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RESEARCH ARTICLE

A Scaffold Diversity Synthesis of Biologically Intriguing Cyclic Sulfonamides

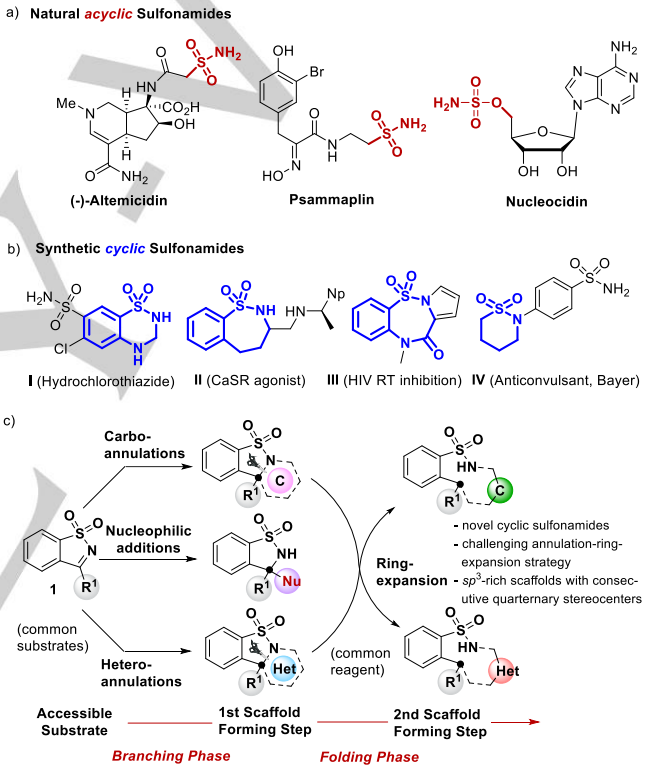
Stefan Zimmermann,[a,b] Mohammad Akbarzadeh[a], Felix Otte,[b] Carsten Strohmann,[b] Muthukumar Gomathi Sankar,[a] Slava Ziegler,[a] Axel Pahl,[a] Sonja Sievers,[a] and Kamal Kumar*[a]

Dedication ((optional))

Abstract: A branching-folding synthesis strategy is presented that affords a range of diverse cyclic benzosulfonamide scaffolds. While different annulation reactions on common ketimine substrates build the branching phase of scaffold synthesis; a common hydrogenative ring-expansion method, facilitated by ring-strain in scaffolds formed in branching phase, led to sulfonamides bearing medium-sized rings in a folding pathway. Cell painting assay was successfully employed to identify tubulin-targeting sulfonamides as novel mitotic inhibitors.

The ability of small molecules to perturb biological systems in a temporal and dose controlled-manner endows them uniqueness to reveal insights of different biological functions. Advancement of chemical biology and drug discovery demands a regular supply of novel bioactive small molecules. The unmet medical needs and limited understanding of life at molecular level urgently call to interrogate biologically intriguing yet least explored areas of chemical space to deliver small molecules as probe and drug candidates.[1] Unfortunately, organic synthesis had remained focused on a narrow range of molecular scaffolds despite the emergence of strategies such as diversity-oriented synthesis which precisely aimed to deliver a range of diverse chemotypes.[2]

Sulfonamides, cyclic and acyclic, are a well-known class of small molecules that represents a number of FDA-approved drugs and developmental candidates for a range of molecular targets and indications. Intriguingly, no natural product is yet known to embody a cyclic sulfonamide moiety. The primary sulfonamide and sulfamate groups too are rarely found in natural product structures (Scheme 1a). While introduction of a sulfonamide moiety on small molecules is relatively easy and well established,[3] development of synthetic approaches affording a range of diverse biologically relevant cyclic sulfonamides remain underexplored.[4] Here we disclose a scaffold diversity synthesis of cyclic benzosulfonamides by employing a sequential branching-folding synthesis approach and using easily accessible Saccharin-derived cyclic *N*-sulfonyl ketimines **1** as the precursors (Scheme 1c).[5] In this approach, the first branching pathway exploits different annulation and nucleophilic addition reactions on common substrates to form complex and cyclic sulfonamides with more sp^3 character and decorated with stereogenic centers. The next folding ring-expansion strategy driven by the ring-strain in the scaffolds formed in branching phase leads to medium ring-sized benzosulfonamides.



Scheme 1. a) Some natural products with acyclic sulfonamides; b) synthetic bioactive cyclic sulfonamides; c) a branching-folding synthesis planning to form diverse, complex and medium ring-sized cyclic sulfonamides.

A *branching synthesis pathway transforms a common substrate into structurally distinct scaffolds*. The plan to employ saccharin-derived ketimine **1** as the substrate for the sequential scaffold generating approach stemmed from both the reported as well as potential and unexplored reactivity of these cyclic ketimines in annulation and addition reactions. In particular, we focused on developing a range of different ring-fusions to the imine moiety *i.e.* from three-membered aziridine to a six-membered piperidine ring. This would offer possibilities for a subsequent and more challenging *folding pathway* wherein *common reaction conditions may induce ring-expansion of different scaffolds* formed in the first branching phase and delivering another set of cyclic sulfonamides (Scheme 1c).

In our first reaction design in branching phase, we planned to make annulation reactions with imine moiety of common

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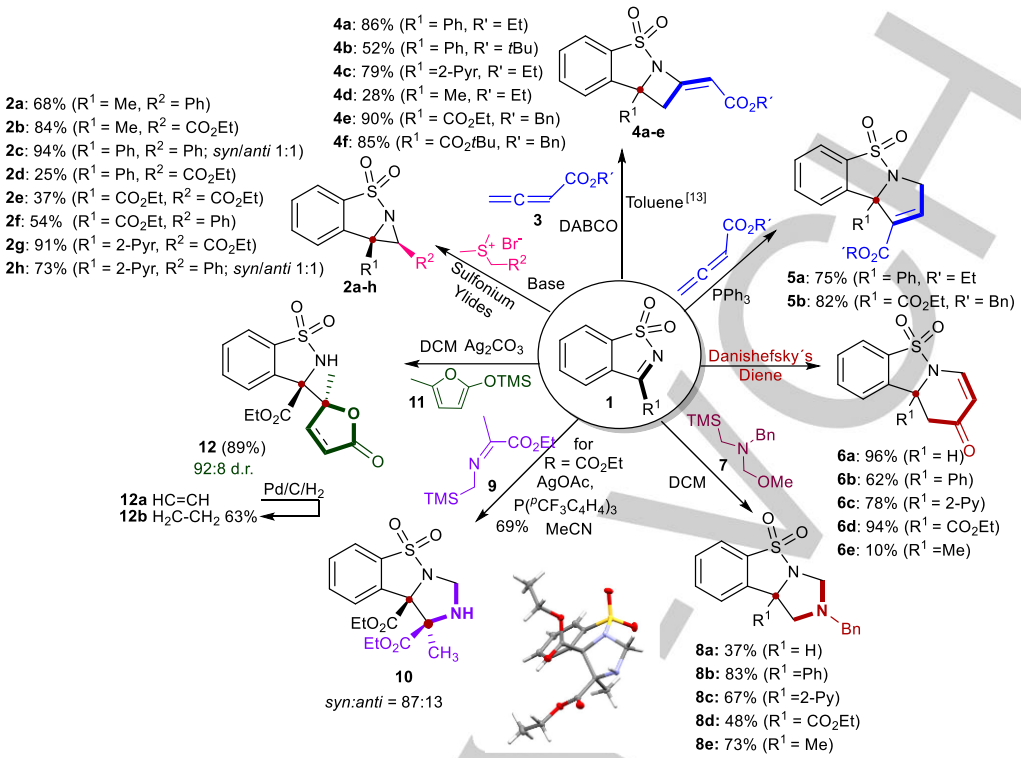

Scheme 2. A branching pathway to cyclic sulfonamides *via* annulation and addition reactions of *N*-sulfonyl ketimines.

substrate **1** employing 1- to 4-carbon annulation partners to afford three to six-membered aza-heterocycle fused sulfonamides. To this end, the first scaffold target was the smallest stable aza-ring system *i.e.* aziridines.[6] Among different possible synthetic strategies to aziridines,[7] the carbenium transfer approach *via* sulfonium ylides was employed affording different aziridine-fused sulfonamides (**2a-h**) with two diversity sites in acceptable to good yields (Scheme 2). Intriguingly, reactions of sulfonium ylides with *N*-sulfonyl-aldimine **1-H** (R^1 = H) did not afford the corresponding aziridines. Except for **2c** and **2h** that bear two neighbouring aryl groups, and formed in equimolar ratio of *syn*- and *anti*- isomers in high yields, aziridines were formed mostly as single *syn*-diastereomers (**2b**, **2d-g**) or as major isomer (**2a**, d.r. 7:1). However, for ketimines with carboethoxy moiety, in particular, **2e-2f**, formation of uncharacterizable by-products (low molecular weight) was observed that led to lower yields of desired products (Scheme 2).

Towards 4- and 5-membered ring-fused benzosulfonamides, Ye and co-workers´ approach[8] of nucleophilic base-catalyzed annulation reactions was exploited. Thus, zwitterionic intermediate formed by addition of DABCO (cat.) and allenoates (**3**) added regioselectively from terminal position of allene to effectively result in a [2+2]-annulation and formed benzosultam-fused (*E*)-azetidines (**4a-f**). We observed that a reduced electrophilicity of imine moiety in **1** (R^1 = Me) negatively influenced the reaction progression and product yield for **4d**. Interestingly, aldimine **1-H** did not react with allene-derived zwitterions at all. Furthermore, five-membered pyrroline based benzosulfonamides were easily synthesized employing triphenylphosphine instead of DABCO as nucleophilic catalyst in the above methodology affording **5a** and **5b** in high yields (Scheme 2). The latter features two orthogonal esters for further selective functional group transformations.

Towards six-membered ring-fused benzosulfonamides, we resorted to the Diels-Alder reaction.[9] After some reaction conditions optimization, reaction of **1** with Danishefsky's diene under microwave irradiation in toluene furnished 1,4-dihydro--pyridones **6a-d** in good to excellent yields (Scheme 2). However, under the optimized microwave heating condition, reaction of relatively electron-rich ketimine **1-Me**, could afford only low yield of adduct **6e**.[10]

In order to introduce more heteroatoms as well as quaternary centers in more diverse and complex benzo-sulfonamides, we employed two different azomethine ylides derived from **7**[11] and α-silyl imines **9** with ketimines **1** in dipolar annulation reactions and yielding imidazolidine based benzosulfonamides **8a-e** and **10** in moderate to high yields (37-83%).[12] Interestingly, reactions of **7** derived dipole performed better with aryl or alkyl ketimine **1** than with aldimine (**1**, R^1 = H) or iminoester (**1**, R^1 = CO_2Et, Scheme 2). Notably, α-silyl imines (**9**) have only rarely been explored in cycloaddition chemistry and are interesting substrates for generating small molecules embodying quaternary centers and thereby complex stereochemical frameworks.[13] Another reaction screening revealed that catalytic AgOAc and phosphine complex in acetonitrile could transform **1-CO_2Et** with **9** into *syn*-imidazolidine **10** (d.r. = 87:13) as major adduct that bear two consecutive quaternary stereocenters (Table S1 in Supporting information).

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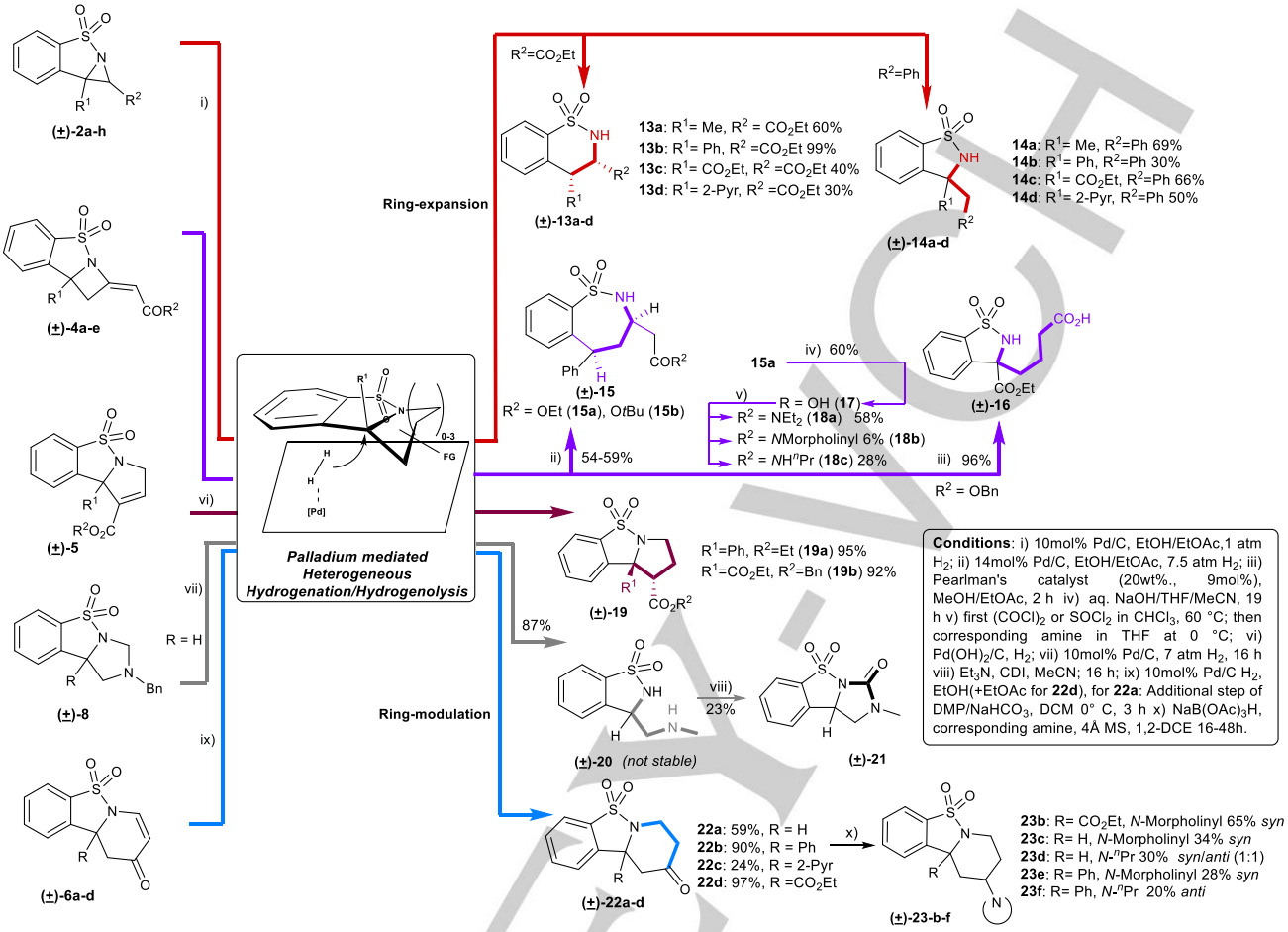

Scheme 3. A ring-expansion and -modulation reactions via palladium mediated heterogeneous hydrogenation/hydrogenolysis.

In the last reaction of branching pathway, a Mannich-type addition of α-angelica lactone[14] as nucleophile to ketimine moiety in **1** was explored.[15] By this way, we targeted molecular complexity both in terms of consecutive quaternary stereocenters[16] in the product, as well as having a natural product fragment – the lactone ring - with a free rotation around newly constructed bond. In our hands, silyl enol ether **11** worked far better in the desired addition reaction than lactone itself. Variation of reaction temperature and Lewis acids identified AgOAc (Table S2) as the best catalyst for vinylogous addition reaction exhibiting high reactivity (quick reaction within 10 min) at -78 °C to form lactone **12a** in good yield (89%) and diastereomeric ratio (25:2) in favor of *syn*-diastereomer (based on nOe experiments). Hydrogenation of **12a** using 10 mol% Pd/C furnished a saturated γ-lactone **12b** in 63%.

With tricyclic scaffolds (**2**, **4–6**, **8** and **10**) in hand, we were curious to realize a common ring-expansion approach in a ´folding pathway´ that could expand the range of distinct sulfonamides,[17] in particular supporting medium-ring-sized frameworks.[18] The key to success in approach was the selective cleavage of carbon-nitrogen bond in the annulation adducts in branching phase. Although C–N bond cleavage does occur in the course of coupling[19] and aziridine-opening reactions,[20] but has not been thoroughly utilized as a strategy to build larger cyclic systems.[21] We hypothesized that, palladium on carbon can be used to cleave N–C bond in adducts from branching phase in analogy to *N*-debenzylation, but in intramolecular and stereoselective[22] fashion to offer an additional set of novel cyclic sulfonamide scaffolds (Scheme 1). Interestingly, aziridines **2a–h** supporting one benzylic N–C bond (R^2 = CO_2Et) under hydrogenation conditions (10 mol% Pd/C, H_2), cleaved from benzylic *quat.* C–N bond to deliver sultams **13a–d** (30-99% yield) exclusively in *syn*-configuration. However, aziridines bearing two benzylic N–C bonds (R^1 and R^2 = Ar) preferred cleavage at benzylic *tert*-C–N bond to provide sulfonamides **14a–d** (30-69% yield). It appears that ring-strain in aziridines with quaternary benzylic carbon indeed could drive the formation of sulfonamides **13** (for details

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see Supporting info). However, when available, a tertiary benzylic C–N cleavage was preferred to form **14a–d** (Scheme 3).

Encouraged by above ring-expansion, other substrates were also subjected to Pd-mediated hydrogenation conditions. In particular, we expected to get medicinally important[3g, 23] seven-membered sulfonamides from azetidines (**4**). To our delight, under same hydrogenative conditions, **4a-b** afforded *syn*-diastereomer of corresponding seven-membered benzo-sulfonamides **15a-b** in moderate yields (Scheme 3). Isolation of a ring-expanded intermediate **15a´** (49% yield, Supp. information)[12] suggests that hydrogenolysis of C–N bond precedes hydrogenation of exocyclic double bond (Scheme 2). We observed that a *double benzylic* substitution (R^1 = Ph) in azetidine **4** is a requisite for ring expansion to happen. For instance, all our efforts for the desired ring expansion of ester substituted azetidine **4e** to seven–membered sulfonamide failed. Infact, the reaction led to extra-cyclic opening of azetidine **4e** yielding **16** in 96% yield. Nevertheless, ester hydrolysis and amide synthesis in **15a** and **15b** was performed to afford amides **18a-c** *via* carboxylic acid **17** (Scheme 3).

Pyrrolinyl sulfonamides **5** did not follow ring-expansion that we assume owes to its lower ring-strain as compared to aziridines or azetidine rings. Instead, hydrogenation of double bond occurred to give pyrrolidine *syn*-**19** in 95% yield. Hydrogenation of aminal **8a** cleaved the ring at the expected aminal carbon to furnish a relatively unstable benzosulfonamide **20** (87% yield). The latter was quickly transformed into a stable tricyclic sulfonyl urea **21** that features a key motif of herbicidal[24] and anti-diabetic sulfonamides,[25] by treating with carbonyl diimidazole in presence of base.

Likewise, six-membered dihydropyridones **6a-d** lacking ring-strain were transformed into 1,4-tetrahydropyridones **22** by heterogeneous catalytic hydrogenation. Furthermore, ketone function in **22** was used for reductive amination reactions using $NaBH(OAc)_3$. We observed that morpholine adducts displayed a higher degree of *syn*-selectivity than *n*-propylamine adducts (Scheme 3). The scaffold diversity generated in branching and folding phase is clearly depicted in terms of three-dimensional chemical space (PMI plot; Fig. S1) and the range of molecular properties (molecular properties plot Fig. S2) represented by the ensuing sulfonamide compound collection. In order to make an unbiased analysis of the novel sulfonamides formed, their biological activity was explored in a cell painting assay (CPA).[26] CPA is an image-based analysis that measures and quantifies a range of morphological changes in cells induced by a compound and condensed to generate a fingerprint for novel as well as annotated(reference) compounds. Identification of reference compounds with a profile similar to the desired molecules may offer insights into the biological activity as well as modes of action of new compounds (Fig 1a).[27] To this goal, U2OS cells were treated with the compounds for 20 h prior to staining of cellular organelles and cellular components, i.e., DNA, endoplasmic reticulum, nucleoli and cytoplasmic RNA, actin, mitochondria, Golgi and plasma membrane. Automated image analysis and data processing results in morphological fingerprints to display the change of 579 parameters in comparison to the DMSO-treated cells (Fig S3). Two derivatives displayed activity in the CPA with induction (i.e. percentage of (**4a**) and 35 % (**5b**). These fingerprints were compared with the changed parameters

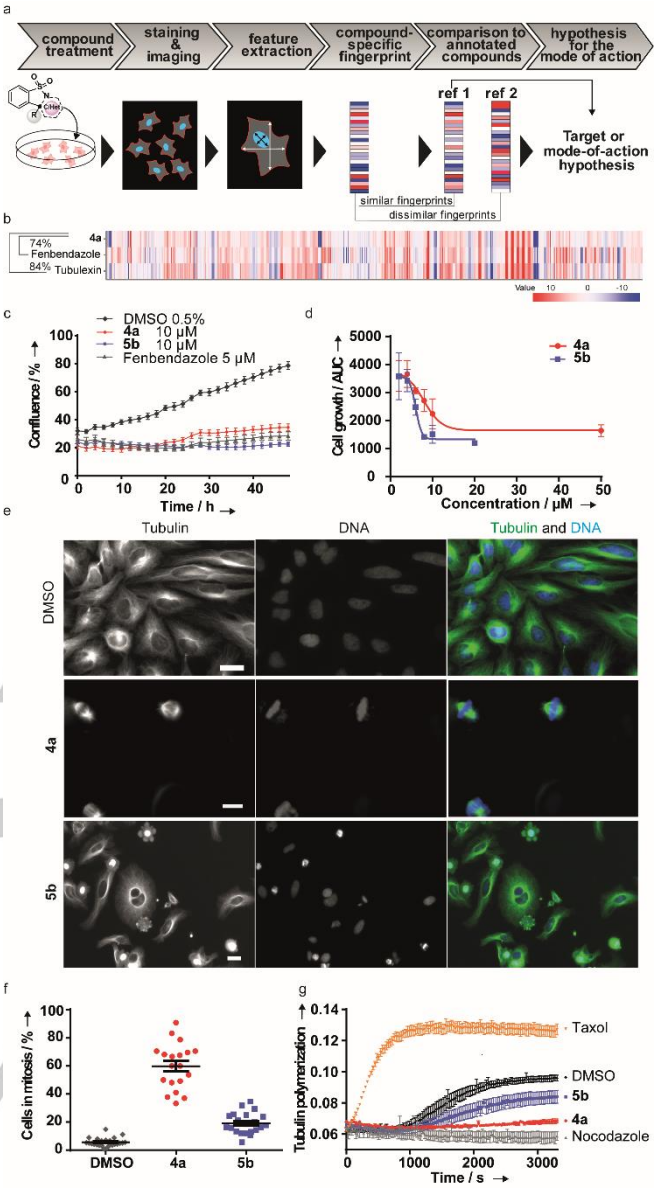

Figure 1. Influence of benzosulfonamides **4a** and **5b** on cell growth, mitosis and tubulin polymerization. a) Schematic representation of morphological profiling, e.g. the Cell painting assay;[28] b) Fingerprint comparison for **4a** (10 µM) with fenbendazole (3 µM) and tubulexin A (50 µM); c) The growth of U2OS cells was monitored for 48 h using kinetic live-cell imaging in presence of the compounds or DMSO and fenbendazole as controls. Data are mean values (N=6) ± SD and are representative of three biological replicates; d) Dose-response analyses for cell growth inhibition were carried out as described in (a). The area under the curve was used to determine IC_{50} for cell growth inhibition. IC_{50} (**4a**) = 7.8 ± 1.6 µM; IC_{50} (**5b**) = 6.0 ± 0.4 µM. Data are mean values (N=3) ± SD and are representative of two biological replicates; e) U2OS cells were treated with the compounds for 24 h prior to staining of DNA and tubulin using DAPI (blue) and anti-alpha-tubulin-FITC antibody (green). Scale bar: 20 µm. f) U2OS cells were treated with the compounds for 24 h prior to staining for phospho-histone 3 as a marker for mitotic arrest and DNA followed by automated image acquisition and analysis to quantify the percentage of cells in metaphase (i.e., phospho-histon 3-positive cells). Data are mean values (N = 2) ± SD and are representative of three biological replicates; g) *In vitro* tubulin polymerization assay. Tubulin polymerization was initiated in presence of GTP and was monitored by means of turbidity measurement at 340 nm at 37 °C. Taxol and nocodazole were used as controls for tubulin-stabilizing and- destabilizing agents, respectively. Data are representative of three biological replicates.

compared to the DMSO control) of 51 % fingerprints of reference compounds, *i.e*., with known biological activity, to generate target hypotheses. Interestingly, the morphological profile of **4a** displayed similarity to tubulin-acting agents (fenbendazole[29] – 74% similarity, tubulexin A[30] – 84% similarity), (Figure 1b and Figure S4a-b), whereas the morphological profile of **5b** was similar to an inhibitor of the mitotic Polo-like kinase 1[31] (PLK1 – 56 % similarity, Figure S5 and Figure S4c).

Both, tubulin and PLK1 have essential function during mitosis. Therefore, we monitored the growth of U2OS in presence of **4a** and **5b** cells by means of real-time live-cell analysis (Figure 1a). Both compounds reduced cell growth dose-dependently with IC_{50} values of 7.8 ± 1.6 µM (**4a**) and 6.0 ± 0.4 µM (**5b)** (Figure 1b and Movies S1-S3). Inspection of cell morphology revealed the accumulation of round cells (Figure S6) with mitotic spindles (Figure 1e) that is indicative of mitotic arrest. Arrest in mitosis was confirmed using phospho-histone 3 staining that revealed increase in the fraction of mitotic cells from 5.2 ± 2.4 % (DMSO-treated cells) to 62.5 ± 15.1 % and 19.8 ± 6.9 % in the presence of 10 µM **4a** and **5b**, respectively (Figure 1f and Figure S6-7). Tubulin polymerization is amenable to modulation by small molecules[32] and interference with microtubule dynamics leads to mitotic arrest. As the CPA revealed similarity of the fingerprints to the tubulin-targeting agents fenbendazole and tubulexin A (Figure 1b), we analyzed the influence of benzosulfonamides **4a** and **5b** on *in vitro* tubulin polymerization. Compound **4a** strongly inhibited tubulin polymerization at 20 µM, whereas compound **5b** was less potent (Figure 1g). These results confirm the CPA-generated mode-of-action hypothesis and identified sulfonamides **4a** and **5b** as novel microtubule-targeting agents. Notably, sulfonamide class of small molecules is not typically known for anti-mitotic activities and therefore CPA was instrumental to offer an unexpected biological annotation to benzosulfonamides.

In conclusion, a novel scaffold diversity synthesis approach employing a branching-folding pathway strategy is presented to offer access to biologically relevant yet under-explored cyclic benzosulfonamides. Different annulation reactions of common substrates formed the core of branching pathway, and a hydrogenolytic ring-expansion strategy was the key for folding-route. Cell painting assay was instrumental in identifying hits from this non-natural class of small molecules and unravelling their unexpected anti-mitotic activity and tubulin inhibition. We believe this approach will find further applications to reach out to novel chemical and biological space and to help advance discovery research.

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Keywords: Sulfonamides • Branching Pathway • Folding Pathway • Cell Painting • Mitotic Inhibitors

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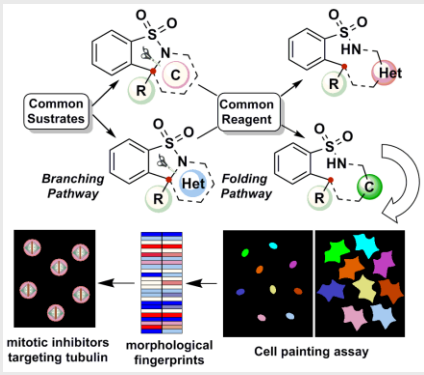
RESEARCH ARTICLE

Branch, Fold and Paint! A branching-folding synthesis strategy delivers a range of diverse cyclic benzosulfonamides and a cell painting analysis led to disclose novel tubulin targeting sulfonamides mitotic inhibitors.



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A Scaffold Diversity Synthesis of Biologically Intriguing Cyclic Sulfonamides