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Design and Synthesis of Fsp^3-Rich, Bis-Spirocyclic-Based Compound Libraries for Biological Screening

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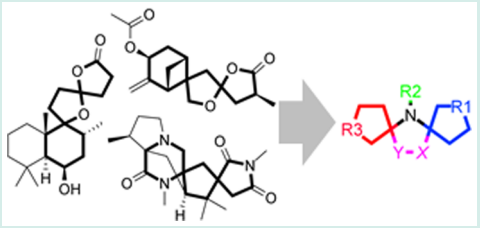
Supporting Information

ABSTRACT: The exploration of innovative chemical space is a critical step in the early phases of drug discovery. Bis-spirocyclic frameworks occur in natural products and other biologically relevant metabolites and show attractive features, such as molecular compactness, structural complexity, and three-dimensional character. A concise approach to the synthesis of bis-spirocyclic-based compound libraries starting from readily available commercial reagents and robust chemical transformations has been developed. A number of novel bis-spirocyclic scaffold examples, as implemented in the European Lead Factory project, is presented.



KEYWORDS: *spirocyclic, spirocenter, compound library design, compound library synthesis, European Lead Factory*

INTRODUCTION

Biologically relevant chemical space represents an ideal starting point for the identification of bioactive compounds to investigate pathophysiological processes and seed drug discovery programs. Biology-oriented synthesis[1,2] is one of the most straightforward strategies for the design of novel, bioactive compound libraries to be used in biological screening campaigns. Here, by focusing on the chemical scaffolds and structural features of known natural products, synthetic procedures are devised to afford natural product-like compounds through the introduction of appropriate diversification elements.[3,4] A peculiar feature of many natural products, when compared to standard small molecules, is their enhanced structural complexity, high degree of saturation and chirality content,[5] which then results in a significant preference for binding and selectivity to proteins,[6] improved physicochemical properties and is generally perceived as having a positive impact on compound developability.[7,8] Natural products' structural complexity often originates from the presence of spirocyclic elements, where rings are connected through a single atom (i.e., the spiroatom). Here, the spiroatom is normally a quaternary carbon, thus offering the potential for chirality when the two rings differ in their size, atomic composition or substitution. Several natural products display bis-spirocyclic elements where two or more spiroatoms are forming three or more connected rings, showing a wide spectrum of biological activities. Because of their inherent structural complexity and novelty contributions, it is not surprising that spirocyclic elements are finding more frequent applications in medicinal chemistry.[9] These include for example derivatives of plant origin from the labdane terpenoid family (e.g., leolorin C[10]) or isoquinoline alkaloids (e.g., roemeridine[11]), marine toxins of the cyclic imine group (e.g., 13-desmethyl spirolide C[12,13]), or aza group (e.g., azaspiracid 1[14−16]), soil fungi's metabolites with sesquiterpene (e.g., expansolide A[17,18]) or alkaloid (e.g., asperparaline A[19−21]) skeletons, as shown in Figure 1a. As part of the European Lead Factory (ELF) efforts to populate innovative chemical space for high throughput screening (HTS) and drug discovery activities,[22−25] we focused our attention on bis-spirocyclic frameworks as structural complexity multipliers for small molecule compound libraries and our approach is herein described.

RESULTS AND DISCUSSION

Overall Concept and Library Design. The majority of naturally occurring bis-spirocycles are spiroketals originating from biosynthetic sequences involving dehydration of the corresponding diols, followed by elimination or lactonization steps. Examples of bis-spirocycles containing hemiaminal ethers, lactams and amines also exist but these are typically parts of more extended fused and bridged frameworks. This mainly results in bis-spirocyclic scaffolds displaying a central tetrahydrofuran ring bearing a 1,3 spiroatomic pattern (Figure 1a). We thus decided to focus on the exploration of general bis-spirocyclic frameworks with spiroatoms in a 1,3 arrangement and opportunities for at least three diversity vectors, as shown in Figure 1b. Here, a five-membered central ring bearing at least one nitrogen atom was preferred to (a) afford novel nitrogen-containing bis-spirocyclic when compared to oxygen-containing natural products, (b) facilitate ring formation via conformational and preorganization effects mediated by the five-membered ring in contrast to less strained six- and seven-membered ring alternatives,[26−30] and (c) offer opportunities for diversification via functionalization of the nitrogen atom. Furthermore, the size and composition of the two terminal rings, alongside any installed functional groups, would provide additional avenues for introducing diversity elements (Figure 1b). Intriguingly, a survey of the scientific

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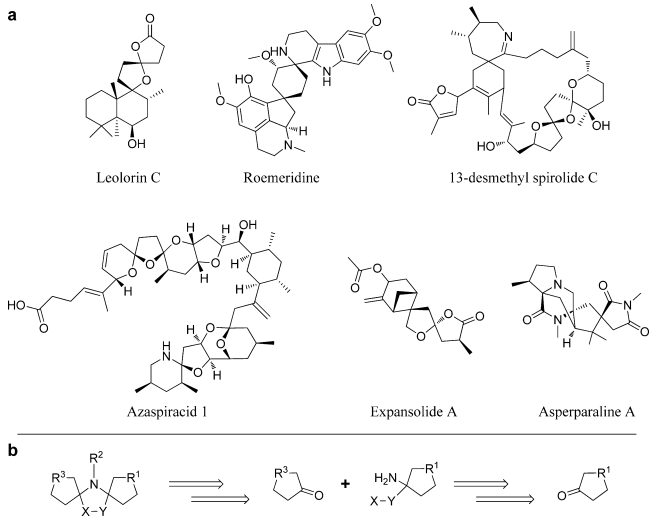


Figure 1. (a) Representative natural products that feature bis-spirocyclic elements in their structures and (b) general structure of the bis-spirocyclic frameworks addressed in the present study and associated synthetic precursors. R^1, R^2, and R^3 indicate diversification elements, while X and Y represent further sites of heteroatomic diversity.

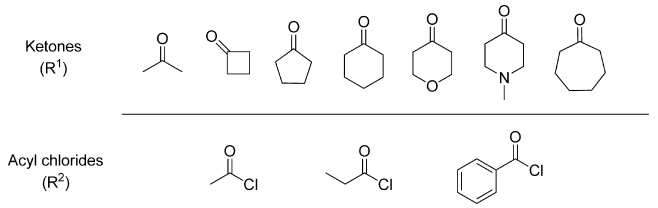
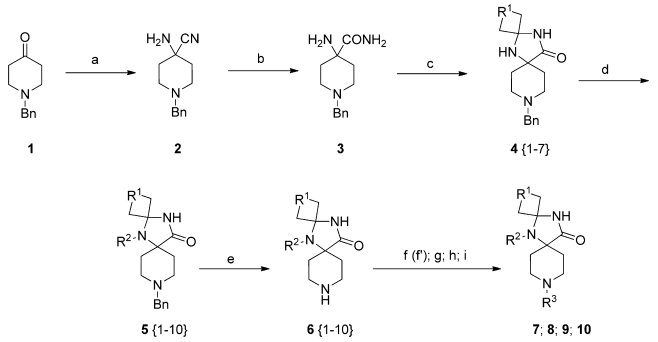


Figure 2. Ketones (R^1) and acyl chlorides (R^2) used as diversification elements in the synthesis of the two libraries.

Scheme 1. Synthesis of the Bis-Spiro-Imidazolinone Library[a]



[a]Reagents and conditions: (a) NaCN (1.25 equiv), NH_4Cl (1.3 equiv), NH_4OH (aq), *i*-PrOH, rt, overnight (**2**, 99%); (b) H_2SO_4 (95−98%, 20.0 equiv), DCM, 0 °C to rt, overnight (**3**, 97%); (c) *p*-TSA (0.2 equiv), ketone (1.2−3.0 equiv), MeOH, reflux, 1−6 day(s) (**4**{*1*−*7*} 61−87%), see Table 1; (d) R^2COCl (2.5−3.0 equiv), DIPEA (4.0−6.0 equiv), DCM, 0 to 40 °C, 1−3 day(s) (**5**{*1*−*10*}, 36−59%), see Table 2; (e) H_2 (1 atm), $Pd(OH)_2/C$ (0.05 equiv), MeOH, rt, 2−6 h (**6**{*1*−*10*} 88−98%); (f) R^3COCl (1.5 equiv), Et_3N (5.0 equiv), THF, rt, overnight; (f′) R^3COOH (2.0 equiv), HOBt (2.0 equiv), EDC*HCl (2.5 equiv), DIPEA (5.0 equiv), DCM, 50 °C, overnight (**7**); (g) R^3CHO (2.0 equiv), $NaBH(AcO)_3$ (2.5 equiv), AcOH (2.0 equiv), DCE, rt, overnight (**8**); (h) R^3SO_2Cl (1.5 equiv), Et_3N (5.0 equiv), THF, rt, overnight (**9**); (i) R^3NCO (1.5 equiv), Et_3N (5.0 equiv), DCM, rt, overnight (**10**).

literature for such bis-spirocyclic substructures revealed a very limited number of examples[31−34] and no reports originating from parallel chemistry approaches, thus reaffirming the high novelty attribute of the concept.

In keeping with a combinatorial approach to the potential synthesis of several thousand compounds from different scaffolds, we envisioned the two spiroatoms to originate from a sequence of well-known, robust manipulations on two different, commercially available cyclic ketones, as indicated in Figure 2. Here, selection of symmetric cyclic ketones would eliminate the issue of separating isomers during synthesis. Additionally, the cyclic ketones could serve as common precursors in branched pathways. For instance, their carbonyl groups could be aptly transformed in diverse synthons for the preparation of several heterocyclic core systems. Lastly, by swapping the order of manipulation of the two cyclic ketones in the planned synthetic scheme, one would further generate regioisomeric scaffolds of clear practical utility during HTS triaging and structure activity relationships (SAR) exploration. To showcase this pragmatic and versatile approach, we exemplify the syntheses of imidazolinone- and oxazolidine-based bis-spirocyclic scaffolds.

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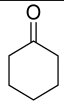
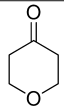
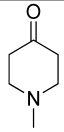
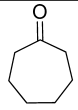
EXPERIMENTAL PROCEDURES

Bis-Spiro-Imidazolinone Library. Synthesis of the bis-spiro-imidazolinone scaffold **6** started with the cyanation of commercially available 4-*N*-benzyl piperidone using sodium cyanide under basic conditions (Scheme 1). Performing the reaction at room temperature overnight afforded the desired product (**2**) in quantitative yield. Acidic hydrolysis of the cyano group using concentrated sulfuric acid to yield **3** (97%) was followed by the key condensation step on an array of ketones, to install the first diversity element. Seven different aliphatic (i.e., linear, cyclic and heterocyclic) ketones in a 1.2−3.0 range of equivalents, in the presence of catalytic amount (0.2 equiv) of *p*-TSA, were refluxed in MeOH for 1−6 days to yield the cyclization products **4**{*1*−*7*} with moderate to good yields (61−87%, Scheme 1 and Table 1).

Table 1. Reaction Conditions for the Cyclization Step c

Entry	Product	Ketone	Ketone (eq)	Reaction time (d)	Yield (%)
1	**4**{1}		3.0	6	74
2	**4**{2}		2.4	2	61
3	**4**{3}		2.4	6	74
4	**4**{4}		1.2	5	72
5	**4**{5}		1.2	1	74
6	**4**{6}		1.2	1	87
7	**4**{7}		2.4	2	68

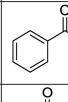
Once optimal conditions for the key condensation step were established, the potential to install a second chemical diversity vector on the imidazolinone nitrogen atoms was explored. Here, the most reactive amine nitrogen atom is severely hindered given that it is connecting two spiroatoms, and it was crucial to verify its reactivity under acylating conditions. As shown in Table 2, the least sterically encumbered imidazolinone **4**{*1*} tended to reacted better than imidazolinone **4**{*4*} to the corresponding acylated product, (cf., 56−67% (Table 2, entry 1 and 2) and 18−59% (Table 2, entry 4 and 5)) with the latter yielding no isolatable product when steric bulk at the acyl chloride increased, as in the case of benzoyl chloride (Table 2, entries 3 and 6). On the basis of these results, introduction of diversity at the central ring of the bis-spirocyclic core was anticipated to be limited to small alkyl and heteroalkyl side chains. The establishment of successful acylation conditions was nevertheless very important to minimize the intrinsic chemical instability of the aminal precursors **4**{*1*−*7*}, as shown in Figure 3.

Exploitation of the third and last diversity handle, required deprotection of the *N*-benzylated-piperidine element under catalytic hydrogenation conditions using palladium hydroxide, which afforded the desired products **6**{1−10} with high to excellent yields (88−98%). These intermediates were then further derivatized through their piperidine nitrogen atoms using combinatorial chemistry protocols for four typical diversity reactions (i.e., amide coupling (f or f′), reductive amination (g), sulfonylation (h) and urea formation (i)) to yield final products **7**−**10**. These were performed in a parallel fashion using a 24 position Mettler Toledo block equipped with 15 mL reaction tubes (Scheme 1).[25,35] As shown in Figure 4 and 5, diversity reagents were selected in order to ensure all final compounds have "lead-like" properties (i.e., calculated LogP (cLogP) ≤ 4 and Molecular Weight (MW) ≤ 400).[36−38]

Bis-Spiro-Oxazolidine Library. Synthesis of the bis-spiro-oxazolidine scaffold **18** started with the cyanation of five different aliphatic ketones (e.g., cyclic and heterocyclic, **11**{*2*−*3*,*5*−*7*}), under the same conditions detailed earlier, and the desired products **12**{*2*−*3*,*5*−*7*} were obtained with high to excellent yields (81−97%).

The cyanation step was then followed by the quantitative acidic hydrolysis of the cyano group in concentrated (37%) HCl. The carboxylic acid functions of the resulting *α*-amino acids **13**{*2*−*3*,*5*−*7*} were converted to their methyl ester (**14**{*2*−*7*}, 45−82%) and then reduced under reflux in toluene with Red-Al (70% in toluene) to afford compounds **15**{*2*−*7*} in moderate to

Table 2. Acylation Conditions for Compounds 4{*1*} and 4{*4*}

Entry	Starting Material	Acyl chloride	Acyl chloride (eq)	DIPEA (eq)	Reaction time	Temp (°C)	Product	Yield (%)
1	**4**{1}		2.5	4.0	1 day	0 →40	**5**{1}	67
2	**4**{1}		2.5	5.0	2 days	0 →40	**5**{8}	56
3	**4**{1}		3	6.0	3 days	0 →40	**5**{9}	42
4	**4**{4}		2.5	4.0	1 day	0 →40	**5**{4}	59
5	**4**{4}		2.5	5.0	2 days	0 →40	**5**{10}	18
6	**4**{4}		3	6.0	3 days	0 →40	**5**{11}	—

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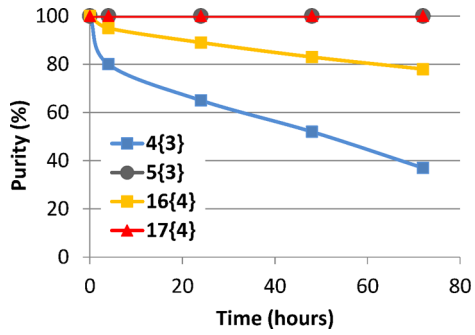

Figure 3. Sample stability profiles in acidic media (pH 2) for aminal **4**{3} and hemiaminal ether **16**{*4*} intermediates, and their acetylated counterparts, **5**{3} and **17**{*4*}, respectively.

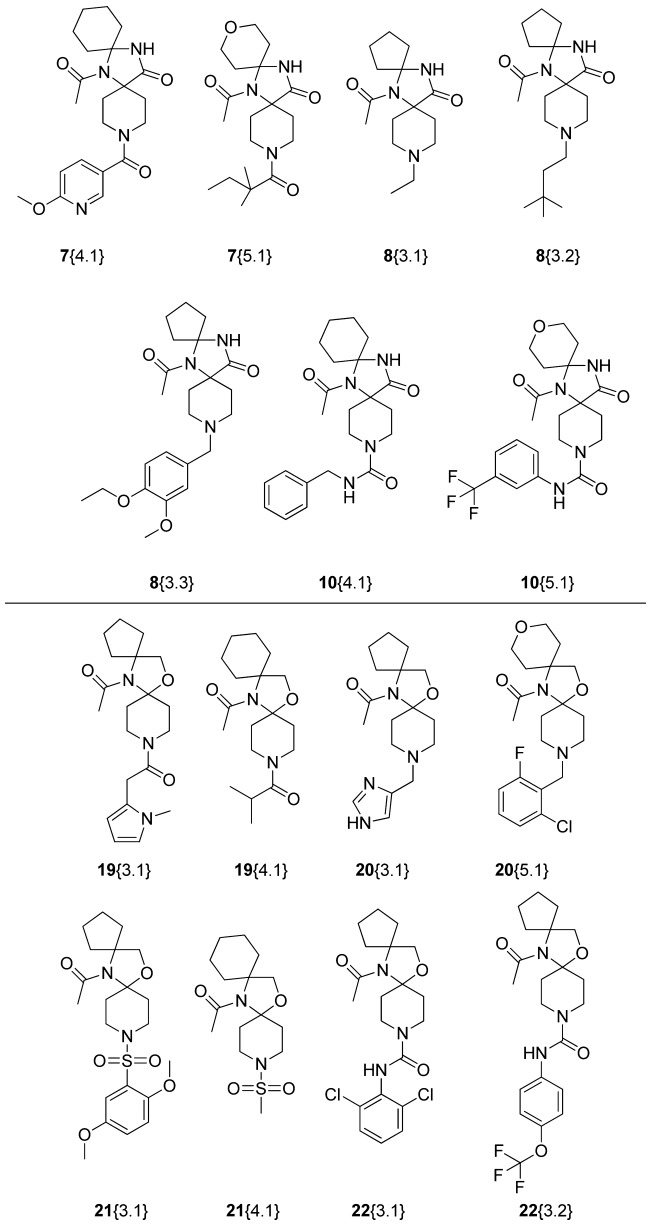

Figure 4. Representative examples of bis-spiro-imidazolinone and bis-spiro-oxazolidine compounds.

high yields (59−81%). Condensation of the six different amino alcohols **15**{2−7} insofar synthesized proceeded smoothly and in moderate yields (**16**{*1*−7}, 38−67%) using *N*-benzylpiperidone

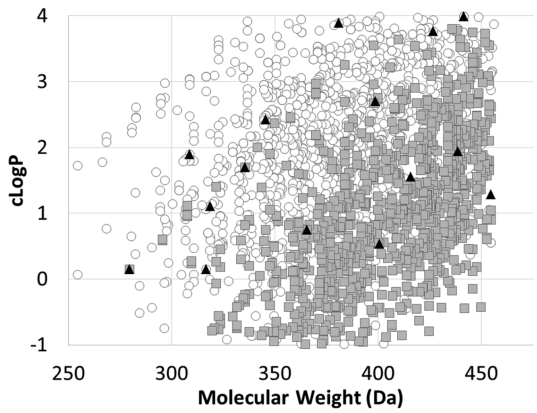

Figure 5. Physicochemical properties (calculated LogP (cLogP) and molecular weight (MW), JChem, ChemAxon 6.3.0) for the theoretical bis-spiro-imidazolinone (gray squares) and bis-spiro-oxazolidine (white circles) libraries. Selected compounds **7**{*4,1*}, **7**{*5,1*}, **8**{*3,1*}, **8**{*3,2*}, **8**{*3,3*}, **10**{*4,1*}, **10**{*5,1*}, **19**{*3,1*}, **19**{*4,1*}, **20**{*3,1*}, **20**{*5,1*}, **21**{*3,1*}, **21**{*4,1*}, **22**{*3,1*}, and **22**{*3,2*}, synthesized to validate the synthetic approach, are marked as black triangles.

in slight excess (1.1 equiv) and refluxing in MeOH for 4 h. The reactivity of the nitrogen atom of the oxazolidine central ring under acylating conditions was limited, in line with observations derived from the bis-spiro-imidazolinone scaffold **6** (d). Here, acetylation of all the cyclized intermediates **16**{*1*−7} proceeded in almost quantitative yields (96% in average) while acylation with bulkier acyl chlorides (i.e., benzoyl chloride) proved to be successful only with the less sterically hindered oxazolidine intermediates (cf., Table 3, entries 2, 4, and 6). Analogously to the aminal intermediates previously described, hemiaminal ethers **16**{*1*−7} also showed marked chemical instability, while their acylated counterparts did not suffer from such limitation, as described in Figure 3.

Catalytic hydrogenation of the acylated bis-spiro-oxazolidine intermediates afforded, in quantitative yields, the *N*-debenzylated piperidine products **18**{*1*−8} which were further derivatized in a combinatorial approach by using appropriate diversity reagents[35,39] (see Scheme 2 and Figure 4).

CONCLUSIONS

The exploration of chemical space remains one of the most critical step toward the identification of novel chemical matters for chemical biology and drug discovery applications. In this context, populating areas of chemical space that have biological relevance is of special importance. As natural products represent privileged, biologically relevant starting points for such explorations, we sought to approximate their structural complexity by focusing on their bis-spirocyclic frameworks. The bis-spirocyclic scaffolds described here demonstrate a high level of saturation and intrinsic three-dimensionality, well in line with recent hypotheses on compound desirability from a molecular properties perspective.[37,40] As they are underrepresented in the scientific literature and commercial sources, they serve an important purpose when evaluation of novel chemical space and generation of intellectual property are concerned.[41] Importantly, as they are derived from highly parallel and robust synthetic schemes using readily available starting materials and reagents, they address typical limitations of natural products such as limited synthetic tractability and cost of final products.[42−44] Furthermore, the concise synthetic schemes validated in the present study allow the introduction of diversity and variation

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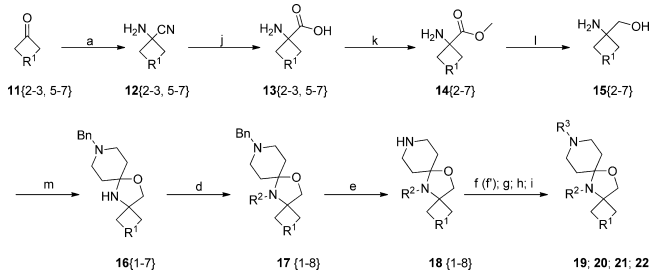
Table 3. Acylation Conditions for Compounds 16{*1*}, 16{*3*}, and 16{*4*}

Entry	Starting Material	Acyl chloride	Acyl chloride (eq)	DIPEA (eq)	Reaction time	Temperature (°C)	Product	Yield (%)
1	**16**{1}		2.5	4.0	1 day	40	**17**{1}	96
2	**16**{1}		3	6.0	3 days	40	**17**{8}	76
3	**16**{3}		2.5	4.0	1 day	40	**17**{3}	96
4	**16**{3}		3	6.0	3 days	40	**17**{9}	traces
5	**16**{4}		2.5	4.0	1 day	40	**17**{4}	99
6	**16**{4}		3	6.0	3 days	40	**17**{10}	—

Scheme 2. Synthesis of the Bis-Spiro-Oxazolidine Library[a]



[a]Reagents and conditions: (a) NaCN (1.25 equiv), NH_4Cl (1.3 equiv), NH_4OH (aq), *i*-PrOH, rt, overnight (**12**{2−3,5−7}, 81−97%); (j) HCl (37%, 20.0 equiv), 1,4-dioxane, reflux, 8 h (quantitative); (k) $SOCl_2$ (6.0 equiv), MeOH, rt, overnight (**14**{2−7}, 45−82%); (l) Red-Al (70% in toluene, 3.0 equiv), toluene, 0 to 110 °C, 2 h (**15**{2−7}, 59−81%); (m) *p*-TSA (0.2 equiv), *N*-benzylpiperidone (1.1 equiv), MeOH (dry), reflux, 4 h (**16**{*1*−7}, 38−67%); (d) R^2COCl (2.5−3.0 equiv), DIPEA (4.0−6.0 equiv), DCM, 0 to 40 °C, 1−3 days (average 96%), see Table 3; (e) H_2 (1 atm), $Pd(OH)_2/C$ (0.05 equiv), MeOH, rt, 2−6 h (quantitative), (f) R^3COCl (1.5 equiv), Et_3N (5.0 equiv), THF, rt, overnight; (f′) R^3COOH (2.0 equiv), HOBt (2.0 equiv), EDC*HCl (2.5 equiv), DIPEA (5.0 equiv), DCM, 50 °C, overnight (**19**); (g) R^3CHO (2.0 equiv), $NaBH(AcO)_3$ (2.5 equiv), AcOH (2.0 equiv), DCE, rt, overnight (**20**); (h) R^3SO_2Cl (1.5 equiv), Et_3N (5.0 equiv), THF, rt, overnight (**21**); (i) R^3NCO (1.5 equiv), Et_3N (5.0 equiv), DCM, rt, overnight (**22**).

elements at virtually every step, thus offering versatile opportunities to afford analogues and matched molecular pairs of clear value during hit evaluation and SAR exploration campaigns. The inclusion of bis-spirocyclic-based libraries in the Public Compound Collection[39] of the ELF and their exposure to >100 HTSs during the ELF project life cycle will provide an important test to evaluate their biological relevance, target class propensity and overall suitability in a drug discovery setting.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscombsci.6b00005.

General procedures and characterization data of representative compounds (PDF)

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Author Contributions

The manuscript was written through contributions of all authors.

Notes

The authors declare no competing financial interest.

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