme 1).[20] This work had an excellent scope, but needed an installation and the subsequent removal of a directing group.

Presumably, absence of a general method to *oxa*-spirocycles is a primary reason why these molecules did not receive a proper recognition by scientific community.[21] An ideal practical method should (a) employ inexpensive starting reagents; (b) not use protecting groups;[22] and (c) provide *oxa*-spirocycles with a functional group that could be easily converted into variety of other functional substituents: amines, alcohols, carboxylic acids, sulfonyl chlorides, *etc*. In this work, we present such an approach.

Results and discussion

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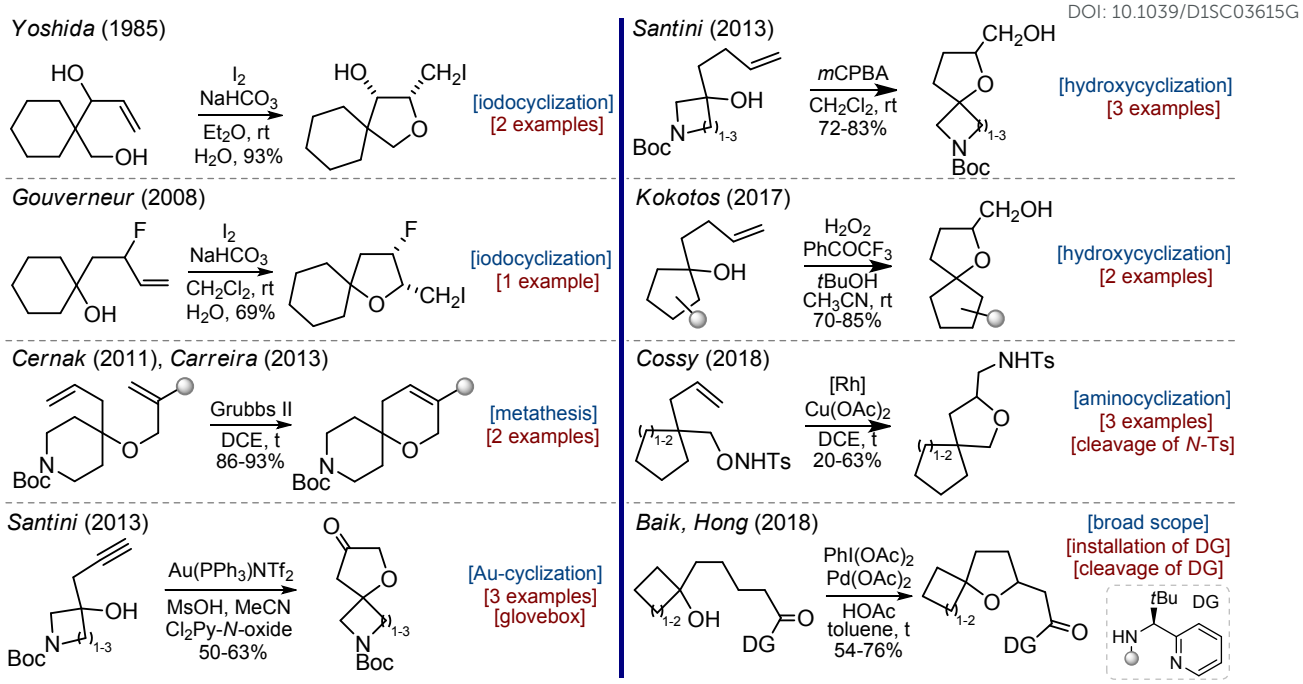
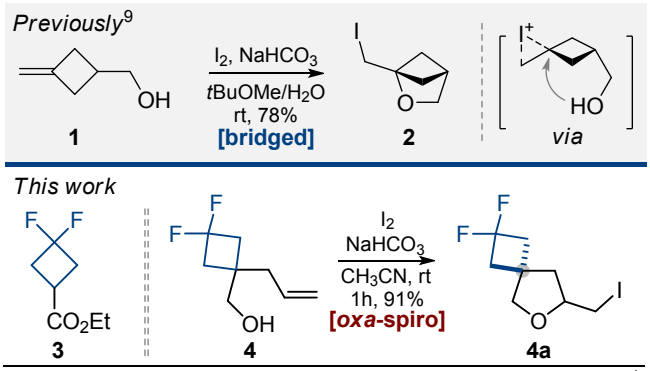


Scheme 1. Literature precedents to *oxa*-spirocycles.

Optimization. Based on our experience,[9] and literature precedents,[12,13] we studied iodocyclization of model alkene **4** (obtained by alkylation of ester **3** with LDA/allyl bromide; reduction with $LiAlH_4$) into *oxa*-spirocyclic core **4a**. We decided to exploit specifically iodocyclization, and not bromocyclization or hydroxycyclization, because the putative alcohols or bromides would be much less active in further modifications.



entry	deviations from literature	NMR yield **4a** (%)[a,b]
1	*t*BuOMe/H_2O as a solvent	71
2	Et_2O as a solvent	67
3	CH_2Cl_2 as a solvent	65
4	$CHCl_3$ as a solvent	69
5	dioxane as a solvent	49
6	THF as a solvent	55
7	CH_3CN as a solvent	96 (91)[c]
8	DMF as a solvent	41
9	DMSO as a solvent	34
10	Na_2CO_3 as a base	83
11	$KHCO_3$ as a base	91
12	NEt_3 as a base	57
13	Py as a base	42
14	NIS instead of I_2	85
15	NBS instead of I_2	83 (Br)

[a] 2 mmol. [b] Yield determined by ^1H NMR with CH_2Br_2 as an internal standard. [c] Isolated yield. NIS = *N*-iodosuccinimide, NIS = *N*-bromosuccinimide.

Table 1. Optimization of the synthesis of compound **4a**.

Under the previously developed conditions (Table 1, entry 1) alkene **4** indeed predominantly afforded iodide **4a**, however formation of side products was also observed. Separation of this mixture was problematic, especially on a gram scale. Performing the reaction in diethyl ether (entry 2) or dichloromethane (entry 3) still led to formation of a mixture of compounds. Finally, we screened solvents and find out that the transformation smoothly proceeded in acetonitrile to provide iodide **4a** in almost quantitative yield (entry 7). Formation of side products was not observed in this experiment. Other inorganic bases also worked well, while pyridine and triethylamine gave moderate yields (entries 10-13). It is worth noting that *N*-iodosuccinimide could also be used although with a bit lower efficiency (entry 14).

Importantly, using the optimized conditions we could easily synthesize iodide **4a** on 26 g scale. The product was isolated from the reaction mixture by simple distillation and no additional purification was needed.

Scope. Having an optimized procedure in hand, we studied next its scope. Indeed, various five-membered *oxa*-spirocyclic iodides **5a**-**31a** were easily prepared in 45-96% yield following the optimized protocol (Scheme 2). Among them were *N*-Boc-protected azetidines (**8a**, **16a**, **21a**), pyrrolidines (**10a**) and piperidines (**14a**, **17a**, **29a**). Labile ketal (**7a**) and ester groups (**19a**) were also compatible with the reaction conditions. Three (**5a**) to eight (**31a**)-membered cycles were incorporated into *oxa*-spirocyclic cores. Importantly, popular oxetane ring[23] was also successfully incorporated without decomposition (**20a**). Next, we decided to construct the oxetane ring via iodocyclization. The corresponding products **32a** and **33a** were obtained, although in low yields of 21-24% because the reaction was not selective.

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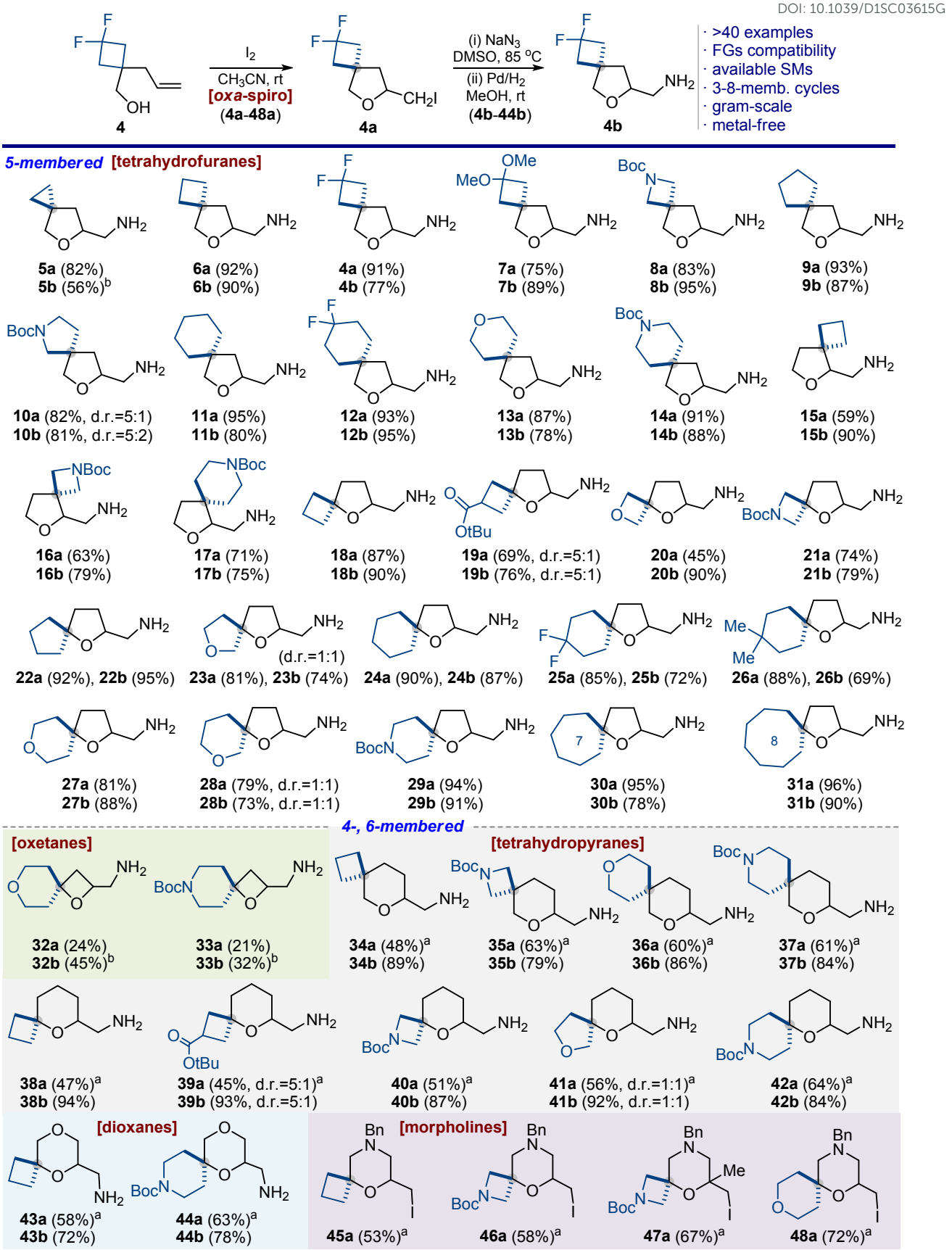

Scheme 2. Scope of iodocyclization step into *oxa*-spirocycles. Iodocyclization conditions: alkene (1 equiv), $NaHCO_3$ (3 equiv), I_2 (3 equiv), CH_3CN, rt, 1h. [a]alkene (1 equiv), K_2CO_3 (4 equiv), I_2 (4 equiv), CH_3CN, rt, 48h. Synthesis of amines, conditions: (i) iodide (1 equiv), NaN_3 (1.5 equiv), DMSO, 85 °C. (ii) H_2/Pd, MeOH, rt. [b](ii) PPh_3 (1.5 equiv), H_2O/THF, 50 °C.

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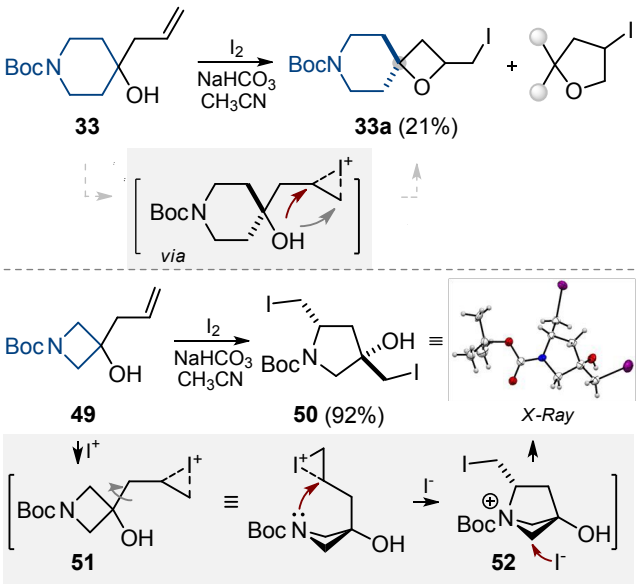
We also tried iodocyclization to construct the six-membered tetrahydropyrane ring. Under the standard conditions, however, incomplete conversions were observed. The reaction was slow, and some starting material remained. After optimization, we found that an excess of molecular iodine and a prolonged reaction time was needed. As a result, products **34a**-**42a** were obtained in 45-64% yield (Scheme 2). Furthermore, the developed conditions were also used to synthesize dioxanes **43a**, **44a** in 58-63% yield and morpholines **45a**-**48a** in 53-72% yield (Scheme 2).

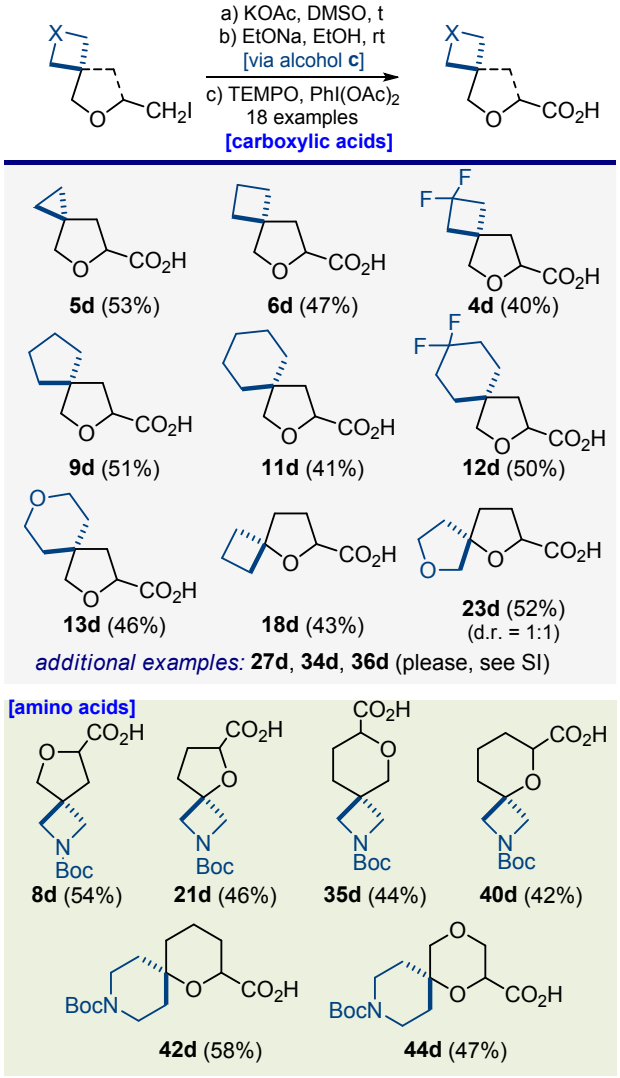
Limitations. The developed protocol was not without limitations, however. While alcohols **32** and **33** provided the needed oxetanes **32a** and **33a** in low yields (Scheme 2, Scheme 3), the corresponding azetidine-containing alcohol **49** unexpectedly afforded pyrrolidine **50** as a single stereoisomer in 92% yield (Scheme 3).[24] Structure of the product was confirmed by X-Ray analysis.[25] Presumably, close proximity of a nitrogen atom and an iodonium moiety in the initially formed intermediate **51** led to an intramolecular nucleophilic attack providing another strained intermediate **52**. Ring-opening of the azetidine ring in **52** with iodide anion gave the observed pyrrolidine **50**.



Scheme 3. Unexpected synthesis of pyrrolidine **50**.

Modifications. Several representative modifications of iodides **4a**-**48a** were undertaken using standard chemical transformations to provide numerous *oxa*-spirocyclic derivatives. First, a simple reaction of iodides **4a**-**44a** with sodium azide followed by reduction with either H_2/Pd or PPh_3 gave amines **4b**-**44b** in 32-95% yield. Among them were not only monofunctional compounds, but also linkers with two functional groups: amino acids **19b**, **39b** and valuable diamines for medicinal chemistry **8b**, **10b**, **14b**, **16b**, **17b**, **21b**, **29b**, **33b**, **35b**, **37b**, **40b**, **42b**, **44b** (Scheme 2).

Reaction of iodide **5a** with potassium acetate in dimethylsulfoxide under heating, followed by hydrolysis of the ester group with sodium ethoxide, and the subsequent oxidation of the formed alcohol with $PhI(OAc)_2$/TEMPO gave acid **5d** (Scheme 4). Using that simple three-step strategy, seventeen other acids were synthesized. Especially worth noting unusual amino acids from Scheme 4 – that type of structures play an important role in drug discovery programs.[26]



Scheme 4. Synthesis of *oxa*-spirocyclic carboxylic acids and amino acids **4d**-**6d**, **8d**, **9d**, **11d**-**13d**, **18d**, **21d**, **23d**, **27d**, **34d**-**36d**, **40d**, **42d** and **44d**.

Next, synthesis of some aliphatic sulfonyl chlorides, - popular reagents for making bioactive sulfonamides[27] - was undertaken. Reaction of iodide **16a** with potassium thioacetate in dimethylsulfoxide at room temperature, followed by a direct oxidation of the formed intermediate with *N*-chlorosuccinimide in methanol gave aminosulfonyl chloride **16e** (Scheme 5). Using this two-step strategy, sixteen other sulfonyl chlorides and aminosulfonyl chlorides - linkers - were easily obtained (Scheme 5).

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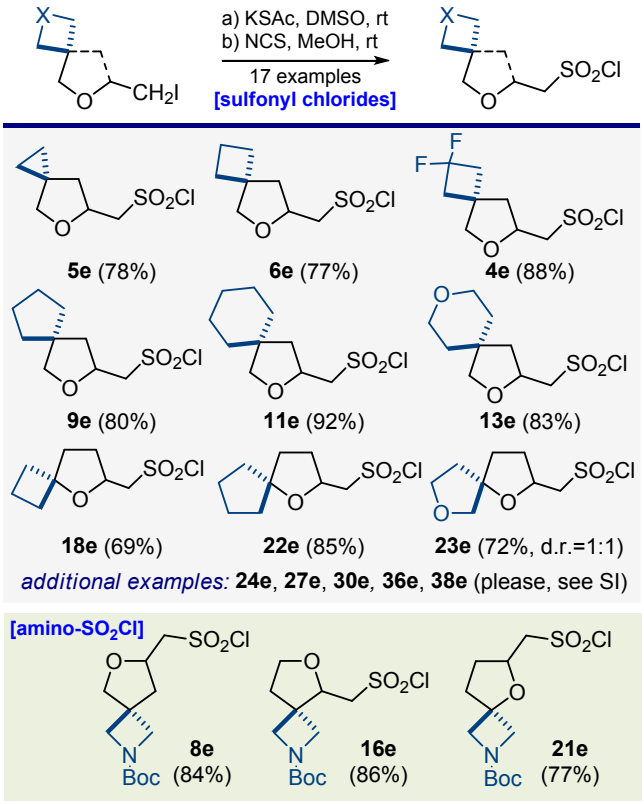
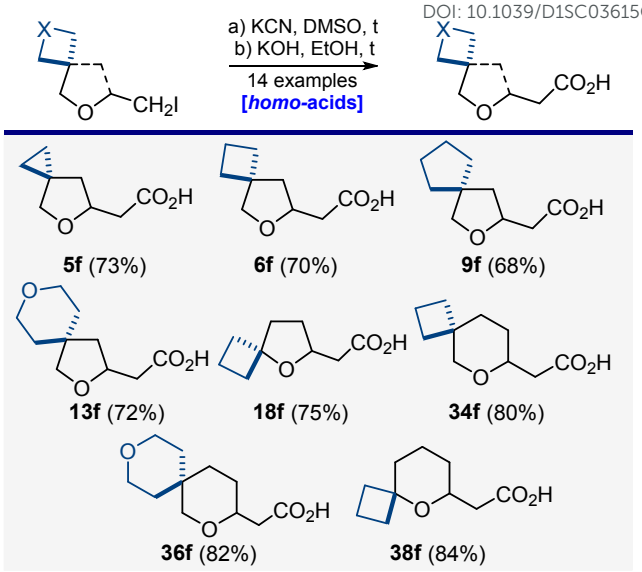


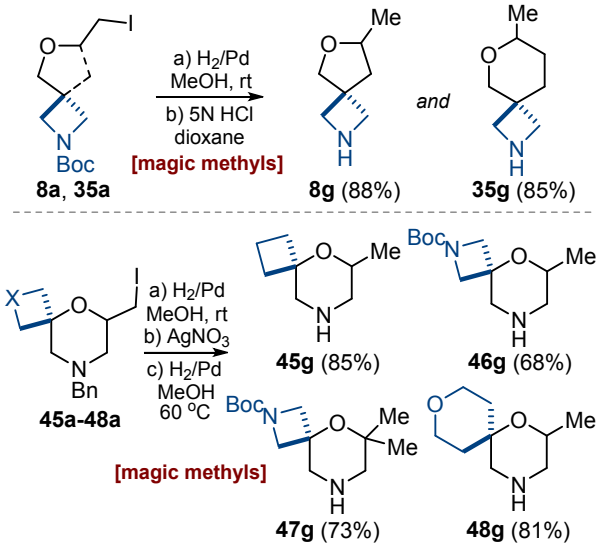
Scheme 5. Synthesis of *oxa*-spirocyclic sulfonyl chlorides **4e**-**6e**, **8e**, **9e**, **11e**, **13e**, **16e**, **18e**, **21e**-**24e**, **27e**, **30e**, **36e**, **38e**.

Synthesis of several substituted acetic acids, homologues of carboxylic acids, was also performed. For example, reaction of iodide **40a** with potassium cyanide, followed by alkali hydrolysis of the intermediate nitrile gave amino acid **40f** (Scheme 6). Likewise, thirteen other mono- and bifunctional derivatives were obtained (Scheme 6).

Recently, methylation was shown to have a profound impact onto activity of bioactive compounds – a "magic methyl" effect.[28] On the other hand, in recent years substituted azetidines gained a lot of popularity in medicinal chemistry.[29] In this context, we reduced C-I bond in compounds **8a**, **35a** with hydrogen using palladium on charcoal and after acidic *N*-Boc cleavage obtained interesting methyl azetidines **8g** and **35g** in 85-88% yield (Scheme 7). Morpholine, in turn, is one of the most popular rings in drugs.[1,30] Reduction of the C-I bond in iodides **45a**-**48a**,[31] followed by a Pd-catalyzed hydrogenative cleavage of *N*-benzyl group afforded methyl-substituted morpholine-containing diamines **45g**-**48g** in 68-85% yield (Scheme 7).



Scheme 6. Synthesis of *oxa*-spirocyclic homoacids **5f**, **6f**, **8f**, **9f**, **13f**, **18f**, **21f**, **29f**, **34f**-**36f**, **40f**, **44f**.



Scheme 7. Synthesis of methyl-azetidines **8g**, **35g** and methyl-morpholines **45g**-**48g**.

Reaction of iodide **6a** with potassium cyanide in dimethylsulfoxide under heating, followed by reduction of the nitrile group with Raney nickel alloy gave amine **6h** in 78% yield (Scheme 8) – a homologue of amine **6b** (Scheme 2). Using the

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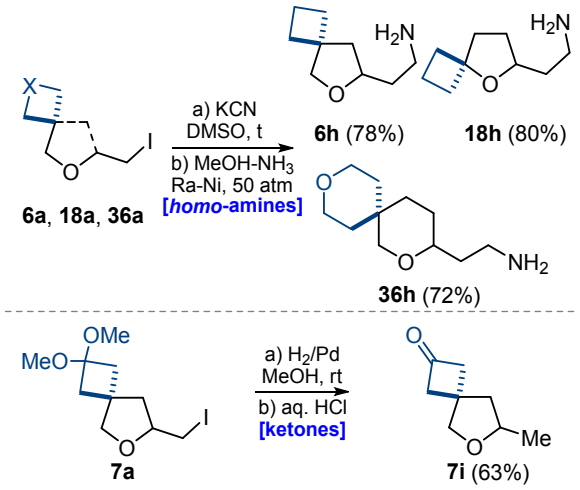
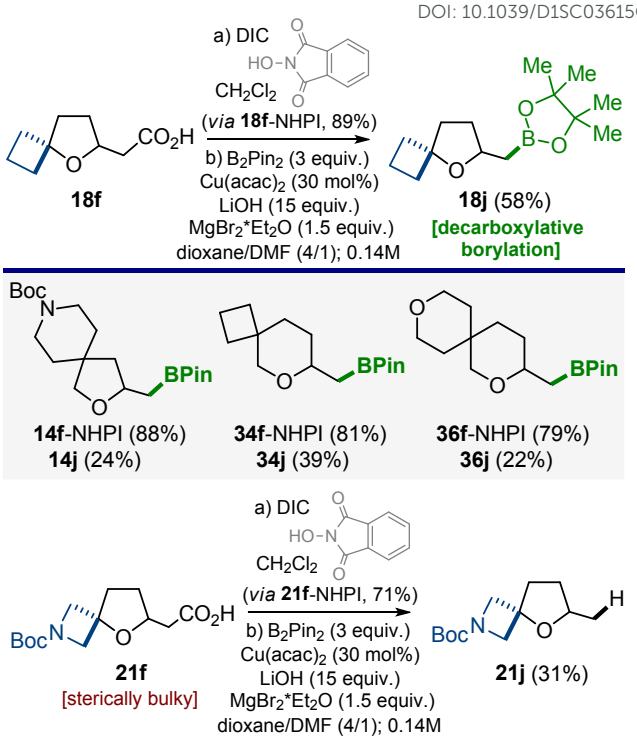
same tactic, amines **18h** and **36h** were also obtained. In addition, reduction of C-I bond in compound **7a** followed by acidic cleavage of the ketal moiety gave methyl ketone **7i** in 63% yield (Scheme 8).



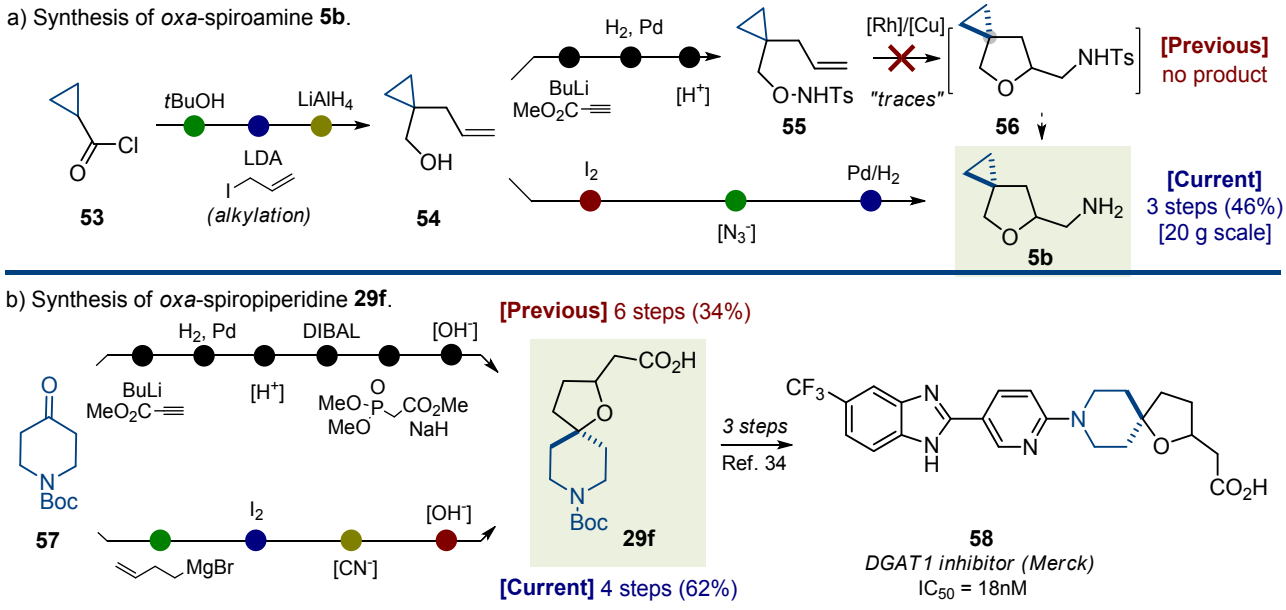
Scheme 8. Synthesis of *oxa*-spirocyclic homoamines **6h**, **18h**, **36h** and ketone **7i**.

All modifications of *oxa*-spirocyclic iodides depicted on Schemes 4-8 represent (2e)-reactions. In this work, we also wanted to show that *oxa*-spirocyclic molecules are also compatible with radical (1e) modifications. Recently, *Blackmond* and *Baran* developed a practical [Cu]-catalyzed decarboxylative borylation of carboxylic acid derivatives.[32] We used that radical transformation to convert *oxa*-spirocyclic acetic acids **14f**, **18f**, **21f**, **34f**, **36f** into the corresponding BPin-products (Scheme 9).[33] In fact, three mono- (**18j**, **34j**, **36j**), and one bifunctional **14j** organoboron compounds were obtained via the *N*-hydroxyphtalimide (NHPI) esters. Acid **21f**, however, under identical conditions, gave reduced product **21j**, presumably due to a steric hindrance around the reaction center.



Scheme 9. Decarboxylative borylation of *oxa*-spirocyclic acids.

In short summary, straightforward two to three step modifications of iodides **4a**-**48a** using common (2e) and radical (1e) reactions allowed rapid synthesis of >150 novel or previously hardly accessible *oxa*-spirocyclic molecules. All products contained one or two appropriately protected functional groups – amino acids, diamines, aminosulfonyl chlorides, amino boronates – suitable for the direct use in medicinal chemistry programs. In terms of diversity and efficiency, this is the most useful method to access *oxa*-spirocyclic cores so far.



Scheme 10. Synthesis of *oxa*-spiroamine **5b** and *oxa*-spiropiperidine **29f**: literature approaches *vs* this work.

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Application in organic synthesis. The synthetic approach to *oxa*-spirocycles described here not only provides entry into novel chemical space, but also significantly simplifies preparation of known molecules. For example, in 2018, [Rh]-catalyzed cyclization of unsaturated alkoxyamines was developed (Scheme 1).[19] In this project, the authors attempted [Rh]-catalyzed cyclization of substrate **55**, but observed only "traces" of the needed *N*-tosyl intermediate **56**. (Scheme 10). Alternatively, our approach allowed rapid preparation of the *N*-deprotected *oxa*-spiroamine **5b** from the same starting alkene **54** in only three steps. Moreover, the synthesis was easily scaled up to 20 g amount.

Compound **58** was recently discovered as a potent DGAT1 inhibitor (Scheme 10).[34] Synthesis of its key intermediate **29f** was undertaken in six steps from the commercially available *N*-Boc piperidone **55** in 34% yield.[14,35] On the contrary, our approach allowed the preparation of *oxa*-spiropiperidine **29f** in four steps from *N*-Boc piperidone in 62% yield.

Characterization. *Acidity/basicity of functional groups*. Incorporation of oxygen atom into organic molecules changes significantly acidity/basicity of the neighboring functional groups.[36] For this reason, we experimentally measured pK_a values of spirocyclic (**59**-**61**) and *oxa*-spirocyclic (**4d**-**6d**) carboxylic acids; spirocyclic (**62**-**64**) and *oxa*-spirocyclic (**4b**-**6b**) amine hydrochlorides (Figure 3). Incorporation of oxygen atom into acids **59**-**62** increased their acidity by ca. one order of a magnitude: pK_a (**59**-**62**) = 4.3-4.6 *vs* pK_a (**4d**-**6d**) = 3.4-3.7. Incorporation of oxygen atom into amines **62**-**64** reduced their basicity also by ca. one order of a magnitude: pK_a (**62***HCl-**64***HCl) = 10.1-10.3 *vs* pK_a (**4b***HCl-**6b***HCl) = 8.9-9.5. Similar ΔpK_a effect on acidity/basicity can be explained in terms of -(*I*)-inductive effect of the oxygen atom. In carboxylic acids **4d**-**6d**, the ether oxygen atom and the carboxylic oxygen atom are separated by three single bonds. Similarly, in amines **4b**-**6b**, the ether oxygen atom and the basic nitrogen atom are also separated by three single bonds. Hence an effect of incorporation of the oxygen atom on acidity and basicity is similar.

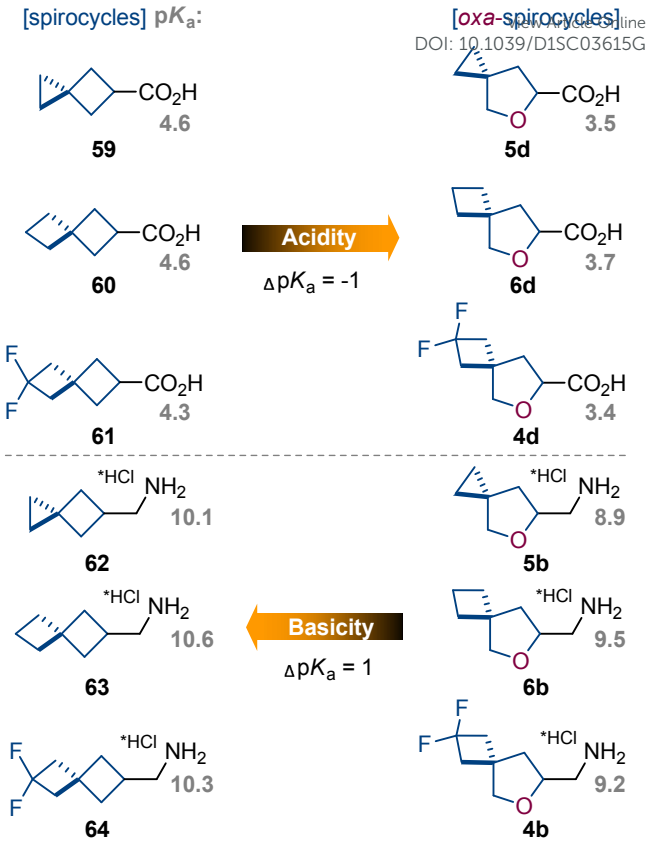

Figure 3. Experimental pK_a values of acids **59**-**61**, **4d**-**6d**; and conjugated amines **62**·HCl-**64**·HCl, **4b**·HCl-**6b**·HCl.

To study an effect of incorporation of oxygen atom on water solubility and lipophilicity of spirocyclic structures, we first synthesized model compounds **65**-**73** by standard amide coupling (Table 2).

Water solubility (Sol.). Replacement of the cycloalkane ring in compounds **65**, **68**, **71** with the spirocyclic bioisosteres **66**, **69**, **72** only slightly increased water solubility (Table 2)[5]. However, incorporation of oxygen atom into spirocyclic unit led to dramatic improvement in water solubility (Table 2). For example, *oxa*-spirocyclic compound **67** was ca. 40-times (!) more soluble than spirocycle **66**: 9 μM (**66**) *vs* 360 μM (**67**) (Table 2). Similar, but less profound, effect was observed in pairs **69**/**70** and **72**/**73**: 7 μM (**69**) *vs* 118 μM (**70**); <5 μM (**72**) *vs* 34 μM (**73**).

Lipophilicity (log$D_{7.4}$). Incorporation of oxygen atom into the spirocyclic unit also decreased lipophilicity. Lipophilicity index (logD) of *oxa*-spirocyclic models **67**, **70**, **73** was ca. one order of a magnitude lower than that of spirocyclic models **66**, **69**, **72**: 4.5 (**66**) *vs* 3.6 (**67**); 4.9 (**69**) *vs* 4.0 (**70**); 4.4 (**72**) *vs* 3.6 (**73**).

In brief summary, *oxa*-spirocylic compounds have (a) dramatically higher solubility (up to 40-times), and (b) lower lipophilicity (ΔlogD = ca. 1) than common spirocycles.

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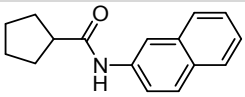
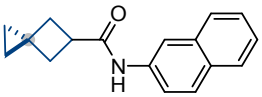
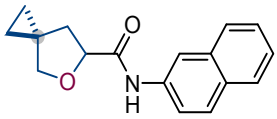
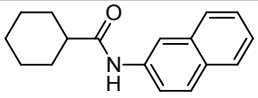
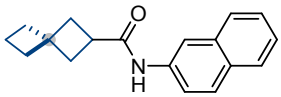
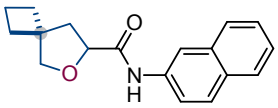
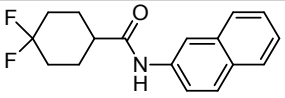
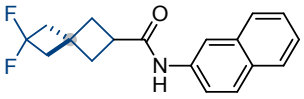
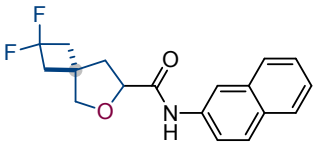
Table 2. Experimental lipophilicity (logD) and water solubility of model compounds **65**-**73**.

	Model compound	LogD(7.4)[a]	Sol(7.4)[b]
65		3.6	<5
66		4.5	9
67		3.6	360
68		4.4	<5
69		4.9	7
70		4.0	118
71		4.0	<5
72		4.4	<5
73		3.6	34

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

Lead-likeness and molecular shape. To analyze lead-likeness and molecular shape of virtual compound libraries that could be synthesized from *oxa*-spirocyclic molecules described here, we used a free online software LLAMA.[37] We selected five representative amines with different structural motifs to achieve maximal diversity: primary - tetrahydrofurane **4b**, oxetane **32b**, dioxane **43b** (Scheme 1); and secondary - azetidine **8g**, morpholine **45g** (Scheme 8). Next, we decorated them with a default set of capping reagents using five standard transformations: (a) amide synthesis; (b) sulfonylation; (c) urea synthesis; (d) reductive amination and (e) Buchwald-Hartwig amination. As a result, a virtual library of 130 molecules was generated. Important to mention that 126 molecules (>96%) lied in the lead-like space: MW< 350; clogP < 3 (Figure 4). The mean lead-likeness index of all 130 compounds was 0.68. To assess the three-dimensionality of the library, **the** principal moments of inertia (PMI) plot was generated (Figure 5). This plot confirmed that many of these lead-like compounds also showed significant shape diversity. The fraction of sp^3-hybridised carbons, *F*(sp^3), in the library was also analyzed, as it was previously shown to correlate with success in drug discovery projects.[2] The average *F*(sp^3) index was 0.79 which is significantly higher than that of a random molecule from the ZINC database (0.33).[38]

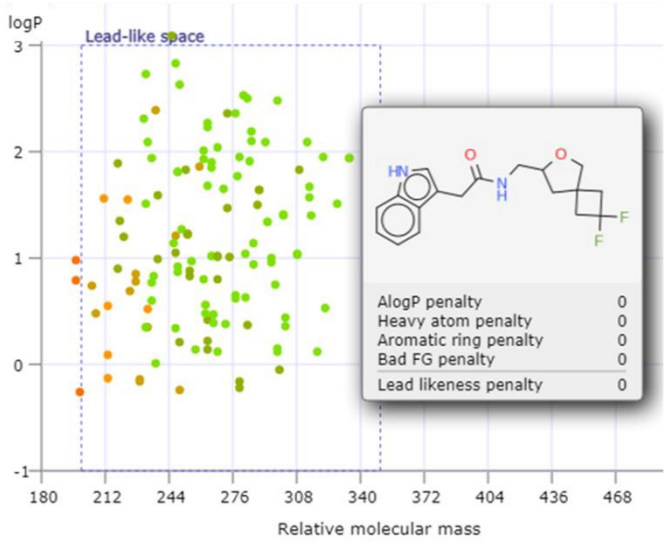


Figure 4. Distribution of virtual molecules, logP(y)-MW(x), obtained by decoration of amines **4b**, **32b**, **43b**, **8g**, **45g** in LLAMA software. Chemical structure of a representative derivative of **4b** is shown.

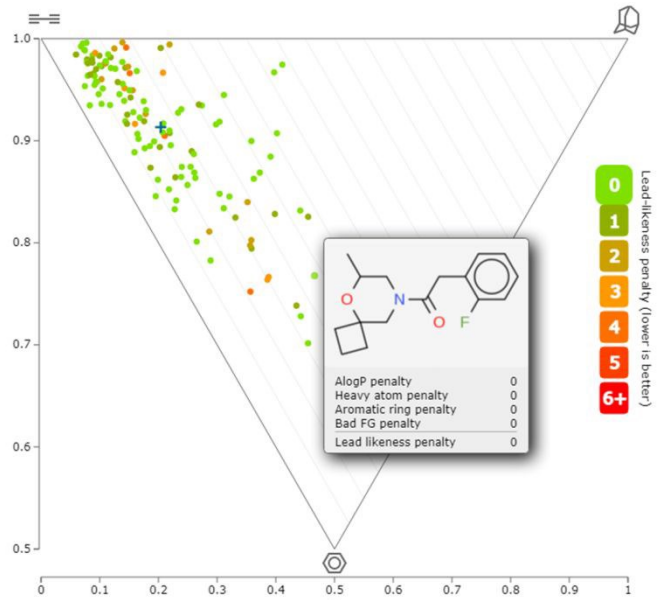


Figure 5. Principal moments of inertia (PMI) plot of virtual molecules, obtained by decoration of amines **4b**, **32b**, **43b**, **8g**, **45g** in LLAMA software. Chemical structure of a representative derivative of **45g** is shown.

Incorporation into bioactive compound. After elaboration of a general method to *oxa*-spirocycles and their physico-chemical characterization, we wanted to experimentally show that these compounds indeed can be used in medicinal chemistry projects. We chose *Terazosin* (**74**) for modifications, because it is a popular antihypertensive drug (Figure 6). In 2018, it was the 198th most commonly prescribed medication in the US, with almost three million prescriptions.[39,40] We synthesized its analogues **75**-**79** where

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the tetrahydrofuran ring was replaced with *oxa*-spirocyclic cores (Figure 6). The synthesis was realized via standard amide coupling of carboxylic acids **5d**, **6d**, **13d**, **18d**, **27d** with the corresponding *N*-substituted piperazine.

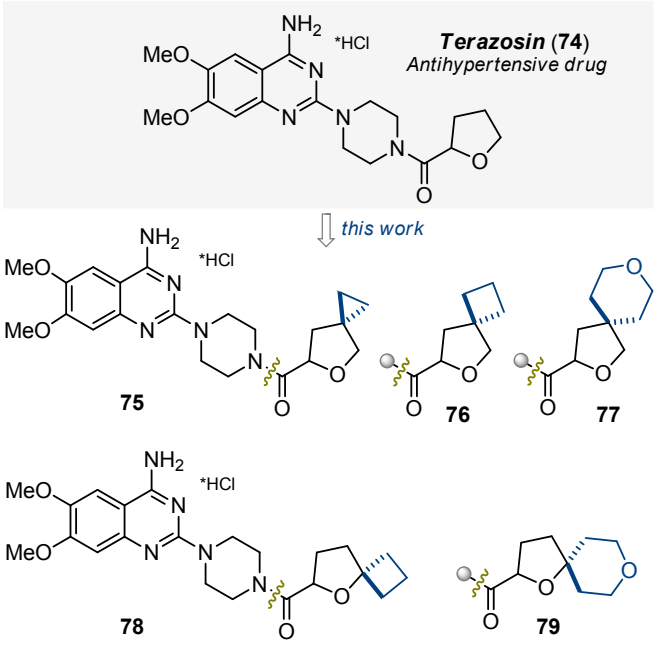

Figure 6. Antihypertensive drug *Terazosin* (**74**) and *oxa*-spiro-substituted analogues **75**, **76**, **77**, **78**, **79**.

Finally, we measured and compared biological activity of *Terazosin* (**74**) and all its analogues **75-79**. Studies were conducted using 7.5-month-old spontaneously hypertensive (SHR) male rats with the average body weight of 329±30 g and basal systolic blood pressure not less than 185 mmHg.[41] The compounds were dissolved in Saline (**74, 76-79**), or water containing 20% captisol (**75**). Animals received 3 mg/kg compound in 5 ml/kg vehicle per os once. Five animals per group were assigned. Systolic and diastolic blood pressure (BP)[42] were measured in 15, 60, 120, 180 and 240 min after the dosing (Figures 7, 8).

Terazosin (**74**) and its *oxa*-spirocyclic analogues **76**, **77**, **78** had similar biological profile *in vivo* - all compounds caused significant systolic and diastolic BP lowering compared with Saline treated groups after 15 min and 60 min, and with no statistical difference between them (Figures 7, 8). At the same time, after 120 min treatment, the BP lowering effect of most tested analogues was still statistically significant, in contrast to the original *Terazosin* (**74**). This effect may suggest that the used modification may contribute to the prolongation of the drug action.

It is important also to mention that cyclopropane-containing analogue **75** after 15 min of treatment behaved much better in both systolic and diastolic BP lowering (Figures 7, 8) than all other analogues including the original drug *Terazosin* (**74**).

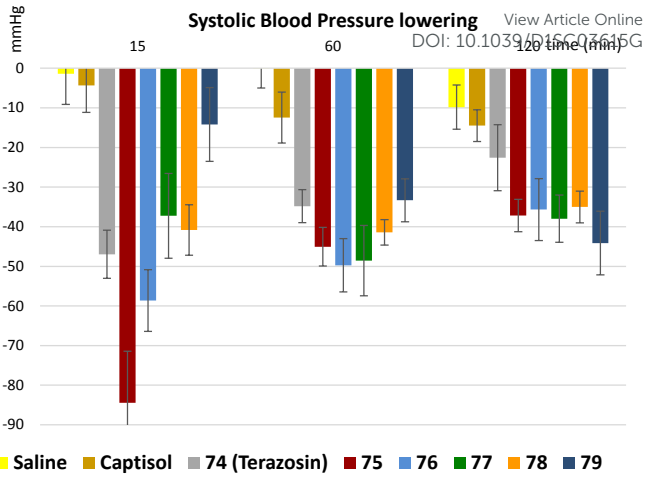

Figure 7. The dynamics of systolic blood pressure in SHR rats at different time-points after single PO administration of Vehicle (saline or 20% captisol) or test substances at dose 3 mg/kg. Compounds were dissolved in saline (**74**, **76-79**) or 20% captisol in water (**75**). Data are expressed as means ± SEM.

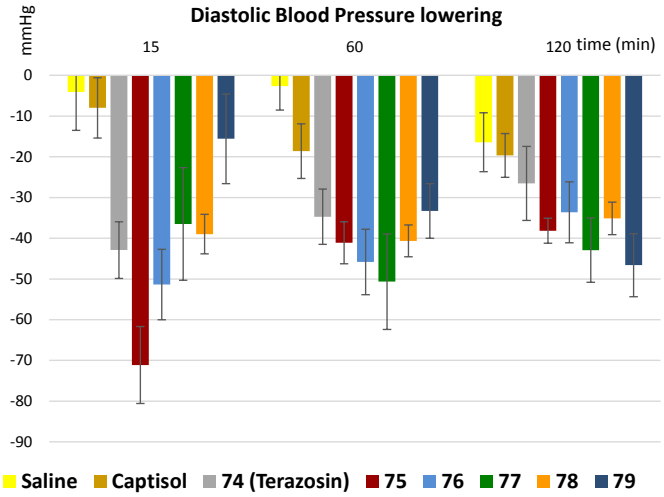

Figure 8. The dynamics of diastolic blood pressure in SHR rats at different time-points after single PO administration of Vehicle (20% captisol) or test substances at dose 3 mg/kg. Compounds were dissolved in saline (**74**, **76-79**) or 20% captisol in water (**75**). Data are expressed as means ± SEM.

Conclusions

During recent decade, *oxa*-spirocycles undeservedly remained in the shadow compared to the more popular spirocyclic analogues (Figure 2). The key reason was an absence of a general practical approach to them. In this work, we developed such an approach. *Oxa*-spirocycles were easily synthesized through the iodocyclization reaction. Using common (2e) and radical (1e) modifications, the obtained iodides **4a**-**48a** were easily converted into >150 *oxa*-spirocyclic derivatives with appropriately protected functional groups, that could be directly used in medicinal chemistry projects. Incorporation of oxygen atom into spirocyclic unit was shown to dramatically increase its solubility (up to 40 times: **66** vs **67**, Table 1)

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and lower lipophilicity. The developed protocol not only gave access to novel molecules, but also significantly simplified the synthesis of the known ones (Scheme 10). In addition, five *oxa*-spirocyclic analogues **75**-**79** of the antihypertensive drug *Terazosin* (**74**) were prepared. Analogue **75** showed significantly higher potency *in vivo* than the original drug (Figures 7,8).

We believe that with this general simple approach to *oxa*-spirocyclic iodides and procedures for their modifications (Schemes 4-9), *oxa*-spirocycles will soon become very popular in chemistry.

Data availability

Supporting data for this article have been uploaded as part of the ESI material.

Author contributions

Conceptualization – PKM; investigation and methodology – KF, TD, DG, TS, VV, OS, VM, IK, EL, VVL, VRB, RIV, AIV, AVB, VVS, RI, KS, ASK, YVD, DV, VR, OP, HK; supervision – IP, PB, AAT, PKM; writing, original draft – PKM; writing, reviewing & editing – ASK, AAT, OP, HK, IP, PB, PKM.

Conflicts of interest

There are no conflicts to declare.

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39. https://clincalc.com/DrugStats/Top300Drugs.aspx
40. https://clincalc.com/DrugStats/Drugs/Terazosin
41. Study design, animal selection, handling and treatment were in accordance with Bienta Animal Care and Use Guidelines, and European Union directive 2010/63/EU.
42. Blood pressure (BP) was measured by Tail-Cuff Method. We used Coda Non-invasive Blood-Pressure System (Kent Scientific Corporation, CT, USA).

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