Chemical Science

Oxa-spirocycles
by Enamine chemists

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Pavel K. Mykhailiuk *et al.*
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 an oxygen atom into the spirocyclic unit dramatically improved water solubility (by up to 40 times) and lowered lipophilicity. More potent oxa-spirocyclic analogues of antihypertensive drug terazosin were synthesized and studied *in vivo*.

Introduction

Saturated monocyclic units – cyclohexane, cyclopentane, piperidine, *etc.* – dominated in chemistry and in drug discovery for a long time.[1] The situation started changing at the beginning of this century. In 2009, Lovering introduced the concept of "escape from flatland",[2] which already changed the way 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 their 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 have appeared during the last decade (Fig. 1).[8]

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 positive feedback from both academy and industry, and therefore we decided to expand this tactic to a new generation of spirocycles – oxa-spirocycles (Fig. 1). Previously, oxa-spirocycles remained mostly in the
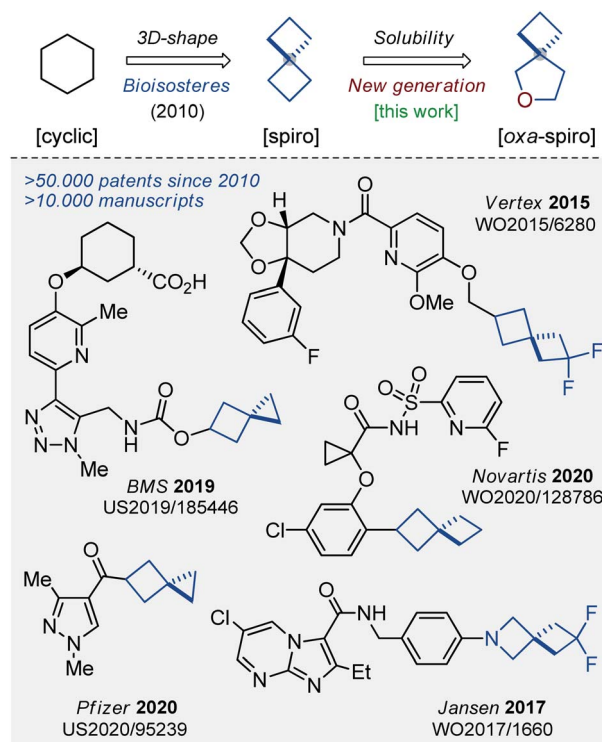

Fig. 1 Spirocycles and their application in chemistry.

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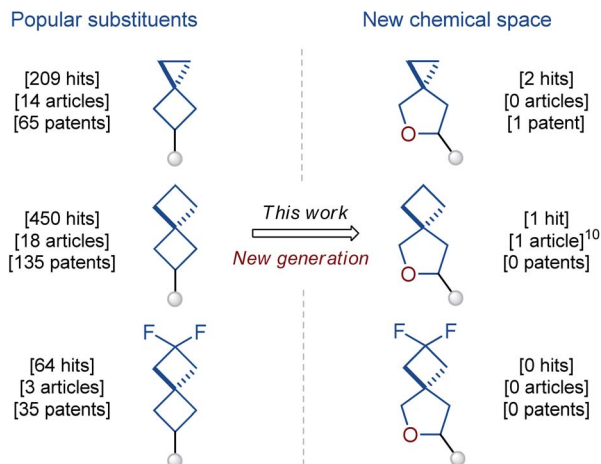
Fig. 2 Spirocycles and their unexplored oxa-counterparts.

shadow. For example, while three representative spirocyclic substituents (left, Fig. 2) are extremely popular in chemistry, the corresponding oxa-spirocyclic counterparts (right, Fig. 2) remain almost unknown.[10]

Of course, there was some interest in oxa-spirocycles before, but examples reported in the literature were rare and non-systematic.[11] In 1985, Yoshida synthesized two substituted oxa-spirocycles *via* iodocyclization (Scheme 1).[12] In 2008, Gouverneur studied the influence of the fluorine atom on the diastereoselectivity of the iodocyclization reaction. In this work, one example of the oxa-spirocyclic core is shown (Scheme 1).[13] In 2011, Cernak and co-workers from Merck employed the 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 described the gold-catalyzed oxidative cyclization of propargyl alcohols into oxa-spirocyclic amines (Scheme 1).[16] In the same

Table 1 Optimization of the synthesis of compound 4a
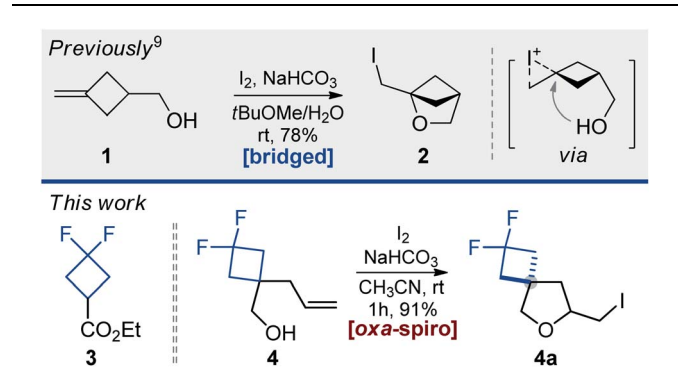
Entry	Deviations from the literature	NMR yield 4a[a,b] (%)
1	tBuOMe/H$_2$O as a solvent	71
2	Et$_2$O as a solvent	67
3	CH$_2$Cl$_2$ as a solvent	65
4	CHCl$_3$ as a solvent	69
5	Dioxane as a solvent	49
6	THF as a solvent	55
7	CH$_3$CN as a solvent	96[c] (91)
8	DMF as a solvent	41
9	DMSO as a solvent	34
10	Na$_2$CO$_3$ 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 ^{1}H NMR with CH$_2$Br$_2$ as an internal standard. [c] Isolated yield. NIS = N-iodosuccinimide, NIS = N-bromosuccinimide.

year, Santini also developed an alternative approach to oxa-spirocyclic amines *via* oxidative intramolecular hydroxycyclization of alkenes.[17] Subsequently, Cocotos realized an
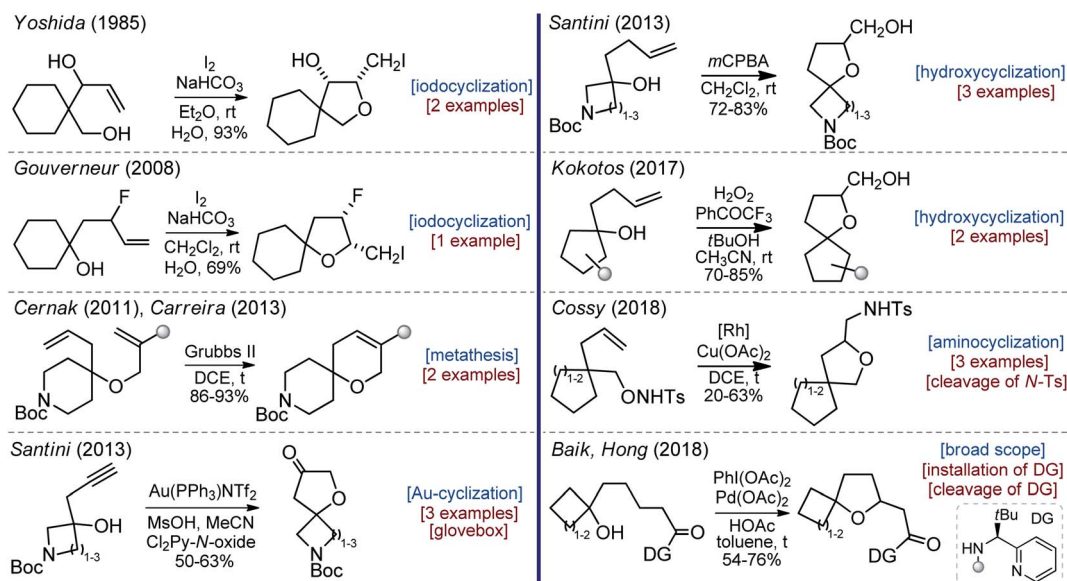

Scheme 1 Literature precedents to oxa-spirocycles.

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. 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, the absence of a general method to oxa-spirocycles is a primary reason why these molecules did not
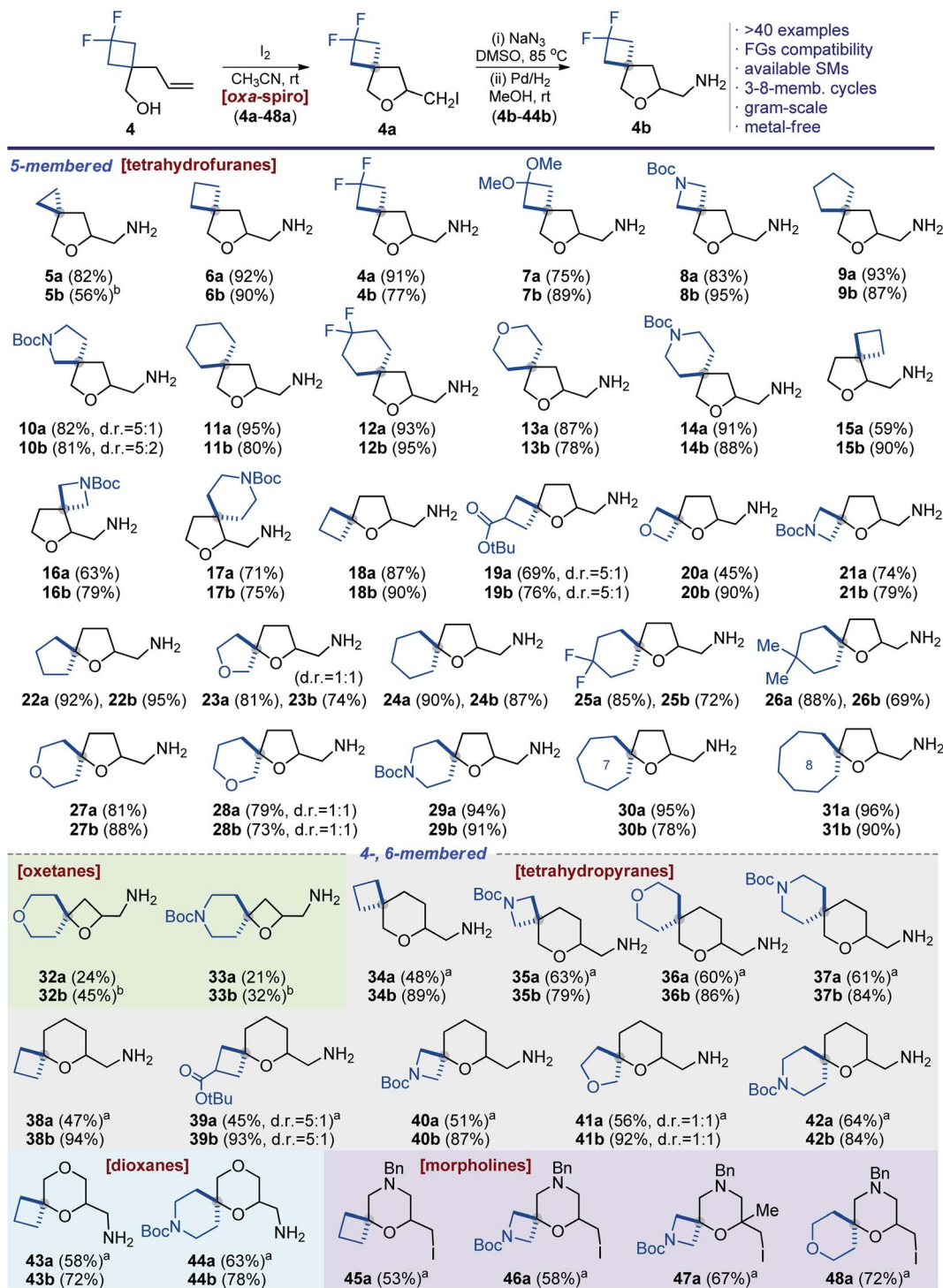
Scheme 2 Scope of the iodocyclization step into oxa–spirocycles. Iodocyclization conditions: alkene (1 equiv.), NaHCO$_3$ (3 equiv.), I$_2$ (3 equiv.), CH$_3$CN, rt, 1 h. [a]Alkene (1 equiv.), K$_2$CO$_3$ (4 equiv.), I$_2$ (4 equiv.), CH$_3$CN, rt, 48 h. Synthesis of amines, conditions: (i) iodide (1 equiv.), NaN$_3$ (1.5 equiv.), DMSO, 85 °C. (ii) H$_2$/Pd, MeOH, rt. [b](ii) PPh$_3$ (1.5 equiv.), H$_2$O/THF, 50 °C.

receive proper recognition from the 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 a variety of other functional substituents: amines, alcohols, carboxylic acids, sulfonyl chlorides, *etc.* In this work, we present such an approach.

Results and discussion

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 specifically exploit iodocyclization, and not bromocyclization or hydroxycyclization, because the putative alcohols or bromides would be much less active in further modifications.
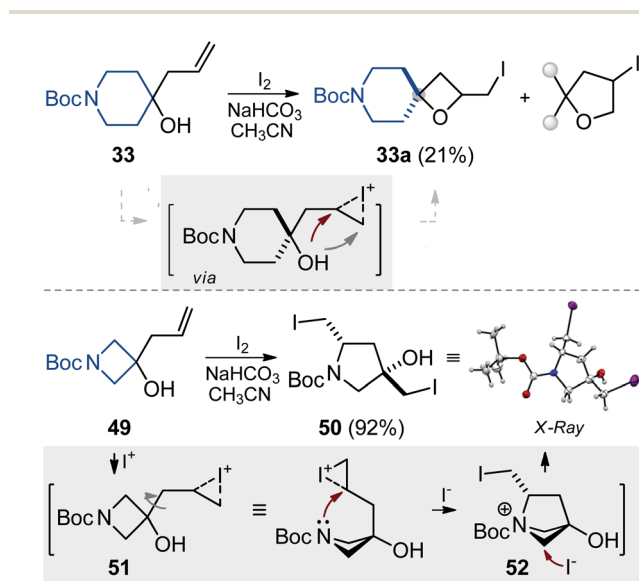
Under the previously developed conditions (Table 1, entry 1) alkene **4** indeed predominantly afforded iodide **4a**, although formation of side products was also observed. Separation of this mixture was problematic, especially on a gram scale. Performing the reaction in diethyl ether (entry 2) or dichloromethane (entry 3) still led to formation of a mixture of compounds. Finally, we screened various solvents and found 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 slightly lower efficiency (entry 14).

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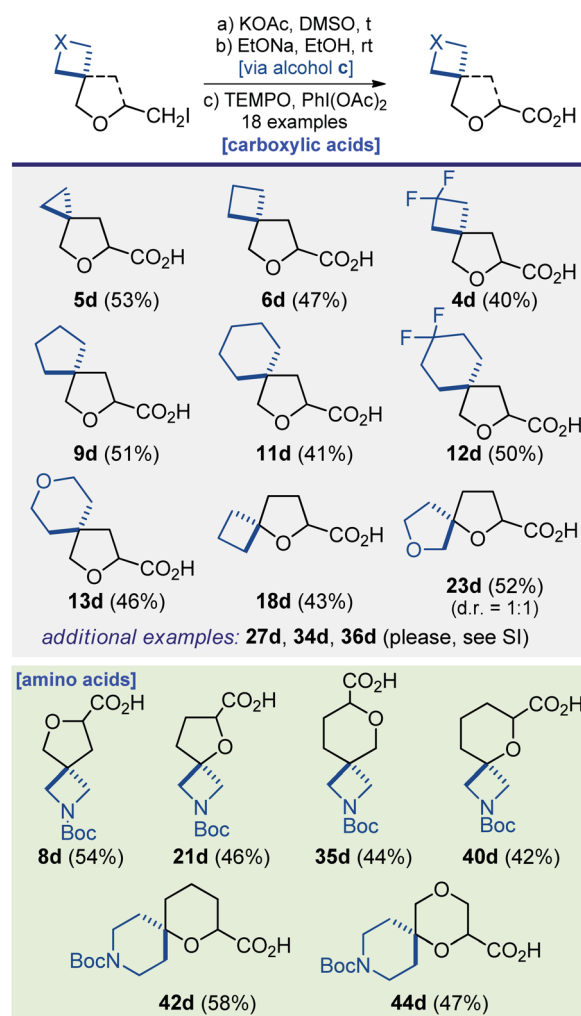
from the reaction mixture by simple distillation and no additional purification was needed.

Scope

Having an optimized procedure in hand, we next studied 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**, and **21a**), pyrrolidines (**10a**) and piperidines (**14a**, **17a**, and **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, the 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.

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.

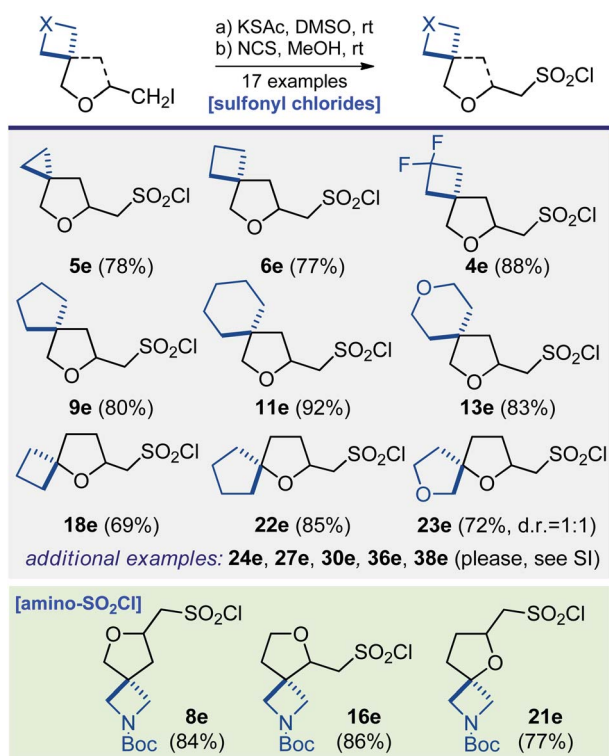**Scheme 3** Unexpected synthesis of pyrrolidine 50.

We also tried iodocyclization to construct the six-membered tetrahydropyran 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 and 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 (Schemes 2 and 3), the corresponding azetidine-containing alcohol 49 unexpectedly afforded pyrrolidine 50 as a single stereoisomer in 92% yield (Scheme 3).[24] The 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 the iodide anion gave the observed pyrrolidine 50.

Modifications

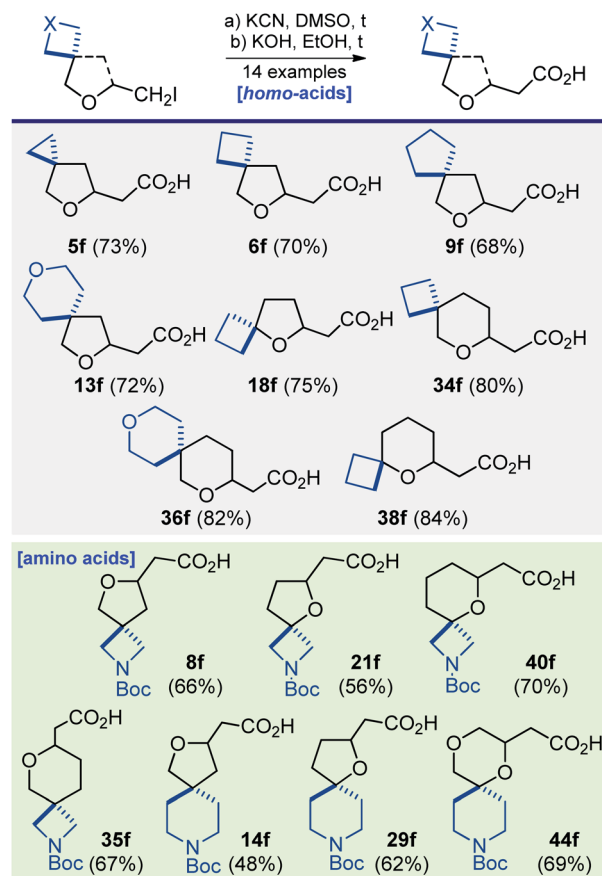Several representative modifications of iodides 4a–48a were undertaken using standard chemical transformations to provide numerous oxa-spirocyclic derivatives. First, a simple reaction of iodides 4a–44a with sodium azide followed by reduction with either H_2/Pd or PPh_3 gave amines 4b–44b in 32–95% yield. Among them were not only monofunctional compounds, but also linkers with two functional groups: amino acids 19b and 39b and valuable diamines for medicinal chemistry 8b, 10b, 14b, 16b, 17b, 21b, 29b, 33b, 35b, 37b, 40b, 42b, and 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 are the unusual amino acids from Scheme 4 – that type of structure plays an important role in drug discovery programs.[26]

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).

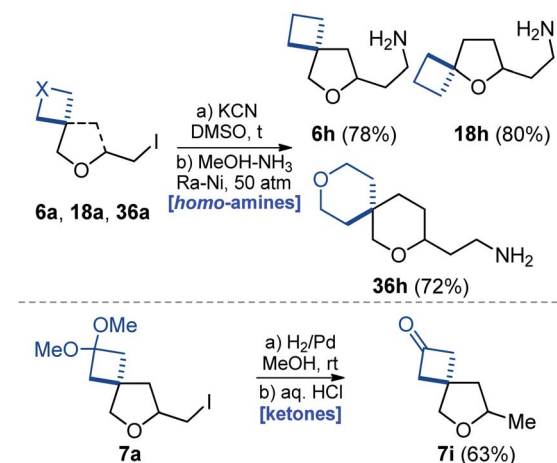

Scheme 5 Synthesis of oxa-spirocyclic sulfonyl chlorides 4e–6e, 8e, 9e, 11e, 13e, 16e, 18e, 21e–24e, 27e, 30e, 36e, and 38e.

Scheme 6 Synthesis of oxa-spirocyclic homoacids 5f, 6f, 8f, 9f, 13f, 18f, 21f, 29f, 34f–36f, 40f, and 44f.
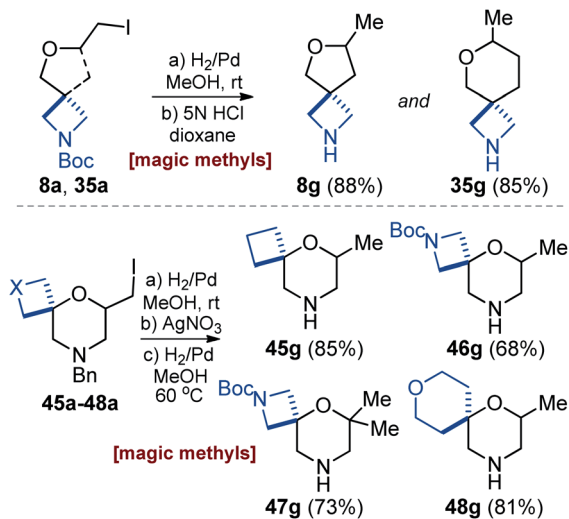
Scheme 7 Synthesis of methyl-azetidines 8g and 35g and methyl-morpholines 45g–48g.

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 on the 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 the C–I bond in compounds 8a and 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 the N-benzyl group afforded methyl-substituted

morpholine-containing diamines 45g–48g in 68–85% yield (Scheme 7).

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

All modifications of oxa-spirocyclic iodides depicted in 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, and 36f into the corresponding BPin-products (Scheme 9).[33] In fact, three mono- (18j, 34j, and 36j) and one bifunctional (14j) organoboron compounds were obtained via the N-hydroxyphthalimide (NHPI) esters. Acid 21f, however, under identical conditions, gave reduced product 21j, presumably due to steric hindrance around the reaction center.

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, and amino boronates – suitable for 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 8 Synthesis of oxa-spirocyclic homoamines 6h, 18h, and 36h and ketone 7i.
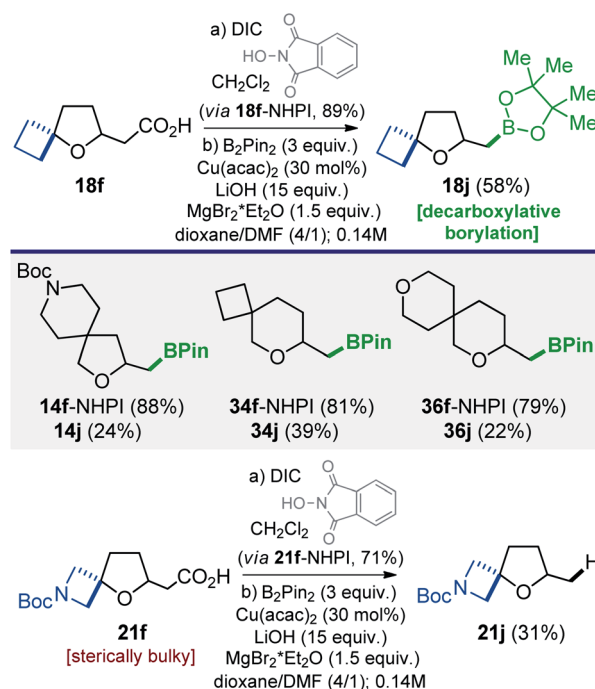
Scheme 9 Decarboxylative borylation of oxa-spirocyclic acids.
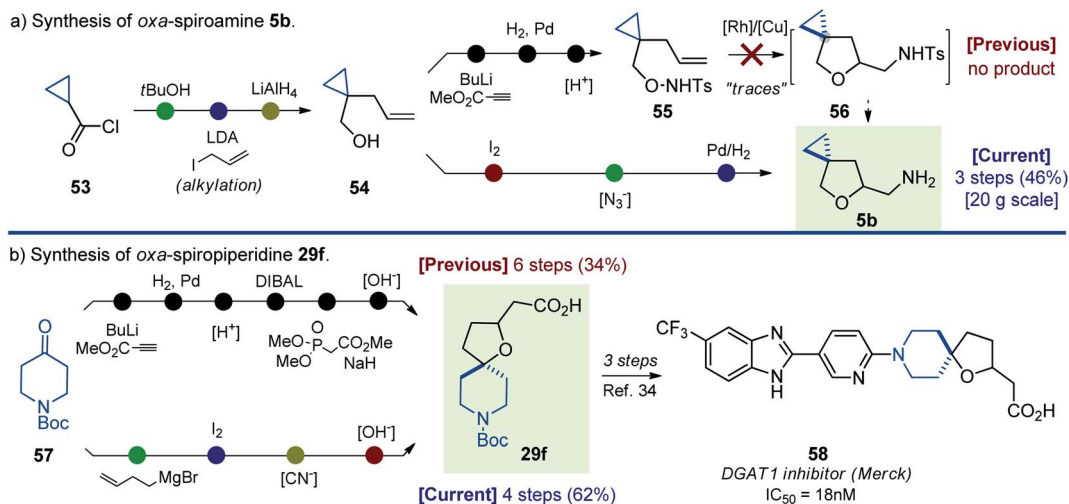
Scheme 10 Synthesis of oxa-spiroamine **5b** and oxa-spiropiperidine **29f**: literature approaches *vs.* this work.

Application in organic synthesis

The synthetic approach to oxa-spirocycles described here not only provides entry into novel chemical space, but also significantly simplifies the 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.

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] In contrast, 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 an oxygen atom into organic molecules significantly changes the acidity/basicity of the neighboring functional groups.[36] For this reason, we experimentally measured the pK_a values of spirocyclic (**59–61**) and oxa-spirocyclic (**4d–6d**) carboxylic acids, and spirocyclic (**62–64**) and oxa-spirocyclic (**4b–6b**) amine hydrochlorides (Fig. 3). Incorporation of an oxygen atom into acids **59–62** increased their acidity by *ca.* one order of magnitude: pK_a (**59–62**) = 4.3–4.6 *vs.* pK_a (**4d–6d**) = 3.4–3.7. Incorporation of an oxygen atom into amines **62–64** reduced their basicity also by *ca.* one order of magnitude: pK_a (**62***HCl–**64***HCl) = 10.1–10.3 *vs.* pK_a (**4b***HCl–**6b***HCl) = 8.9–9.5. The similar ΔpK_a effect on acidity/basicity can be explained in terms of the −(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 the effect of incorporation of the oxygen atom on acidity and basicity is similar.

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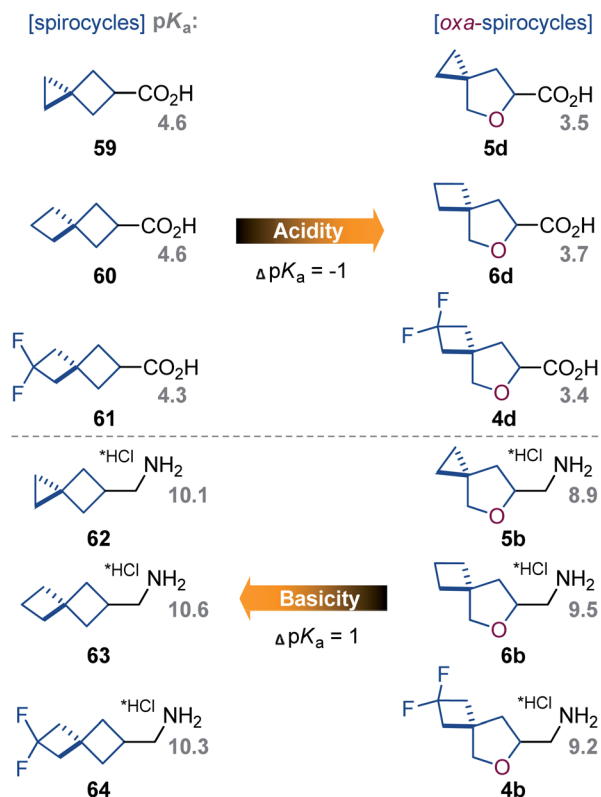

Fig. 3 Experimental pK_a values of acids **59–61** and **4d–6d**, and conjugated amines **62**·HCl–**64**·HCl and **4b**·HCl–**6b**·HCl.

Table 2 Experimental lipophilicity (log D) and water solubility of model compounds 65–73

Model compound	Log D (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 (μM) in 50 mM phosphate buffer (pH 7.4).

Water solubility (sol.). Replacement of the cycloalkane ring in compounds 65, 68, and 71 with the spirocyclic bioisosteres 66, 69, and 72 only slightly increased water solubility (Table 2).[5] However, incorporation of an oxygen atom into the spirocyclic unit led to a 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). Similarly, but less profound, the 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 an oxygen atom into the spirocyclic unit also decreased lipophilicity. The lipophilicity index (log D) of oxa-spirocyclic models 67, 70, and 73 was $ca.$ one order of magnitude lower than that of spirocyclic
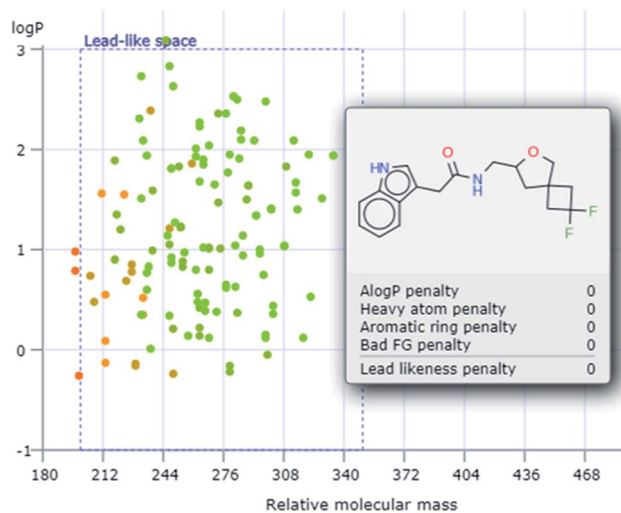

Fig. 4 Distribution of virtual molecules, log P (y)–MW (x), obtained by decoration of amines 4b, 32b, 43b, 8g, and 45g in LLAMA software. The chemical structure of a representative derivative of 4b is shown.

models 66, 69, and 72: 4.5 (66) $vs.$ 3.6 (67); 4.9 (69) $vs.$ 4.0 (70); 4.4 (72) $vs.$ 3.6 (73).

In brief, oxa-spirocyclic compounds have (a) dramatically higher solubility (up to 40 times), and (b) lower lipophilicity (Δlog $D = ca.$ 1) than common spirocycles.

Lead-likeness and molecular shape. To analyze the lead-likeness and molecular shape of virtual compound libraries that could be synthesized from oxa-spirocyclic molecules described here, we used free online software LLAMA.[37] We selected five representative amines with different structural motifs to achieve maximal diversity: primary – tetrahydrofurane
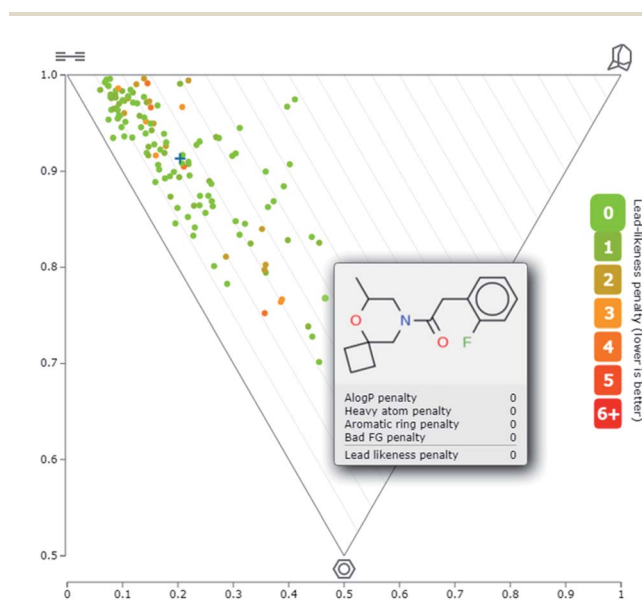

Fig. 5 Principal moments of inertia (PMI) plot of virtual molecules, obtained by decoration of amines 4b, 32b, 43b, 8g, and 45g in LLAMA software. The chemical structure of a representative derivative of 45g is shown.

4b, oxetane **32b**, and dioxane **43b** (Scheme 1), and secondary – azetidine **8g** and 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. It is important to mention that 126 molecules (>96%) lay in the lead-like space: MW < 350; $c \log P < 3$ (Fig. 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 (Fig. 5). This plot confirmed that many of these lead-like compounds also showed significant shape diversity. The fraction of sp³-hybridised carbons, $F(\mathrm{sp}^3)$, in the library was also analyzed, as it was previously shown to correlate with success in drug discovery projects.[2] The average $F(\mathrm{sp}^3)$ index was 0.79 which is significantly higher than that of a random molecule from the ZINC database (0.33).[38]

Incorporation into a bioactive compound. After elaboration of a general method to oxa-spirocycles and their physicochemical characterization, we wanted to experimentally show that these compounds can indeed be used in medicinal chemistry projects. We chose terazosin (**74**) for modifications, because it is a popular antihypertensive drug (Fig. 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 the tetrahydrofuran ring was replaced by oxa-spirocyclic cores (Fig. 6). The synthesis was realized via standard amide coupling of carboxylic acids **5d**, **6d**, **13d**, **18d**, and **27d** with the corresponding N-substituted piperazine.

Finally, we measured and compared the biological activity of terazosin (**74**) and all its analogues **75–79**. Studies were conducted using 7.5 month-old spontaneously hypertensive (SHR)
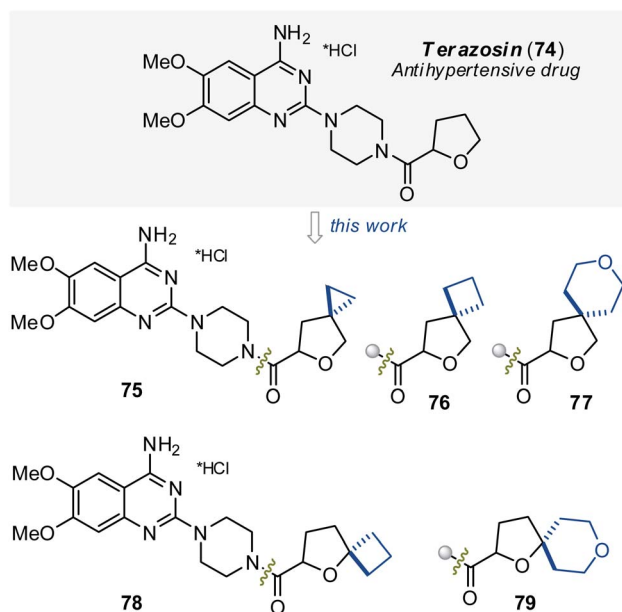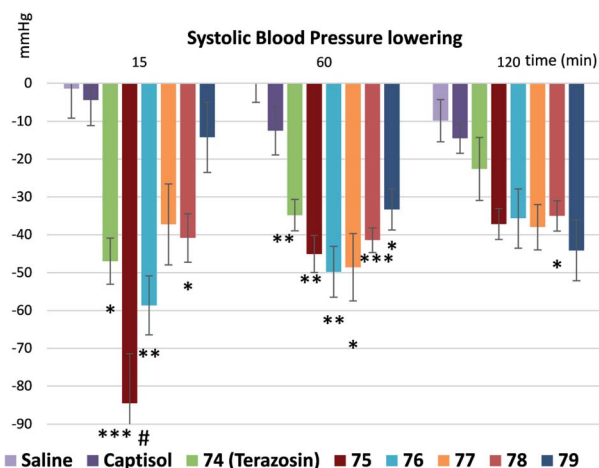
Fig. 7 The dynamics of systolic blood pressure in SHR rats at different time-points after single PO administration of vehicle (saline or 20% Captisol) or test substances at a dose of 3 mg kg⁻¹. Compounds were dissolved in saline (**74** and **76–79**) or 20% Captisol in water (**75**). Data are expressed as means ± SEM. *, **, *** – $P < 0.05, 0.01, 0.001$ compared with vehicle groups; # – $P < 0.01$ compared with terazosin treated group for the same time point.

male rats with an average body weight of 329 ± 30 g and basal systolic blood pressure not less than 185 mm Hg.[41] The compounds were dissolved in saline (**74** and **76–79**), or water containing 20% Captisol (**75**). Animals received 3 mg kg⁻¹ compound in 5 ml kg⁻¹ vehicle per os once. Five animals per group were assigned. Systolic and diastolic blood pressure (BP)[42] were measured 15, 60, 120, 180 and 240 min after the dosing (Fig. 7 and 8). Statistical analysis was performed using two-way ANOVA with Tukey's multiple comparisons test.

Fig. 6 Antihypertensive drug terazosin (**74**) and oxa-spiro-substituted analogues **75**, **76**, **77**, **78**, and **79**.
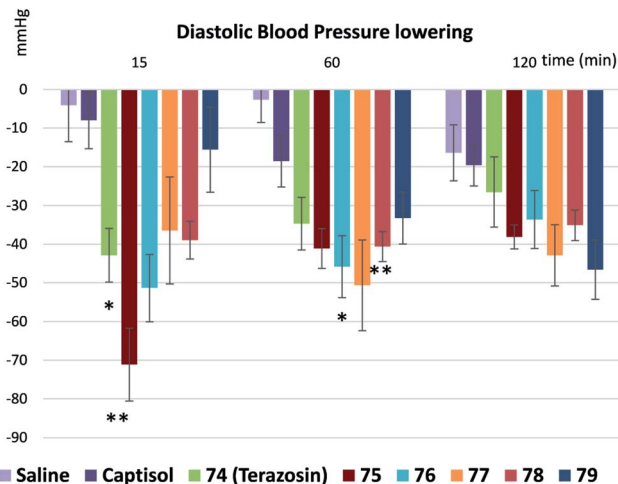
Fig. 8 The dynamics of diastolic blood pressure in SHR rats at different time-points after single PO administration of vehicle (20% Captisol) or test substances at a dose of 3 mg kg⁻¹. Compounds were dissolved in saline (**74** and **76–79**) or 20% Captisol in water (**75**). Data are expressed as means ± SEM. *, ** – $P < 0.05, 0.01$ compared with vehicle groups for the same time point.

Terazosin (**74**) and its oxa-spirocyclic analogues **75**, **76**, and **78** had similar biological profiles *in vivo* – all compounds demonstrated significant systolic BP decrease in comparison with corresponding vehicle groups after 15 min and 60 min of treatment (Fig. 7); while compounds **77** and **79** – only after 60 min (Fig. 7). For the 120 min time point, the BP lowering effect was statistically significant only for compound **78** in comparison with the vehicle. Compound **78** demonstrated prolonged effect even compared to terazosin (**74**), whereby terazosin had no statistically significant activity at 120 min. This effect may suggest that compound **78** modification may contribute to the prolongation of the drug action.

It should be noted that systolic BP decrease of the cyclopropane-containing analogue **75** after 15 min of treatment was significantly higher (Fig. 7) than that of the original drug terazosin (**74**).

Conclusions

During the recent decade, oxa-spirocycles undeservedly remained in the shadow compared to the more popular spirocyclic analogues (Fig. 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, which could be directly used in medicinal chemistry projects. Incorporation of an oxygen atom into the spirocyclic unit was shown to dramatically increase its solubility (by up to 40 times: 66 *vs.* 67, Table 1) 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 (Fig. 7 and 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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