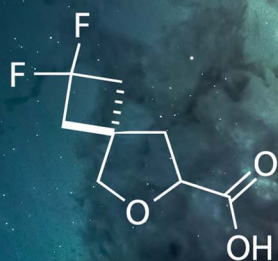


Chemical Science

Volume 12
Number 34
14 September 2021
Pages 11239–11606

rsc.li/chemical-science



Oxa-spirocycles
by Enamine chemists

ISSN 2041-6539

Cite this: *Chem. Sci.*, 2021, 12, 11294

All publication charges for this article have been paid for by the Royal Society of Chemistry

Oxa-spirocycles: synthesis, properties and applications†

Kateryna Fominova,^a Taras Diachuk,^a Dmitry Granat,^a Taras Savchuk,^a Vladyslav Vilchynskiy,^{ib} Oleksiy Svitlychnyi,^a Vladyslav Meliantsev,^a Igor Kovalchuk,^a Eduard Litskan,^a Vadym V. Levterov,^a Valentyn R. Badlo,^a Ruslan I. Vaskevych,^b Alla I. Vaskevych,^c Andrii V. Bolbut,^b Volodymyr V. Semeno,^{ib} Rustam Iminov,^a Kostiantyn Shvydenko,^b Anastasiia S. Kuznetsova,^d Yurii V. Dmytriv,^{ac} Daniil Vysochyn,^a Vasyl Ripenko,^a Andrei A. Tolmachev,^a Olexandra Pavlova,^e Halyna Kuznietsova,^{ib} Iryna Pishel,^{ib} Petro Borysko^{ib} and Pavel K. Mykhailiuk^{ib}*^a

Received 2nd July 2021

Accepted 20th July 2021

DOI: 10.1039/d1sc03615g

rsc.li/chemical-science

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(sp³)-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

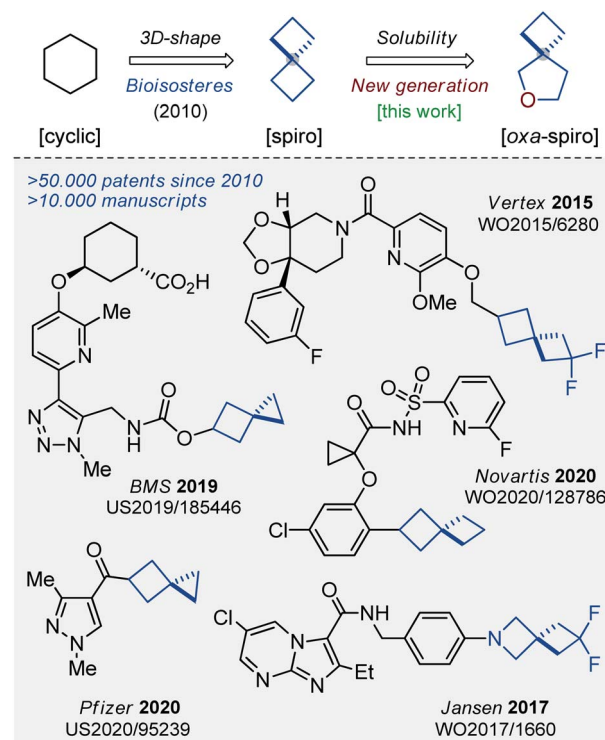


Fig. 1 Spirocycles and their application in chemistry.

^aEnamine Ltd, Chervonotkatska 78, 02094 Kyiv, Ukraine. E-mail: Pavel.Mykhailiuk@gmail.com; Web: <http://www.enamine.net>; <http://www.mykhailiukchem.org>

^bInstitute of Organic Chemistry, National Academy of Sciences of Ukraine, Murmanska St. 5, 02094 Kyiv, Ukraine

^cNational Technical University of Ukraine, Igor Sikorsky Kiev Polytechnic Institute, Prosp. Peremohy 37, 03056 Kyiv, Ukraine

^dNational Research Tomsk Polytechnic University, Lenin Ave. 30, 634050 Tomsk, Russia

^eBienta, Chervonotkatska 78, 02094 Kyiv, Ukraine; Web: <http://www.bienta.net>

† Electronic supplementary information (ESI) available. CCDC 2046173. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d1sc03615g

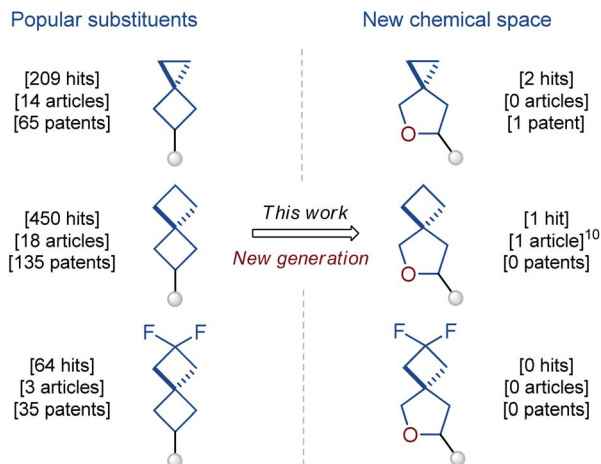


Fig. 2 Spirocycles and their unexplored oxa-counterparts.

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

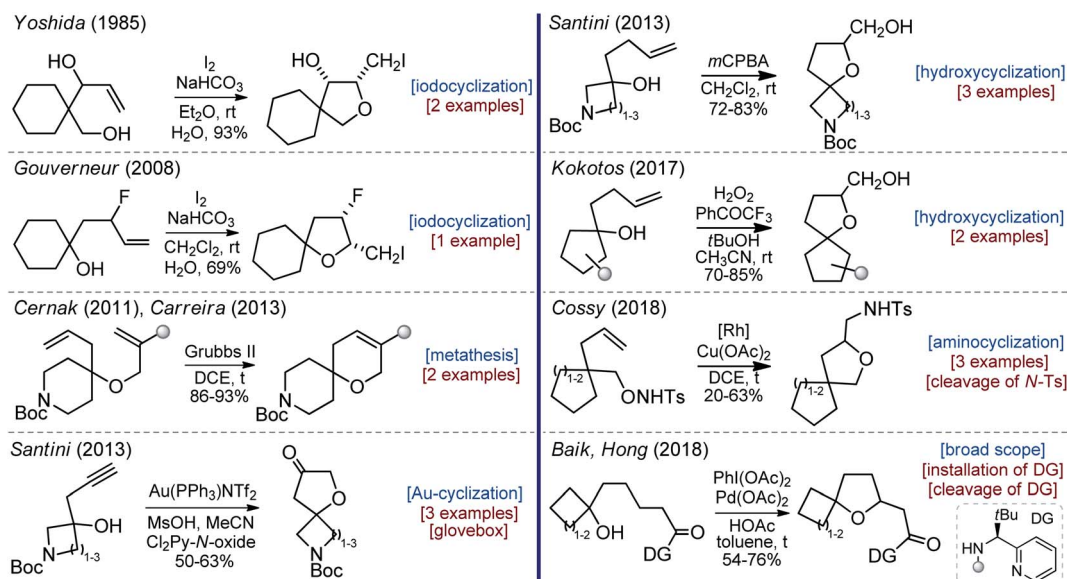
Of course, there was some interest in oxa-spirocycles before, but examples reported in the literature were rare and non-systematic.¹¹ In 1985, Yoshida synthesized two substituted oxa-spirocycles *via* iodocyclization (Scheme 1).¹² In 2008, Gouverneur studied the influence of the fluorine atom on the 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

<p><i>Previously</i>⁹</p> <p>1 $\xrightarrow[\text{rt, 78%}]{\text{I}_2, \text{NaHCO}_3, \text{tBuOMe/H}_2\text{O}}$ 2 [bridged]</p> <p><i>This work</i></p> <p>3 $\xrightarrow[\text{1h, 91%}]{\text{I}_2, \text{NaHCO}_3, \text{CH}_3\text{CN, rt}}$ 4a [oxa-spiro]</p>		
Entry	Deviations from the literature	NMR yield 4a ^{a,b} (%)
1	<i>t</i> BuOMe/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 ¹H NMR with CH₂Br₂ as an internal standard. ^c Isolated yield. NIS = *N*-iodosuccinimide, NBS = *N*-bromosuccinimide.

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



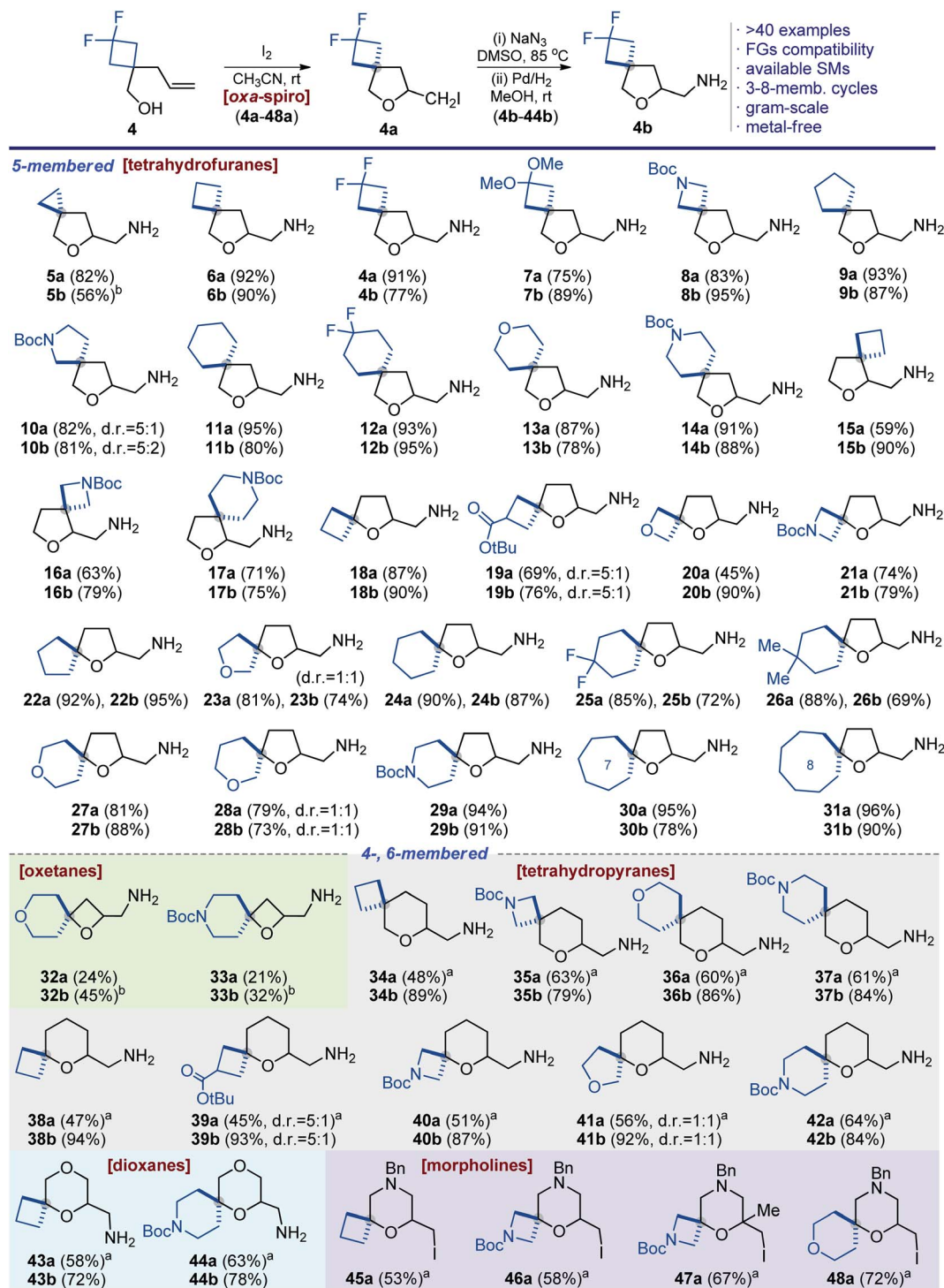
Scheme 1 Literature precedents to oxa-spirocycles.



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_3CN , rt, 1 h. ^aAlkene (1 equiv.), K_2CO_3 (4 equiv.), I_2 (4 equiv.), CH_3CN , 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_2O/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 oxaspirocycles 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 LiAlH₄) into oxaspirocyclic 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.

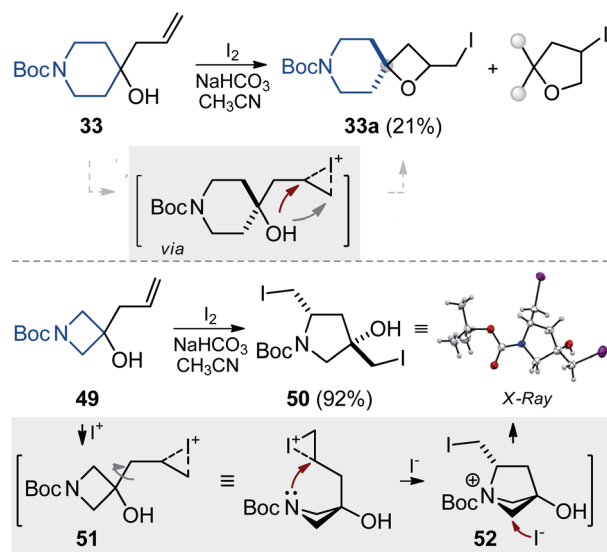
Under the previously developed conditions (Table 1, entry 1) alkene **4** indeed predominantly afforded iodide **4a**, although formation of side products was also observed. Separation of this mixture was problematic, especially on a gram scale. Performing the reaction in diethyl ether (entry 2) or dichloromethane (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

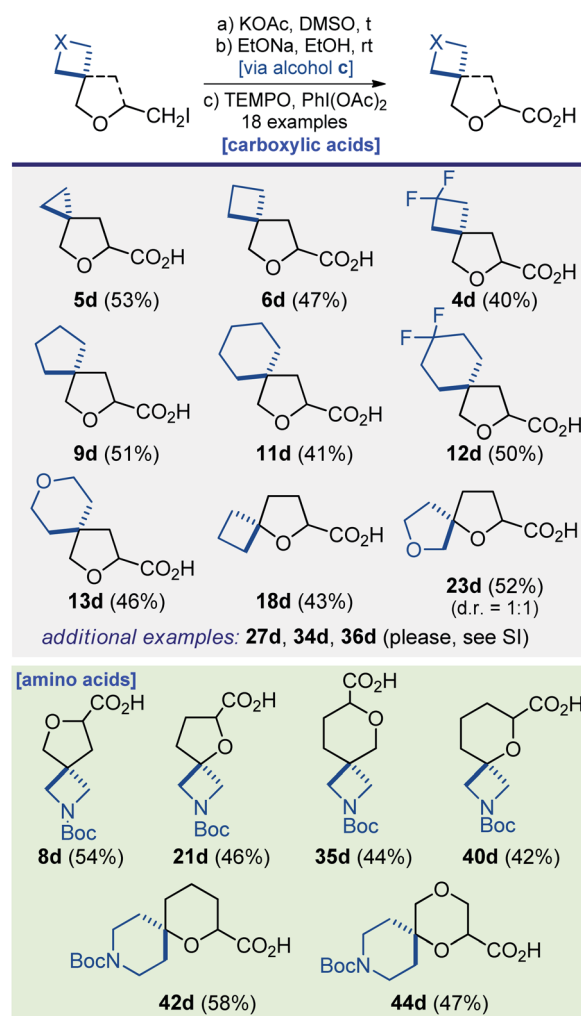
from the reaction mixture by simple distillation and no additional purification was needed.

Scope

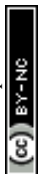
Having an optimized procedure in hand, we next studied its scope. Indeed, various five-membered oxaspirocyclic iodides **5a–31a** were easily prepared in 45–96% yield following the optimized protocol (Scheme 2). Among them were *N*-Boc-protected azetidines (**8a**, **16a**, and **21a**), pyrrolidines (**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 oxaspirocyclic cores. Importantly, the popular oxetane ring²³ 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 3 Unexpected synthesis of pyrrolidine **50**.



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



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**.

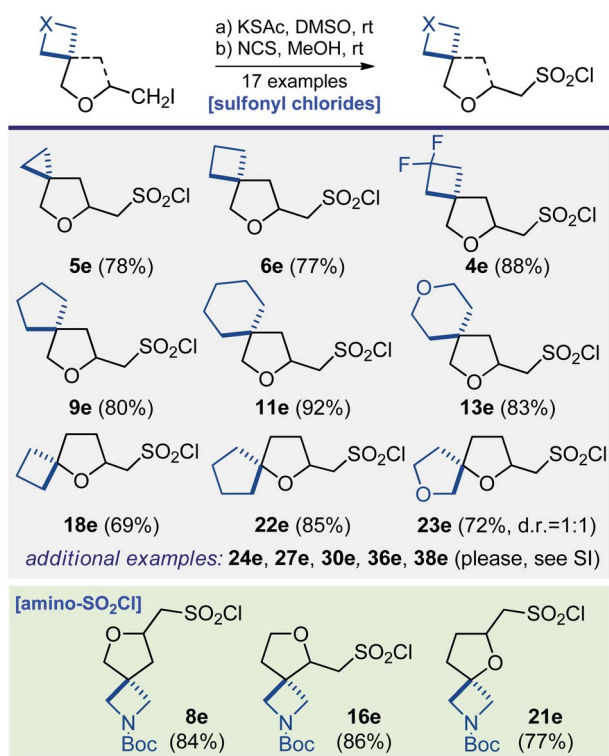
Modifications

Several representative modifications of iodides **4a–48a** were undertaken using standard chemical transformations to provide numerous oxa-spirocyclic derivatives. First, a simple

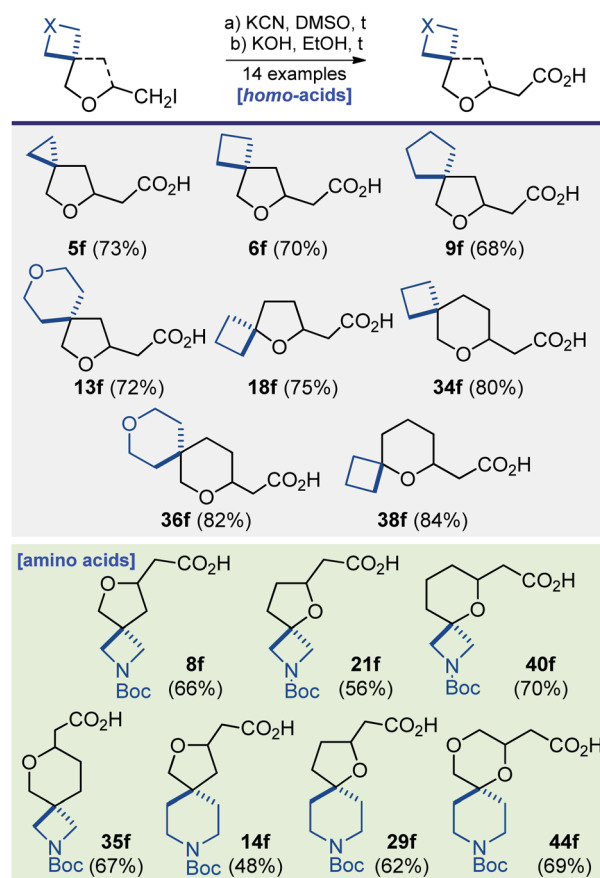
reaction of iodides **4a–44a** with sodium azide followed by reduction with either H₂/Pd or PPh₃ gave amines **4b–44b** in 32–95% yield. Among them were not only monofunctional compounds, but also linkers with two functional groups: amino acids **19b** and **39b** and valuable diamines for medicinal 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

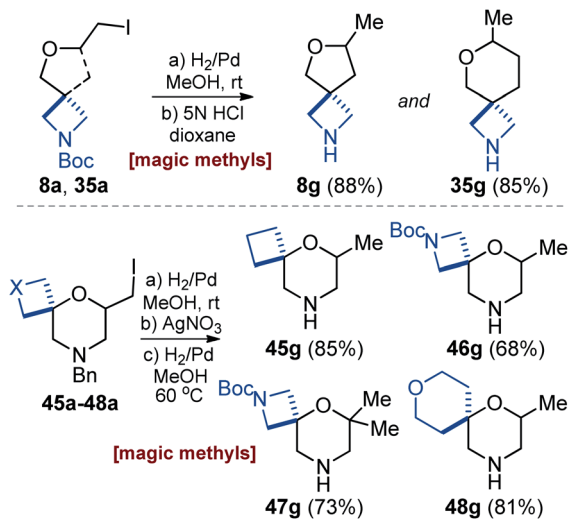
Next, synthesis of some aliphatic sulfonyl chlorides – popular reagents for making bioactive sulfonamides²⁷ – was undertaken. Reaction of iodide **16a** with potassium thioacetate in dimethylsulfoxide at room temperature, followed by a direct oxidation of the formed intermediate with *N*-chlorosuccinimide 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**.



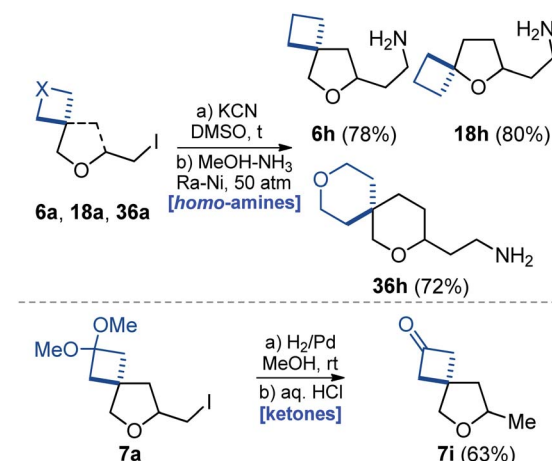
Scheme 6 Synthesis of oxa-spirocyclic homoacids **5f**, **6f**, **8f**, **9f**, **13f**, **18f**, **21f**, **29f**, **34f–36f**, **40f**, and **44f**.



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



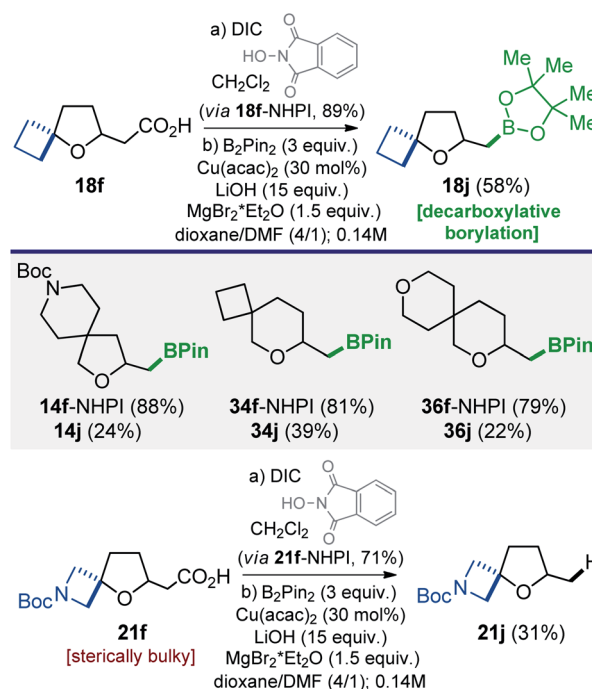
Scheme 8 Synthesis of oxa-spirocyclic homoamines **6h**, **18h**, and **36h** and ketone **7i**.

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).

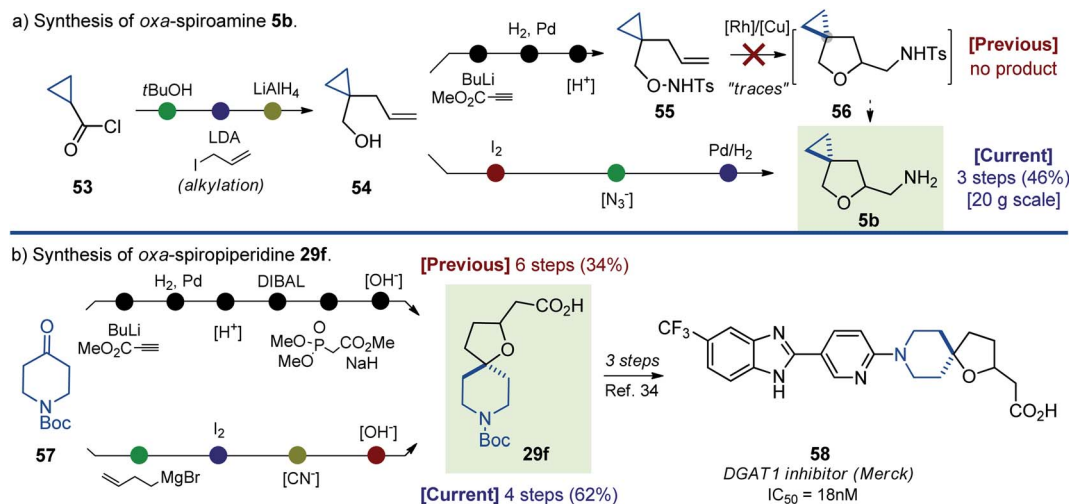
All modifications of oxa-spirocyclic iodides depicted in Schemes 4–8 represent (2e)-reactions. In this work, we also wanted to show that oxa-spirocyclic molecules are also compatible with radical (1e) modifications. Recently, Blackmond and Baran developed a practical [Cu]-catalyzed decarboxylative borylation 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 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).

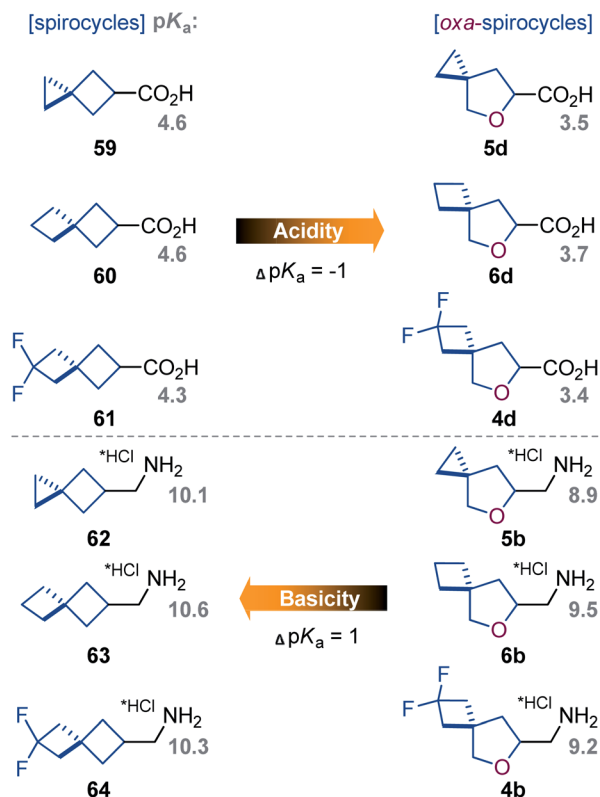


Fig. 3 Experimental pK_a values of acids 59–61 and 4d–6d, and conjugated amines 62·HCl–64·HCl and 4b·HCl–6b·HCl.

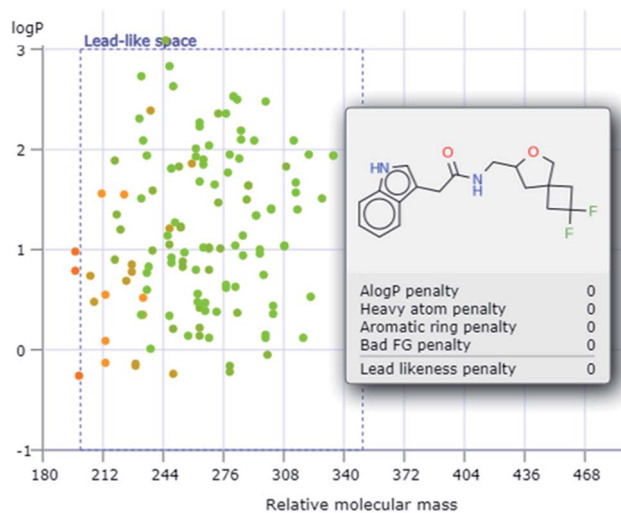
Table 2 Experimental lipophilicity (log *D*) and water solubility of model compounds 65–73

Model compound	Log <i>D</i> (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).

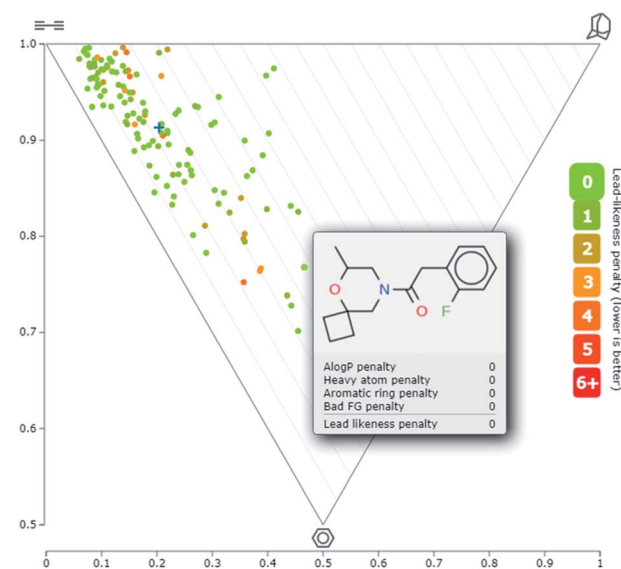
Lipophilicity (log *D*_{7.4}). Incorporation of an oxygen atom into the spirocyclic unit also decreased lipophilicity. The lipophilicity index (log *D*) of oxa-spirocyclic models 67, 70, and 73 was *ca.* one order of magnitude lower than that of spirocyclic

**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 – tetrahydrofuran

**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 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

Incorporation into a bioactive compound. After elaboration of a general method to oxa-spirocycles and their physico-chemical 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)

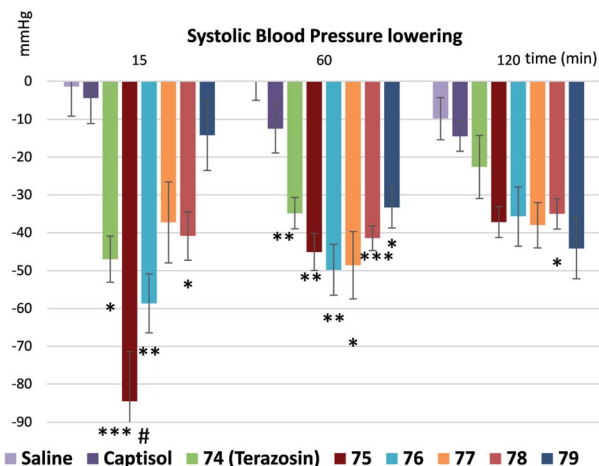


Fig. 7 The dynamics of systolic blood pressure in SHR rats at different time-points after single PO administration of vehicle (saline or 20% Captisol) or test substances at a dose of 3 mg kg⁻¹. Compounds were dissolved in saline (**74** and **76–79**) or 20% Captisol in water (**75**). Data are expressed as means \pm 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.

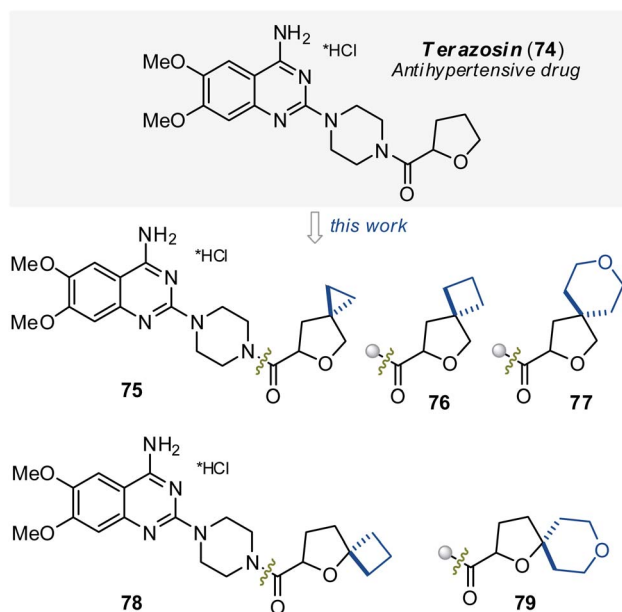


Fig. 6 Antihypertensive drug terazosin (**74**) and oxa-spiro-substituted analogues **75**, **76**, **77**, **78**, and **79**.

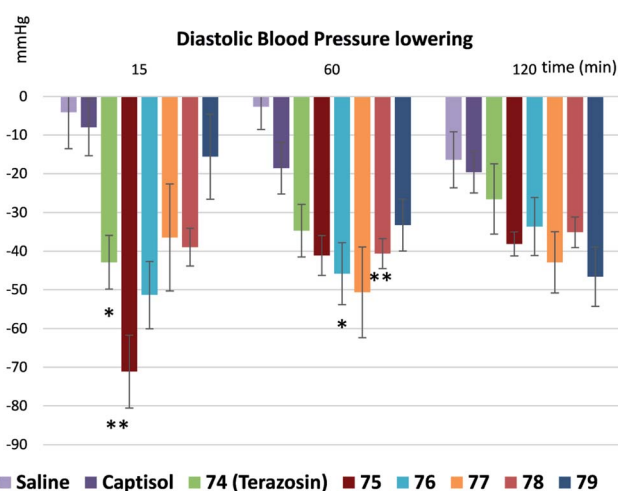


Fig. 8 The dynamics of diastolic blood pressure in SHR rats at different time-points after single PO administration of vehicle (20% Captisol) or test substances at a dose of 3 mg kg⁻¹. Compounds were dissolved in saline (**74** and **76–79**) or 20% Captisol in water (**75**). Data are expressed as means \pm 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.

Acknowledgements

The authors are grateful to Enamine Ltd for financial support. The authors are also grateful to Mr A. Zhemera and Dr D. Panov for the synthesis of model compounds **65–73**. PM is grateful to Mrs I. Sadkova for the help with the preparation of the manuscript, and to Dr E. Rusanov (IOC) for X-ray analysis of compound **50**. A part of this project has received funding from the European Research Council (ERC) under the European Union's Horizon 2020 research and innovation program (grant agreement No. 101000893 – BENOVELTY).

Notes and references

- (a) A. R. D. Taylor, M. Maccoss and A. D. G. Lawson, *J. Med. Chem.*, 2014, **57**, 5845–5859; (b) E. Vitaku, D. T. Smith and J. T. Njardarson, *J. Med. Chem.*, 2014, **57**, 10257–10274.
- (a) F. Lovering, J. Bikker and C. Humblet, *J. Med. Chem.*, 2009, **52**, 6752–6756; (b) F. Lovering, *RSC Med. Chem.*, 2013, **4**, 515–519.
- For recent interesting examples on building 3D-shaped molecules, see: (a) M. S. Oderinde, E. Mao, A. Ramirez, J. Pawluczyk, C. Jorge, L. A. M. Cornelius, J. Kempson, M. Vetrichelvan, M. Pitchai, A. Gupta, A. Kumar Gupta, N. A. Meanwell, A. Mathur and T. G. M. Dhar, *J. Am. Chem. Soc.*, 2020, **142**(6), 3094–3103; (b) A. Denisenko, P. Garbuz, S. Shishkina, N. M. Voloshchuk and P. Mykhailiuk, *Angew. Chem., Int. Ed.*, 2020, **59**, 20515–20521; (c) T.-G. Chen, L. M. Barton, Y. Lin, J. Tsien, D. Kossler, I. Bastida, S. Asai, C. Bi, J. S. Chen, M. Shan, H. Fang, F. G. Fang, H.-W. Choi, L. Hawkins, T. Qin and P. S. Baran, *Nature*, 2018, **560**, 350–354; (d) B. A. Chalmers, H. Xing, S. Houston, C. Clark, S. Ghassabian, A. Kuo, B. Cao, A. Reitsma, C.-E. P. Murray, J. E. Stok, G. M. Boyle, C. J. Pierce, S. W. Littler, D. A. Winkler, P. V. Bernhardt, C. Pasay, J. J. De Voss, J. McCarthy, P. G. Parsons, G. H. Walter, M. T. Smith, H. M. Cooper, S. K. Nilsson, J. Tsanaktisidis, G. P. Savage and C. M. Williams, *Angew. Chem., Int. Ed.*, 2016, **55**, 3580–3585; (e) R. Gianatassio, J. M. Lopchuk, J. Wang, C.-M. Pan, L. R. Malins, L. Prieto, T. A. Brandt, M. R. Collins, G. M. Gallego, N. W. Sach, J. E. Spangler, H. Zhu, J. Zhu and P. S. Baran, *Science*, 2016, **351**, 241–246; (f) D. F. J. Caputo, C. Arroniz, A. B. Dürr, J. J. Mousseau, A. F. Stepan, S. J. Mansfield and E. A. Anderson, *Chem. Sci.*, 2018, **9**, 5295–5300; (g) M. L. J. Wong, J. J. Mousseau, S. J. Mansfield and E. A. Anderson, *Org. Lett.*, 2019, **21**, 2408–2411; (h) J. Nugent, C. Arroniz, B. R. Shire, A. J. Sterling, H. D. Pickford, M. L. J. Wong, S. J. Mansfield, D. F. J. Caputo, B. Owen, J. J. Mousseau, F. Duarte and E. A. Anderson, *ACS Catal.*, 2019, **9**, 9568–9574; (i) J. Nugent, B. R. Shire, D. F. J. Caputo, H. D. Pickford, F. Nightingale, I. T. T. Houlsby, J. J. Mousseau and E. A. Anderson, *Angew. Chem., Int. Ed.*, 2020, **59**, 11866–



- 11870; (j) J. M. Lopchuk, K. Fjelbye, Y. Kawamata, L. R. Malins, C.-M. Pan, R. Gianatassio, J. Wang, L. Prieto, J. Bradow, T. A. Brandt, M. R. Collins, J. Elleraas, J. Ewanicki, W. Farrell, O. O. Fadeyi, G. M. Gallego, J. J. Mousseau, R. Oliver, N. W. Sach, J. K. Smith, J. E. Spangler, H. Zhu, J. Zhu and P. S. Baran, *J. Am. Chem. Soc.*, 2017, **139**, 3209–3226; (k) X. Ma, D. L. Sloman, Y. Han and D. J. Bennett, *Org. Lett.*, 2019, **21**, 7199–7203; (l) J.-X. Zhao, Y. Chang, J. Elleraas, T. P. Montgomery, J. E. Spangler, S. K. Nair, M. D. Bel, G. M. Gallego, J. J. Mousseau, M. A. Perry, M. R. Collins, J. C. Vantourout and P. S. Baran, 1,2-Difunctionalized Bicyclo[1.1.1]pentanes: Long Sought After Mimetics for ortho/meta-Substituted Arenes, *Proc. Natl. Acad. Sci. U. S. A.*, 2021, **118**, e2108881118; (m) A. R. Gomez-Angel, J. R. Donald, J. D. Firth, C. De Fusco, R. I. Storer, D. J. Cox and P. O'Brien, *Tetrahedron*, 2021, **83**, 131961; (n) T. D. Downes, S. P. Jones, H. F. Klein, M. C. Wheldon, M. Atobe, P. S. Bond, J. D. Firth, N. S. Chan, L. Waddelove, R. E. Hubbard, D. C. Blakemore, C. De Fusco, S. D. Roughley, L. R. Vidler, M. A. Whatton, A. J. A. Woolford, G. L. Wrigley and P. O'Brien, *Chem.-Eur. J.*, 2020, **26**, 8969–8975; (o) S. Rice, D. J. Cox, S. P. Marsden and A. Nelson, *Chem. Commun.*, 2021, **57**, 599–602; (p) S. Rice, D. J. Cox, S. P. Marsden and A. Nelson, *Tetrahedron*, 2019, **75**, 130513; (q) A. F. Trindade, E. L. Faulkner, A. G. Leach, A. Nelson and S. P. Marsden, *Chem. Commun.*, 2020, **56**, 8802–8805; (r) T. A. King, H. L. Stewart, K. T. Mortensen, A. J. P. North, H. F. Sore and D. R. Spring, *Eur. J. Org. Chem.*, 2019, **2019**, 5219–5229; (s) T. J. Osberger, S. L. Kidd, T. A. King and D. R. Spring, *Chem. Commun.*, 2020, **56**, 7423–7426; (t) A. Svecizer, A. J. P. North, N. Mateu, S. L. Kidd, H. F. Sore and D. R. Spring, *Org. Lett.*, 2019, **21**, 4600–4604; (u) F. E. Held, A. A. Guryev, T. Fröhlich, F. Hampel, A. Kahnt, C. Hutterer, M. Steingruber, H. Bahsi, C. von Bojničić-Kninski, D. S. Mattes, T. C. Foertsch, A. Nesterov-Mueller, M. Marschall and S. B. Tsogoeva, *Nat. Commun.*, 2017, **8**, 15071; (v) F. E. Held, A. A. Guryev, T. Fröhlich, F. Hampel, A. Kahnt, C. Hutterer, M. Steingruber, H. Bahsi, C. von Bojničić-Kninski, D. S. Mattes, T. C. Foertsch, A. Nesterov-Mueller, M. Marschall and S. B. Tsogoeva, *Nat. Commun.*, 2017, **8**, 15071.
- 4 (a) F. W. Goldberg, J. G. Kettle, T. Kogej, M. W. D. Perry and N. P. Tomkinson, *Drug Discovery Today*, 2015, **20**, 11–17; (b) P. K. Mykhailiuk, *Org. Biomol. Chem.*, 2019, **17**, 2839–2849; (c) G. M. Locke, S. S. R. Bernhard and M. O. Senge, *Chem.-Eur. J.*, 2019, **25**, 4590–4647.
- 5 J. A. Burkhard, B. Wagner, H. Fischer, F. Schuler, K. Müller and E. M. Carreira, *Angew. Chem., Int. Ed.*, 2010, **49**, 3524–3527.
- 6 For recent examples, see: (a) M. Espinosa, H. Noda and M. Shibasaki, *Org. Lett.*, 2019, **21**, 9296–9299; (b) N. J. Floden, N. J. Flodén, A. Trowbridge, D. Willcox, S. M. Walton, Y. Kim and M. J. Gaunt, *J. Am. Chem. Soc.*, 2019, **141**, 8426–8430; (c) W.-Y. Siau and J. W. Bode, *J. Am. Chem. Soc.*, 2014, **136**, 17726–17729; (d) G. Müller, T. Berkenbosch, J. C. J. Benningshof, D. Stumpfe and J. Bajorath, *Chem.-Eur. J.*, 2017, **23**, 703–710; (e) A. Svecizer, A. J. P. North, N. Mateu, S. L. Kidd, H. F. Sore and D. R. Spring, *Org. Lett.*, 2019, **21**, 4600–4604.
- 7 Our contribution to the field: (a) A. A. Kirichok, I. Shton, M. Kliachyna, I. Pishel and P. K. Mykhailiuk, *Angew. Chem., Int. Ed.*, 2017, **56**, 8865–8869; (b) A. A. Kirichok, I. O. Shton, I. M. Pishel, S. A. Zozulya, P. O. Borysko, V. Kubyshev, O. A. Zaporozhets, A. A. Tolmachev and P. K. Mykhailiuk, *Chem.-Eur. J.*, 2018, **24**, 5444–5449; (c) B. A. Chalyk, A. A. Isakov, M. V. Butko, K. V. Hrebenuik, O. V. Savych, O. V. Kucher, K. S. Gavrilenko, T. V. Druzhchenko, V. S. Yarmolchuk, S. Zozulya and P. K. Mykhailiuk, *Eur. J. Org. Chem.*, 2017, **2017**, 4530–4542; (d) B. Chalyk, M. Butko, O. Yanshyna, K. Gavrilenko, T. Druzhchenko and P. K. Mykhailiuk, *Chem.-Eur. J.*, 2017, **23**, 16782–16786; (e) K. Fominova, T. Diachuk, I. V. Sadkova and P. K. Mykhailiuk, *Eur. J. Org. Chem.*, 2019, **2019**, 3553–3559.
- 8 Recent reviews: (a) K. Undheim, *Synthesis*, 2015, **47**, 2497–2522; (b) E. M. Carreira and T. C. Fessard, *Chem. Rev.*, 2014, **114**, 8257–8322; (c) Y. Zheng, C. M. Tice and S. B. Singh, *Bioorg. Med. Chem. Lett.*, 2014, **24**, 3673–3682.
- 9 V. V. Levterov, Y. Panasyuk, V. O. Pivnytska and P. K. Mykhailiuk, *Angew. Chem., Int. Ed.*, 2020, **59**, 7161–7167.
- 10 Only one compound from Fig. 2 with an oxa-spirocyclic core was reported before in a peer-reviewed manuscript: S. T. Tang, Y. Liu, X. Gao, P. Wang, P. Huang and A. Lei, *J. Am. Chem. Soc.*, 2018, **140**, 6006–6013 (compound **3q**, Scheme 3).
- 11 (a) F. J. Sayago, M. Ángeles Pradera, C. Gasch and J. Fuentes, *Tetrahedron*, 2006, **62**, 915–921; (b) A. Roy, B. Achari and S. B. Mandal, *Tetrahedron Lett.*, 2006, **47**, 3875–3879; (c) Y. Nassar and O. Piva, *Org. Biomol. Chem.*, 2020, **18**, 5811–5815.
- 12 Y. Tamaru, S. Kawamura and Z. Yoshida, *Tetrahedron Lett.*, 1985, **26**, 2885–2888.
- 13 M. Tredwell, J. A. R. Luft, M. Schuler, K. Tenza, K. N. Houk and V. Gouverneur, *Angew. Chem., Int. Ed.*, 2008, **47**, 357–360.
- 14 T. Cernak, K. Dykstra, D. Levorse, A. Verras, J. Balkovec, R. Nargund and R. DeVita, *Tetrahedron Lett.*, 2011, **52**, 6457–6459.
- 15 D. B. Li, M. Rogers-Evans and E. M. Carreira, *Org. Lett.*, 2013, **15**, 4766–4769.
- 16 T. O. Painter, J. R. Bunn, F. J. Schoenen, J. T. Douglas, V. W. Day and C. Santini, *J. Org. Chem.*, 2013, **78**, 3720–3730.
- 17 S. Kumar, P. D. Thornton, T. O. Painter, P. Jain, J. Downard, J. T. Douglas and C. Santini, *J. Org. Chem.*, 2013, **78**, 6529–6539.
- 18 A. Theodorou and C. G. Kokotos, *Green Chem.*, 2017, **19**, 670–674.
- 19 J. Escudero, V. Bellosta and J. Cossy, *Angew. Chem., Int. Ed.*, 2018, **57**, 574–578.
- 20 Y. Kim, S. T. Kim, D. Kang, T. I. Sohn, E. Jang, M. H. Baik and S. Hong, *Chem. Sci.*, 2018, **9**, 1473–1480.
- 21 J. T. Kohrt, P. H. Dorff, M. Burns, C. Lee, S. V. O'Neil, R. J. Maguire, R. Kumar, M. Wagenaar, L. Price and



- M. S. Lall, *Org. Process Res. Dev.*, 2021, DOI: 10.1021/acs.oprd.1c00075, asap.
- 22 T. Gaich and P. S. Baran, *J. Org. Chem.*, 2010, **75**, 4657–4673.
- 23 J. A. Bull, R. A. Croft, O. A. Davis, R. Doran and K. F. Morgan, *Chem. Rev.*, 2016, **116**, 12150–12233.
- 24 For similar types of expansion of azetidines into pyrrolidines, see: (a) B. Drouillat, I. V. Dorogan, M. Kletskii, O. N. Burov and F. Couty, *J. Org. Chem.*, 2016, **81**, 6677–6685; (b) J. Dolfen, E. B. Boydas, V. Van Speybroeck, S. Catak, K. Van Hecke and M. D'hooghe, *J. Org. Chem.*, 2017, **82**, 10092–10109; (c) S. Dekeukeleire, M. D'hooghe and N. De Kimpe, *J. Org. Chem.*, 2009, **74**, 1644–1649; (d) S. Dekeukeleire, M. D'hooghe, K. W. Törnroos and N. De Kimpe, *J. Org. Chem.*, 2010, **75**, 5934–5940.
- 25 The CCDC number of compound **50** is 2046173.
- 26 M. A. T. Blaskovich, *J. Med. Chem.*, 2016, **59**, 10807–10836.
- 27 A. V. Bogolubsky, Y. S. Moroz, P. K. Mykhailiuk, S. E. Pipko, A. I. Konovets, I. V. Sadkova and A. Tolmachev, *ACS Comb. Sci.*, 2014, **16**, 192–197.
- 28 (a) E. J. Barreiro, A. E. Kümmerle and C. A. M. Fraga, *Chem. Rev.*, 2011, **111**, 5215–5246; (b) H. Schönherr and T. Cernak, *Angew. Chem., Int. Ed.*, 2013, **52**, 12256–12267.
- 29 For recent examples, see: (a) N. E. Behnke, K. Lovato, M. Yousufuddin and L. Kürti, *Angew. Chem., Int. Ed.*, 2019, **58**, 14219–14223; (b) M. R. Becker, A. D. Richardson and C. S. Schindler, *Nat. Commun.*, 2019, **10**, 5095; (c) S. Stanković, H. Goossens, S. Catak, M. Tezcan, M. Waroquier, V. Van Speybroeck, M. D'hooghe and N. De Kimpe, *J. Org. Chem.*, 2012, **77**, 3181–3190; (d) S. Kenis, M. D'hooghe, G. Verniest, T. A. D. Thi, C. P. The, T. Van Nguyen and N. De Kimpe, *J. Org. Chem.*, 2012, **77**, 5982–5992; (e) B. J. Wang and M. A. J. Duncton, *J. Org. Chem.*, 2020, **85**, 13317–13323; (f) R. Gianatassio and D. Kadish, *Org. Lett.*, 2019, **21**, 2060–2063; (g) A. Fawcett, A. Murtaza, C. H. U. Gregson and V. K. Aggarwal, *J. Am. Chem. Soc.*, 2019, **141**, 4573–4578.
- 30 A. Kumaria and R. K. Singh, *Bioorg. Chem.*, 2020, **96**, 103578.
- 31 After reduction of the C–I bond in iodides **45a–48a**, we washed the reaction mixture with aq. AgNO₃ to completely remove the iodide-anion. Otherwise, the next step – Pd-catalyzed cleavage of the N–Bn bond – could be slow.
- 32 J. Wang, M. Shang, H. Lundberg, K. S. Feu, S. J. Hecker, T. Qin, D. G. Blackmond and P. S. Baran, *ACS Catal.*, 2018, **8**, 9537–9542.
- 33 We tried three different protocols for decarboxylative borylation of redox-active ester **18f**-NHPI. Two other protocols that we tried: (a) C. Li, J. Wang, L. M. Barton, S. Yu, M. Tian, D. S. Peters, M. Kumar, A. W. Yu, K. A. Johnson, A. K. Chatterjee, M. Yan and P. S. Baran, *Science*, 2017, **356**, 6342; (b) A. Fawcett, J. Pradeilles, Y. Wang, T. Mutsuga, E. L. Myers and V. K. Aggarwal, *Science*, 2017, **357**, 283–286. [Ni]- and [B₂Cat₂]-protocols did not provide the needed product, while the [Cu]-protocol (ref. 32) gave the needed BPin derivative **18j** on a ca. 500 mg scale in 58% yield.
- 34 T. Cernak, N. J. Gesmundo, K. Dykstra, Y. Yu, Z. Wu, Z. C. Shi, P. Vachal, D. Sperbeck, S. He, B. A. Murphy, L. Sonatore, S. Williams, M. Madeira, A. Verras, M. Reiter, C. H. Lee, J. Cuff, E. C. Sherer, J. Kuethe, S. Goble, N. Perrotto, S. Pinto, D. M. Shen, R. Nargund, J. Balkovec, R. J. DeVita and S. D. Dreher, *J. Med. Chem.*, 2017, **60**, 3594–3605.
- 35 O. Dirat, J. M. Elliott, I. T. Huscroft, R. A. Jelley, J. J. Kulagowski, P. A. Raubo, D. E. Shaw, F. Sternfeld, C. J. Swain. WO 2004/078750 A1, 2004.
- 36 M. Morgenthaler, E. Schweizer, A. Hoffmann-Roeder, F. Benini, R. E. Martin, G. Jaeschke, B. Wagner, H. Fischer, S. Bendels, D. Zimmerli, J. Schneider, F. Diederich, M. Kansy and K. Muller, *ChemMedChem*, 2007, **2**, 1100–1115.
- 37 I. Colomer, C. J. Empson, P. Craven, Z. Owen, R. G. Doveston, I. Churcher, S. P. Marsden and A. Nelson, *Chem. Commun.*, 2016, **52**, 7209–7212.
- 38 J. J. Irwin, T. Sterling, M. M. Mysinger, E. S. Bolstad and R. G. Coleman, *J. Chem. Inf. Model.*, 2012, **52**, 1757–1768.
- 39 <https://clincalc.com/DrugStats/Top300Drugs.aspx>.
- 40 <https://clincalc.com/DrugStats/Drugs/Terazosin>.
- 41 The study design, animal selection, handling and treatment were in accordance with Bienta's Animal Care and Use Guidelines, and European Union directive 2010/63/EU.
- 42 Blood pressure (BP) was measured by a tail-cuff method. We used a Coda non-invasive blood-pressure system (Kent Scientific Corporation, CT, USA).

