Reagent based DOS: A "Click, Click, Cyclize" strategy to probe chemical space†

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The synthesis of small organic molecules as probes for discovering new therapeutic agents has been an important aspect of chemical-biology. Herein we report a reagent-based, diversity-oriented synthetic (DOS) strategy to probe chemical and biological space *via* a "Click, Click, Cyclize" protocol. In this DOS approach, three sulfonamide linchpins underwent cyclization protocols with a variety of reagents to yield a collection of structurally diverse *S*-heterocycles. *In silico* analysis is utilized to evaluate the diversity of the compound collection against chemical space (PC analysis), shape space (PMI) and polar surface area (PSA) calculations.

Introduction

The synthesis of small organic molecules as probes for discovering new therapeutic agents has been an important aspect of chemical-biology.[1] Essential to this goal are two fundamental features i) the production and access to libraries of skeletally diverse small molecules and ii) biological evaluation and identification of new probes.[2] Such small molecules have had a dramatic effect in recent years providing invaluable insight into biological targets and the development of therapeutic agents for curing disease.[3] The generation of an open-data, high-throughput screening environment of diverse small-molecule libraries has provided both a number of new molecular probes as well as a novel insight into unmined chemical space.[2] In contrast to natural product-based targeted libraries premised on improving the biological activity of the corresponding natural product, diversity-oriented-synthesis (DOS) derived libraries aim to discover new molecules that exhibit biological effects beyond those associated with the natural product. In this regard, DOS has emerged as a powerful strategy in the generation of structurally complex and skeletally diverse small molecules.[4]

Synthetic protocols combined with rational design of small molecules based on structural diversity, complexity and inherent physiochemical properties, has emerged as a rich area in chemical biology.[5] The ability to generate a collection of small molecules that combine not only skeletal and peripheral complexity from a central building block, while remaining diverse in comparison to each other has been a challenging goal. Libraries synthesized utilizing a DOS approach have been generated through a number of approaches. Seminal papers by Evans in 1988 and Schreiber 2000 reported the generation of substructural motifs as ligands for diverse receptors.[6] Recently, notable examples of DOS strategies have been reported by Spring, Park and Shair.[3,4] One of the more notable strategies employing both reagent-based[7] and functional group pairing attributes is the build/couple/pair (B/C/P) paradigm pioneered by Schreiber and coworkers.[8]

Recently, a number of reports of sultams, the cyclic analogs of sulfonamides, have emerged demonstrating a broad-spectrum bioactivity (Fig. 1), yet not "preordained bioactivity" as is the case with targeted, medicinally active natural products. In particular, reports include anti-HIV activity,[9] antidepressant activity,[10] inhibitors of RSV,[11] selective tumour necrosis factor,[12] and metalloproteinase.[13] In addition to this potent biological profile, sultams and their sulfonamide precursors possess a number of advantageous chemical properties. This potency, when coupled with their unique chemical properties, elevates sultams as promising candidates for drug discovery.

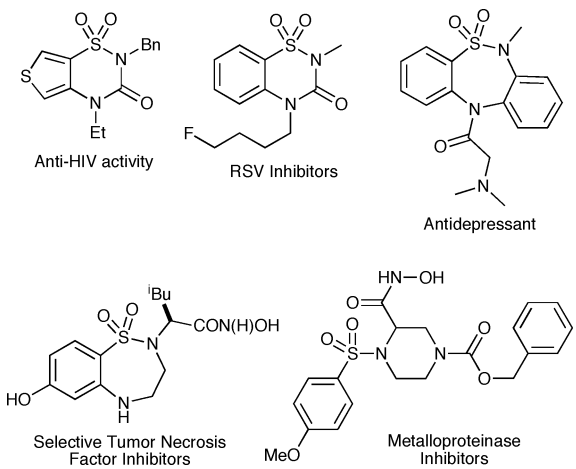

Fig. 1 Biologically active sultams and sulfonamides.

Despite these attributes, general strategies towards the synthesis of sultam libraries are lacking in the literature.[14] To address this challenge, we report a reagent-based DOS strategy termed

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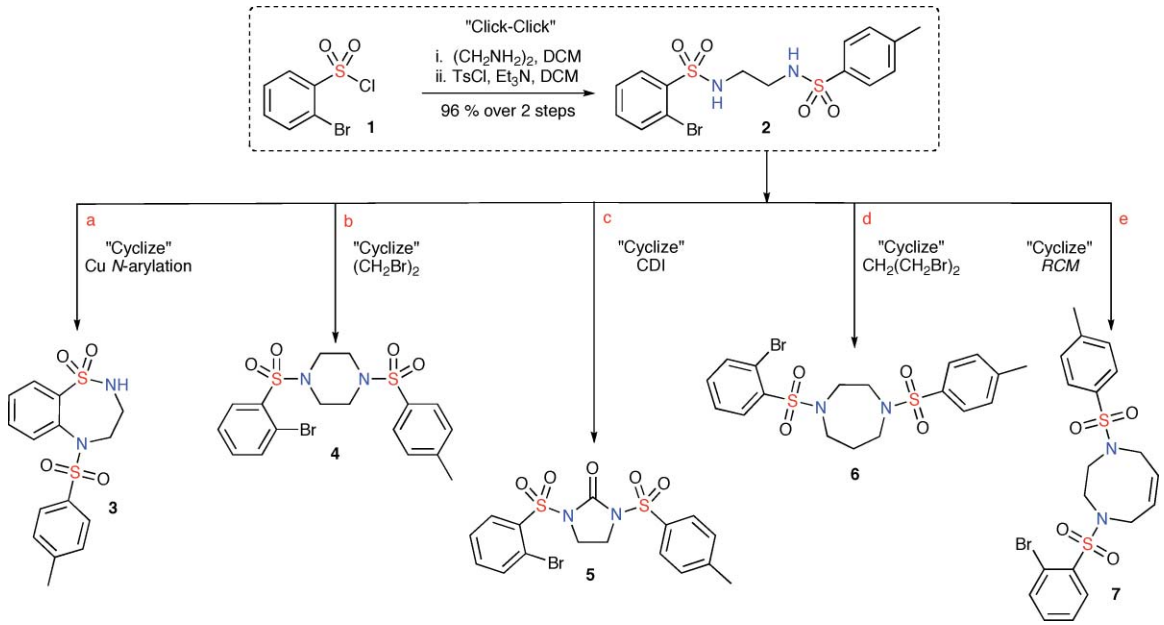
"Click, Click, Cyclize" en route to structurally diverse sultams from common sulfonamide linchpins.[15,16] In this strategy, skeletal diversity is incorporated into each small molecule *via* a chosen orthogonal reagent used to cyclize each linchpin. As in functional-group pairing approaches, this DOS strategy provides a pathway to a collection of diverse sultams.

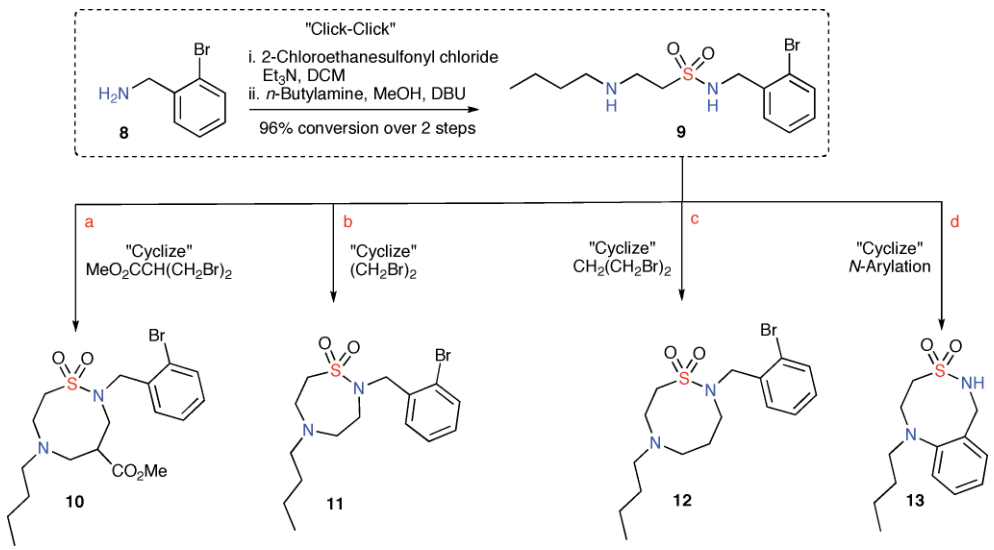
Results and discussion

Linchpin synthesis *via* "Click, Click, Cyclize" protocol

Taking the aforementioned approach into hand, three unique sulfonamide linchpins **2**, **9** and **15** were designed to yield a collection of sultams utilizing the aforementioned "Click, Click, Cyclize" protocol.[15] In this regard, linchpin **2** was synthesized *via* a "Click" mono-sulfonylation of ethylenediamine with 2-bromobenzene sulfonamide **1**, followed by a second "Click" sulfonylation with tosychloride (TsCl) to generate the desired linchpin **2** in high yield (Scheme 1).[17] Utilizing a variety of reagents, five sultams and bis-sulfonamides (**3–7**) were readily synthesised. Initial cyclization of linchpin **2** was achieved *via* a microwave-assisted, Cu-catalyzed, intramolecular *N*-arylation yielding the corresponding sultam **3** in 70%.[18] Alternatively, cyclization of linchpin **2** with either 1,2-dibromoethane or 1,3-dibromopropane provided the desired piperazine **4** and diazepine **6** in good yield. In contrast, cyclization of linchpin **2** with carbonyl diimidazole



Scheme 1 a) CuI, 1,10-phenanthroline, Cs_2CO_3, DMF, *MW*, 70%. b) $(CH_2Br)_2$, Cs_2CO_3, DMF, 60 °C, 90%. c) CDI, Et_3N, DMF, 60 °C, 92%. d) $CH_2(CH_2Br)_2$, Cs_2CO_3, DMF, 60 °C, 85%. e) i. Allyl bromide, NaH, THF, RT, ii. Grubbs 2nd Generation, DCM, reflux, 88% (over steps).



Scheme 2 a) Cs_2CO_3, $MeO_2CCH(CH_2Br)_2$, DMF, 64%. b) $(CH_2Br)_2$, Cs_2CO_3, DMF, 60 °C, 84%. c) $CH_2(CH_2Br)_2$, Cs_2CO_3, DMF, 60 °C, 76%. d) CuI, 1,10-Phenanthroline, K_2CO_3, DMF, *MW*, 56%.

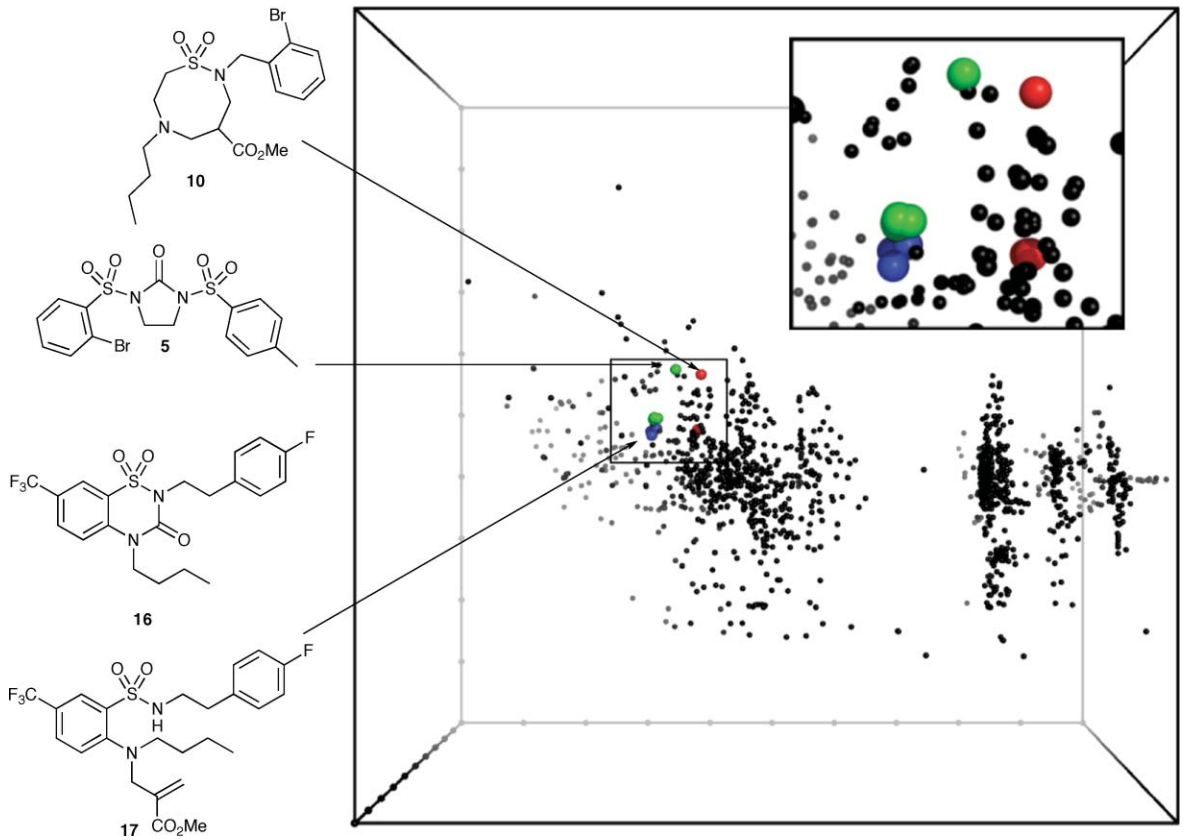


Fig. 2 Three-dimensional chemical diversity plot of compounds **2–7** (green), **9–13** (red) and **14–19** (blue) relative to 3770 FDA approved compounds as reported in the ZINC database. The axes reflect normalized projections of three H-sensitive three-dimensional BCUT metrics chosen as having optimal variance levels within the MLSMR screening set, including the 600 projection of the Burden H-donor (horizontal axis), and the 500 (vertical axis) and 600 (out-out-plane axis) projections of the Burden tab-polar projections, as computed *via* DiverseSolutions.[20]

gave the corresponding imidazolidin-2-one **5** in 92% yield. Finally, allylation followed by RCM yielded **7** in 88% yield, *via* a "click-cyclize" 2-step protocol.

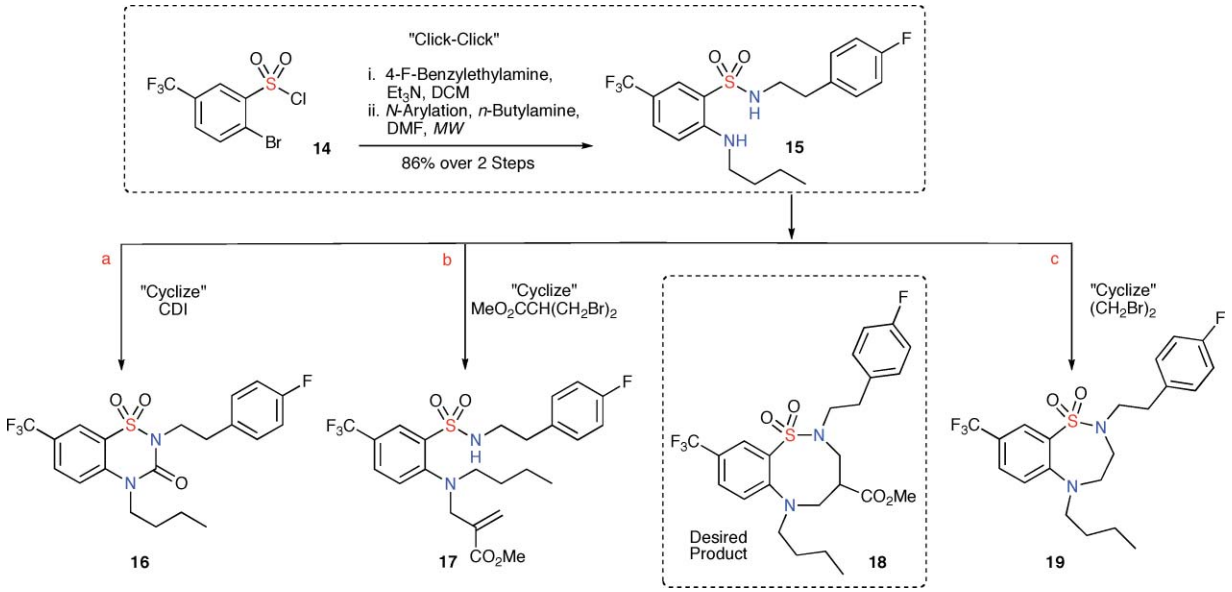
Building on these results, sulfonamide linchpin **9** was synthesized *via* sulfonylation of 2-bromobenzylamine **8** with 2-chloroethanesulfonyl chloride followed by an aza-Michael reaction with n-butylamine (Scheme 2).[19] It was envisioned that cyclization with four commercially available reagents would yield four skeletally diverse sultams (**10–13**).

Sultam **10** was synthesised *via* cyclization of linchpin **9** utilizing methyl 3-bromo-2-(bromomethyl)propionate. Utilizing the same cyclization protocol as for the synthesis of **4** and **5**, sultams **11** and **12** were synthesized *via* cyclization of linchpin **9** with 1,2-dibromoethane or 1,3-dibromopropane, respectfully. Finally, sultam **13** was synthesized utilizing a microwave-assisted, copper-catalyzed *N*-arylation protocol.

Utilizing a previously developed Cu-catalyzed, *N*-arylation protocol, sulfonamide linchpin **15** was readily synthesized on scale from sulfonylchloride **14** (Scheme 3).[18] The first cyclization route, utilized a CDI cyclization protocol yielding sultam **16** in good yield. In an attempt to synthesize sultam **18**, linchpin **15** was treated with 3-bromo-2-(bromomethyl)propionate in DMF at 60 °C. However, the desired product **18** was not isolated and instead sulfonamide **17** was isolated in 78% yield. Finally, linchpin **15** readily underwent cyclization with 1,2-dibromoethane to yield bicyclic sultam **19** in good yield.

To evaluate the diversity that is contributed by this collection of molecules and hence their associated chemical descriptors, *in silico* algorithms were utilized to evaluate the *S*-heterocycles reported. With each molecule possessing its own set of unique descriptors, every small molecule has a discrete point in chemical space. Therefore, the more chemical space probed by a collection of molecules, the greater the associated diversity. This metric of diversity in chemical space can be represented by a principle component (PC) analysis (Fig. 2). In order to gauge the chemical diversity of the sultams and sulfonamides (**3–7**, **10–13** and **16–19**) reported herein, we plotted them in a chemical space plot corresponding to a set of five BCUT descriptors relative to 3770 FDA approved compounds as reported in ZINC database (Fig. 2).[20] This plot demonstrated that this collection of molecules both covered a significant area of chemical space but also the compounds did not cluster together according to the corresponding linchpin they were derived from.

Building on this analysis, sultams and sulfonamides (**3–7**, **10–13** and **16–19**), were plotted according to the normalized principal moment of inertia (PMI) formalism of Sauer and Schwartz, in order to gauge the shape-based distribution (Fig. 3).[21] The PMI plot is a rapid and visual way to demonstrate diversity corresponding to the area of shape space covered by a collection of molecules. This



Scheme 3 a) CDI, Et_3N, DMF, 60 °C, 96%. b) Cs_2CO_3, $MeO_2CCH(CH_2Br)_2$, DMF, 78%. c) $(CH_2Br)_2$, Cs_2CO_3, DMF, 60 °C, 87%.

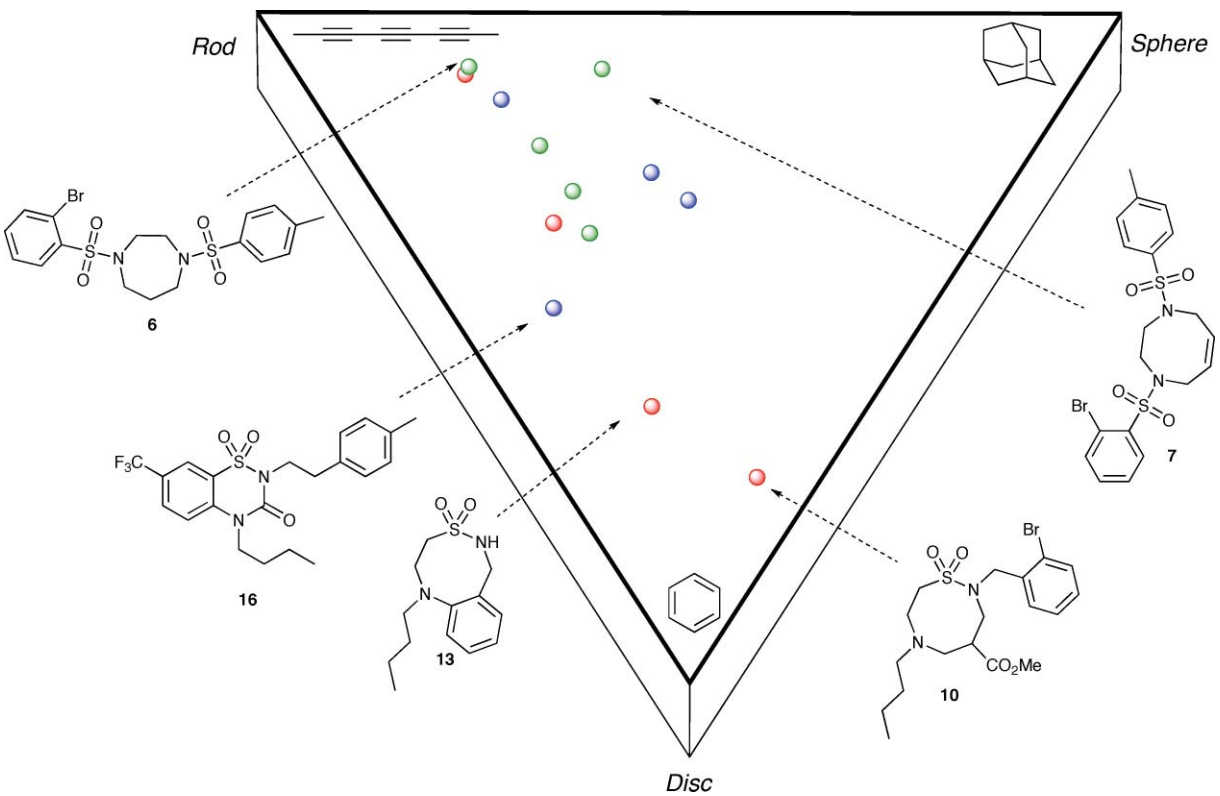


Fig. 3 Principal moment of inertia (PMI) plot of compounds **3–7** (green), **10–13** (red) and **16–19** (blue) as computed for energetically minimized conformers of the compounds using Gasteiger-Marsili electrostatics.

is a significant property for a collection of molecules to possess, as broad biological activity has been correlated to shape space.[21] Hence, screening collections possessing a high degree of molecular shape diversity increases the chances of a broad range of biological activity. Each molecule was aligned to principal inertial moment axes in SYBYL,[22] and the normalized PMI values were computed *via* a program developed in-house (available upon request to the authors). With this plot in hand, Fig. 3 demonstrates a large coverage of shape space for sultams and sulfonamides (**3–7**, **10–13** and **16–19**). Of note is the coverage by compounds **10–13** (red data points) derived from linchpin **8** further demonstrating the diversity achieved utilizing a "Click, Click, Cyclize" approach.

In addition to diversity in both chemical and shape space, polar surface area of a small molecule is a key feature in terms of

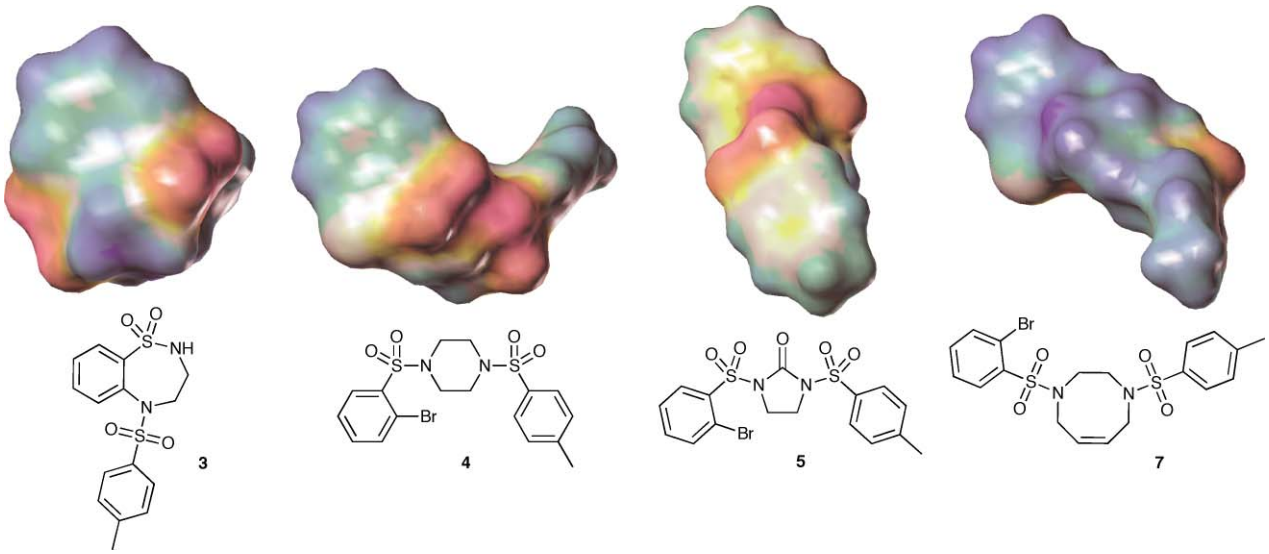


Fig. 4 Surface electrostratic profiles of sultams and sulfonamides **3** (78.33), **4** (100.61), **5** (125.49) and **7** (92.95). The compounds have been mutually aligned so that the conserved phenylsulfonyl moiety is located in the upper left corner for each molecule. The surface corresponds to the H_2O-accessible Connolly surface, and the colouring reflects the Gasteiger-Marsili charge distribution, such that electronegative areas are colored red, electro positive areas are blue.

diverse bioactive molecules involved in ligand-receptor binding. Rigid scaffolds bearing diverse polar surface areas interact differently with various key interactions such as hydrogen bonding, electrostatic and other non-covalent interactions. This is further exemplified by reports that demonstrate the diverse biological activity associated with small molecules with diverse polar surface areas resulting from different orientations of heteroatoms.[4a] In this regard, polar surface area distribution of sultams **3**, **4**, **5** and **7** were plotted (Fig. 4). Comparison among the four further demonstrates the degree of diversity achieved from linchpin **2** utilizing a "Click, Click, Cyclize" protocol. Surface electrostatic profiles were calculated by projecting the Gasteiger-Marsili charge distribution onto a Connolly surface generated *via* the MOLCAD tool in SYBYL.[22]

Conclusions

In summary, we have utilized a "Click, Click, Cyclize" strategy to synthesize a collection of skeletally diverse heterocycles in a DOS approach. Three distinct sub-sets of molecules were prepared *via* the cyclization of sulfonamide linchpins with a variety of reagents. *In silico* analysis using a variety of metrics demonstrates the degree of diversity from this collection in regards of chemical space, shape space and polar surface area.

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