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# Facile (Triazolyl)methylation of MACOS-derived Benzofused Sultams Utilizing ROMP-derived OTP Reagents

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#### **Abstract**

A combination of MACOS scale-out and ROMP-derived oligomeric triazole phosphates ( $OTP_n$ ) have been successfully utilized for the preparation of a 106-member library of triazole containing benzothiaoxazepine-1,1-dioxides. This report demonstrates the utilization of a suite of soluble  $OTP_n$  reagents for facile (triazoly1)methylation of 10 MACOS-derived sultam scaffolds in purification-free process for parallel synthesis of small molecule collections for HTS.

## Keywords

Dihydro-2H-benzothiaoxazepine-1,1-dioxide; sultams; OTP; MACOS; ROMP; (triazolyl)methylation

### Introduction

The growing demand for the identification and development of new pharmaceutical leads and probes has prompted current advances in high-throughput screening. <sup>1</sup> Key to this approach is the development of emerging synthetic methods and technologies that give rapid access to collections of diverse small molecules addressing classical bottlenecks in this process. In this regard, the development of enabling technologies that allow for the assembly of diverse small molecule collections where synthesis, diversification and purification are integrated into one parallel process is a critical facet of early stage drug discovery. Classical synthetic approaches to small molecule libraries have suffered from multi-step processes requiring costly and time-consuming purification at every stage. In addition, issues relating low yielding or unreliable reactions for the preparation of compounds and key intermediates has a negative effect on early stage drug discovery. <sup>2</sup>

In recent years, a variety of enabling technologies have been developed to address these limitations, giving rapid access to small molecule HTS screening collections.<sup>3</sup> One such technology has been the development and utilization of continuous flow technology platforms, which can carry out multi-step processes, combined with inline diversification/purification, utilizing immobilized reagents/scavengers.<sup>4</sup> In addition to inline purification, the ability for automation,<sup>6</sup> safe *in-situ* generation of reactive intermediates,<sup>7</sup> rapid reaction optimization and multi-gram scale-out makes this a powerful enabling technology in early stage drug discovery.<sup>8</sup> Building on these efforts, we herein report the utilization of a microwave-assisted, continuous flow organic synthesis (MACOS) platform in combination with soluble oligomeric reagents derived from ring opening metathesis polymerization for the rapid, purification-free synthesis of a 106-member library of benzothiaoxazepine-1,1-dioxides (Scheme 1).

## **Results and Discussion**

Sultams (cyclic sulfonamide analogues) have emerged in recent years as important targets in drug discovery due to their extensive chemical and biological profiles. Recently, a number of enabling synthetic methodologies have been developed give rapid access to diverse sultam libraries for HTS. Building on these reports, it was envisioned that a variety of core sultam scaffolds prepared via MACOS could be quickly diversified in a facile, purification-free process utilizing a suite of ROMP-derived reagents. Towards this goal, a suite of soluble, high-load ROMP-derived benzyl- and triazole- phosphates have been developed for the facile, purification-free diversification of nucleophilic small molecules. ROMP-derived OTP reagents are bench stable, free flowing solids that are readily soluble in a variety of solvents to generate stock solutions, making them ideally suited for parallel synthesis. With these reagents in hand, the (triazolyl)methylation of core benzthiaoxazepine-1,1-dioxide scaffolds 1–10 scaled-out on the MACOS platform was investigated with a suite of oligomeric (triazolyl)methyl phosphate (OTP) reagents { 1–14}. Initially, a 16-member prototype library was investigated for the generation of triazole containing benzothiaoxazepine-1,1-dioxides (Table 1).

Utilizing reported conditions for the *(triazolyl)methylation* of a variety of nucleophilic species, <sup>13a</sup> the generation of a 16-member prototype library was successfully achieved in good yield and crude purity (85–100%, <sup>1</sup>H NMR), demonstrating both substrate and reagent scope. With the synthesis of a 16-member prototype library, a 96-member library was designed with benzothiaoxazepine-1,1-dioxide scaffolds **1–10** and OTP<sub>20</sub> oligomers { *1–14*}.

#### **Library Design**

A *full-matrix* library was designed using in silico analysis, literature precedence, and observed synthetic results. <sup>15</sup> A virtual library incorporating all possible building block combinations of sultam scaffolds **1–10** with OTP reagents { *1–14*} (Figure 1) was evaluated. Physicochemical property filters were applied, guiding the elimination of undesirable building blocks that led to products with undesirable in-silico properties. <sup>16</sup> These metric filters included standard Lipinski Rule of 5 parameters (molecular weight <500, ClogP <5.0, number of H-acceptors <10, and number of H-donors <5), in addition to consideration of the number of rotatable bonds (<10) and polar surface area. Absorption, distribution, metabolism and excretion (ADME) properties were calculated along with diversity analysis using standard H-aware 3D BCUT descriptors compared against the MLSMR screening set (~7/2010; ~330,000 unique chemical structures). Guided by this library design analysis, a 96-member library was designed.

# **Library Generation**

The proposed 96-member library was prepared in 1-dram vials via a mix-and- match approach using stock solutions of scaffold (1-10) and  $OTP_{20}$  reagents { I-14}. Crude purity analysis of the 96-member library demonstrated that 66 compounds had crude purities of 80–99%, 16 compounds at 70–80% and 8 compounds <70%. Final analysis of this library after purification by automated mass-directed LCMS resulted in the successful synthesis of 90 compounds with 84/90 compounds possessing >90% final purity (Graph 1). 17

#### Conclusion

In conclusion, a 90-member library (out of 96) of triazole containing benzothiaoxazepine-1,1-dioxides was successfully prepared combining two enabling technologies, namely MACOS platform and ROMP-derived OTP reagents. Utilization of a suite of soluble OTP<sub>n</sub> reagents { *1–14*}, 10 MACOS-derived sultam scaffolds **1–10** were successfully diversified in a purification-free parallel process amenable for automation. Taken collectively, with the prototype library (16 member), a total of 106 out of 112 sultams were successfully generated (95% success rate) with 100/112 (89% rate) possessing purities >90%. The compound libraries we report in this manuscript have been submitted to the University of Kansas Center for Chemical Methodologies and Library Development (KU-CMLD) for delivery to the NIH Molecular Library Small Molecule Repository (MLSMR) for distribution and broad screening for biological activity within the MLPCN screening network.

# **Experimental Section**

General procedure **A**, for the *(triazolyl)methylation* of sultams **1–10** with  $OTP_{20}$  reagents { I-14}. To a 1-dram vial with a teflon cap was added a stock solution of  $OTP_{20}$  { I-14} (1.5 equiv.) in dry DMF (0.2M), followed by the addition of NaI (0.5 equiv.) and  $Cs_2CO_3$  (3 equiv.). After stirring for 30 seconds, the corresponding sultam (1 equiv.) was added, and the reaction mixture was heated to 90 °C for 2–14 hrs (TLC analysis). Upon completion, the DMF was removed in vacuo, crude diluted in EtOAc, filtered via  $SiO_2$  SPE, rinsed several times with EtOAc and concentrated in vacuo to yield the desired product. The crude reaction was concentrated and QC/purified by an automated preparative reverse phase HPLC (detected by mass spectroscopy).

# **Supplementary Material**

Refer to Web version on PubMed Central for supplementary material.

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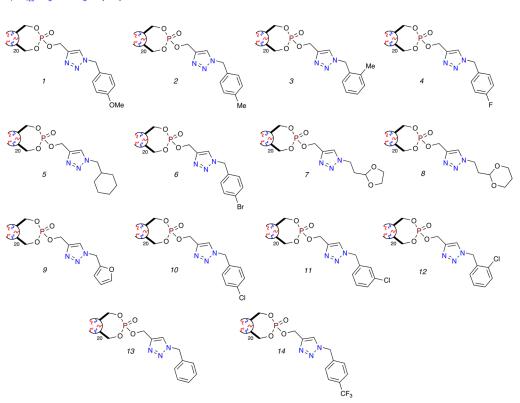
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- 14. We have generated the benzofused sultam scaffolds **1–10** using "Microwave-Assisted Continuous Flow Organic Synthesis (MACOS)" in collaboration with Professor Michael G. Organ at York University in Toronto, Canada. These samples were shipped to us at KU, whereby we next introduced the (trizolyl)methyl group by combinatorial parallel synthesis using the oligomeric (triazolyl)methyl phosphates { *1–14*}.
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- Full in-silico data and detailed calculation information is provided in the supplementary information
- 17. Representative compounds with full data set available in supplementary information

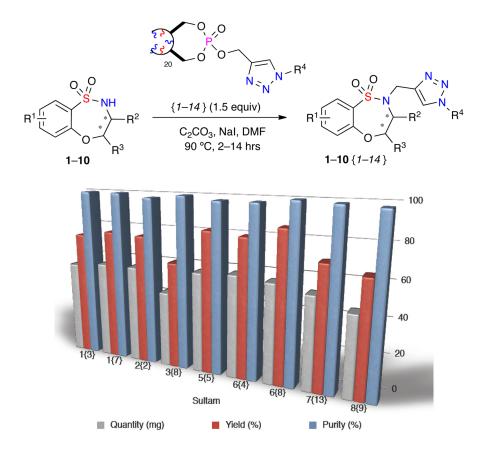
Benzthiaoxazepine-1,1-dioxide Scaffolds 1-10

(OTP)<sub>20</sub> Oliogmeric Reagents {1–14}



**Figure 1.** Scaffolds (**1-10**) and OTP<sub>20</sub> Reagents { 1-14} Library Building Blocks.

 $\label{eq:Scheme 1.} Scheme \ 1.$  Facile Library Generation Utilizing MACOS Scale-out Sultam Scaffolds and ROMP-derived OTP\_n Reagents.



**Graph 1.** Final Mass, Purity and Yield Analysis for Benzothiaoxazepine-1,1-dioxide Library.

Table 1

Prototype Library Demonstrating Utilization of Scaffolds **1–3**, **5**, **6**, **8–10** with OTP<sub>20</sub> Oligomers { *1*, *2*, *4*, *9*, *11*, *12*}.

entry <sup>a</sup>	scaffold	$OTP_{20}\{X\}$	yield %
1	1	{ 11}	85
2	2	{ 12}	62
3	3	{ 11}	97
4	3	{ 12}	92
5	5	{ 12}	70
6	6	{ 11}	98
7	8	{ 11}	98
8	8	{ 12}	94
9	9	{ 1}	63
10	9	{2}	89
11	9	{ 4}	82
12	9	<i>{9</i> }	79
13	10	{ 1}	68
14	10	{2}	75
15	10	{ 4}	72
16	10	{ <i>9</i> }	75

<sup>&</sup>lt;sup>a</sup>Reaction conditions: OTP<sub>20</sub> (1.5 equiv.), NaI (0.5 equiv.), Cs<sub>2</sub>CO<sub>3</sub> (3 equiv.), dry DMF (0.2M) and sultam **1–10** (1 equiv.). Reaction heated at 90 °C for 2–14 hrs (TLC analysis).