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Synthesis and screening of 3-substituted thioxanthen-9-one-10,10-dioxides

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Abstract—This manuscript describes methods appropriate for the parallel synthesis of libraries based on the tricyclic thioxanthen-9-one-10,10-dioxide scaffold. The novel compounds were synthesized from previously reported 3-chlorothioxanthen-9-one-10,10-dioxide and commercially available 3-carboxylic acid thioxanthen-9-one-10,10-dioxide. The library members were screened for activity in a fluorescence polarization assay for inhibitors of BRCT domains of breast cancer gene 1 and in cell-based secreted alkaline phosphatase reported replicon system for activity against hepatitis C virus.

The generation of novel structures amenable to rapid and efficient lead optimization constitutes an important strategy in modern drug discovery. This paper reports the utilization of thioxanthen-9-one-10,10-dioxides as such in structure. Thioxanthenones and thioxanthen-9-one-10,10-dioxides have been shown to possess a number of potentially useful biological activities including anti-tumor,[1,2] anti-allergic[3–6] and monoamine oxidase (MAO) inhibitory activity.[7–9] However, some of the most promising drug candidates arising from this class of compounds have shown to have adverse toxic properties in Phase I clinical trials.[10,11] Because of the potential demonstrated by this scaffold, an approach to the synthesis of these types of structures utilizing parallel synthesis methods was developed. The molecules synthesized by this approach were screened for their activity in a Hep C replicon assay[12] as well as for their ability to inhibit the BRCT(BRCA1)-BACH1 interaction known to have a role in tumor suppression, cell cycle regulation, and DNA repair.[13]

Based on preliminary biological activity data, it was envisioned that introduction of suitably functionalized amino as well as amide derivatives at the three-position of the thioxanthenone scaffold would not only increase the solubility of this class of compounds but would also retain the postulated pharmacophoric motif required for biological activity. With the goal of synthesizing a small focused library of such molecules, a solution-phase parallel synthesis protocol for the synthesis of 10,10-dioxo-3-piperidin-1-yl/piperizin-1-yl-thioxanthen-9-one **1** as well as 10,10-dioxo-3-carboxamide derivatives **2** (Fig. 1) was developed.

The availability of 3-chloro-10,10-dioxide-thioxanthen-9-one **7** proved to be crucial for the development of a microwave-assisted protocol for the synthesis of a focused library of 36 novel 10,10-dioxo-3-piperidin-1-yl/piperizin-1-yl-thioxanthen-9-one derivatives (**1**).[14] Under basic conditions the nucleophilic substitution of thiophenol **3** with the suitably substituted 2-iodo-3-chlorobenzoic acid building block **4** in the presence of a catalytic amount of copper for 8 h affords the desired coupled sulfide **5** in virtually quantitative yield (Scheme 1).

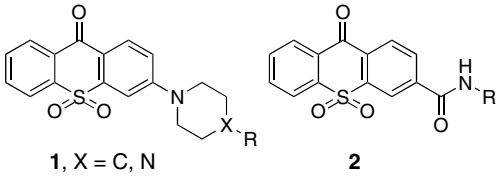

Figure 1.

Keywords: Thioxanthen-9-one; Microwave; Amine; Amide.
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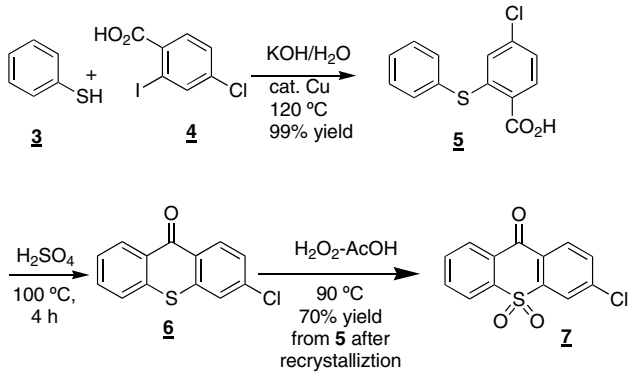


Scheme 1.

Treatment of **5** with concentrated sulfuric acid at 100 °C over 4 h affords the Friedel–Crafts adduct, thioxanthenone **6**. Upon pouring the reaction mixture onto ice, the product precipitates out as an off-white solid. Oxidation of **6** with hydrogen peroxide at 90 °C provided the desired sulfone **7**, which could be purified by recrystallization from ethyl acetate–hexanes.

Literature precedent for the synthesis of similar amino derivatives requires a multi-step synthesis of the 3-amino substrate followed by appropriate functionalization of the amino moiety or a low yielding acidic hydrolysis of the 3-tetrazole to the corresponding 3-amino product.[8] The latter can then be further functionalized only under vigorous basic conditions due to inherent lack of reactivity of the amino functionality.[8] The approach reported here makes use of this ring system's electron-withdrawing properties (carbonyl and sulfone moieties) which allow for efficient aromatic nucleophilic displacement at the 3-chloro position by a variety of commercially available piperidines and piperazines.

Treatment of a solution of 3-chloro-10,10-dioxide-thioxanthen-9-one in DMF with K_2CO_3 (1.2 equiv) followed by the addition of the corresponding piperidine or piperazine (1.2 equiv) under microwave conditions led to the formation of the corresponding 3-piperidin-1-yl/piperizin-1-yl-thioxanthen-9-ones in good to excellent yields (68–99%) (Table 1). Purification of the final products was achieved in a very practical and efficient manner by simple aqueous work-up using citric acid (1 M solution) and dichloromethane as extraction solvent. This purification protocol proved equally adaptable to the more basic piperazine products (e.g. **1k**–**1t**), albeit replacement of citric acid by hydrochloric acid (0.5 M solution) was found to be necessary for a more efficient removal of unreacted or slight excess of piperazine. It is also worth noting that this slightly modified acidic work-up resulted in only small amounts of product (<5%) going into the mildly acidic water layer, as monitored by LC–MS. Because of its greater basicity, compound **1k** could not be purified by this simple acidic work-up protocol. Instead, it was purified by automated flash chromatography. In some cases within the piperazine series of compounds, and despite the acidic work-up, trace amounts of piperazine (<5%) were found to be present by both ^{1}H NMR and LC–MS analysis.

Given the general good yields at which these reactions proceed, screening of alternative reaction conditions was not actively pursued. Primary amines such as isopropyl amine, benzylamine, 4-(2-aminoethyl)morpholine, and cyclopentyl amine were examined. In all cases the expected products were presented in reaction mixtures as judged by LC–MS and proton NMR but further purification was required.

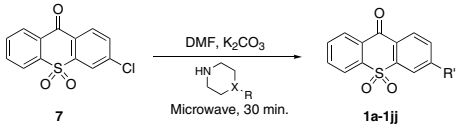
Taking advantage of the commercially available 9-oxo-9H-thioxanthene-3-carboxylic acid 10,10-dioxide (**8**) a small number of 3-substituted carboxylamides thioxanthen-9-one-10,10-dioxide **9** (**9a**–**9k**) were synthesized. Substituted carboxylic amides at the three-position of the thioxanthen-9-one-10,10-dioxide have been reported to be selective inhibitors of monoamine oxidases.[4] Although Harfenist et al. have reported the synthesis of various 3-substituted carboxylamides thioxanthen-9-one 10,10-dioxide from the acid chloride derived from the 3-substituted carboxylic acid, we opted to use coupling reagents to synthesize the desired amides. Several common coupling reagents, bases, and solvents were screened, ranging from polymer-supported reagents such as PS-piperidinomethyl as base as well as PS-DCC as coupling reagent. Ultimately, the best results were obtained using diisopropylethylamine (DIPEA) as base, methylene chloride or DMF as solvents, and BOP or HBTU as coupling reagents with methylene chloride generally being the preferred solvent. In both cases, using either BOP or HBTU, automated flash chromatography was employed in the purification of the desired amides (Table 2).

The compounds were screened for activity in a cell-based secreted alkaline phosphatase reported replicon system for activity against hepatitis C assay[12] and a fluorescence polarization assay for inhibition of the BRCT–BACH1 interaction.[13]

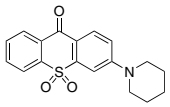
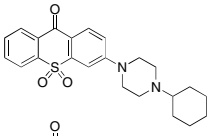
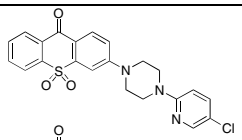
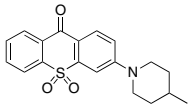
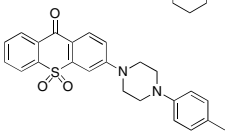
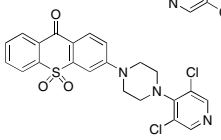
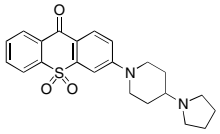
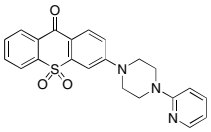
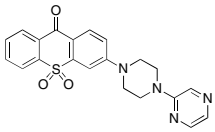
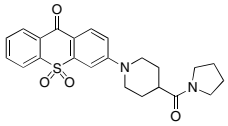
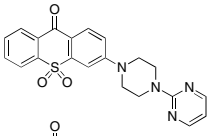
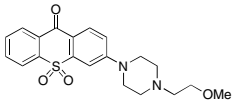
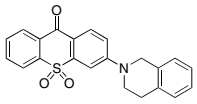
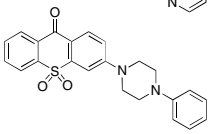
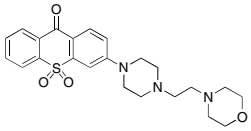
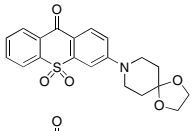
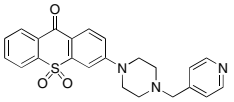
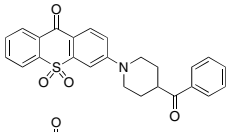
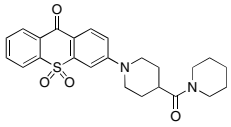
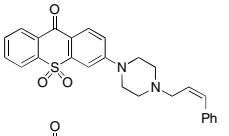
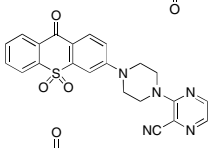
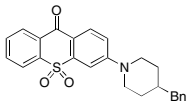
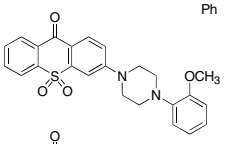
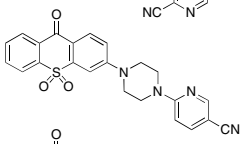
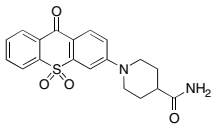
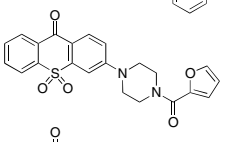
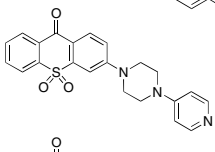
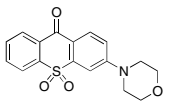
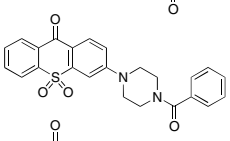
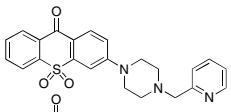
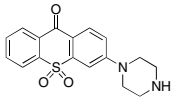
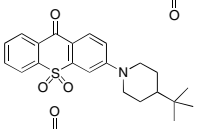
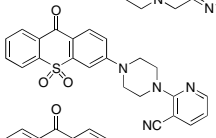
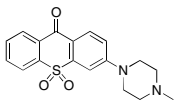
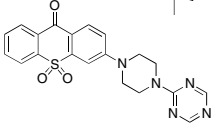
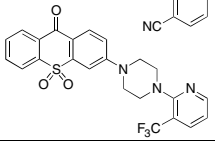
In the case of the hepatitis C replicon system no significant activity was observed. While in the BRCT–BACH1 assay system three compounds **1h**, **1i**, and **1b** exhibited moderate K_i values 38 ± 1, 30 ± 6, and 39 ± 3 μM, respectively. We are currently synthesizing bifunctional versions of these molecules for further testing in the BRCT–BACH1 system.

In summary, a focused library of 3-substituted thioxanthenones was synthesized by the facile nucleophilic aromatic substitution and amide bond formation. In general, this reaction was found to work well with secondary amines providing products in greater than or equal to 90% purity after simple extraction. A small collection of amides was also obtained in comparable purity from the HBTU or BOP coupling of the corresponding acid with an amine. All of the synthesized compounds were screened for biological activity in two different assays with three compounds providing moderate inhibition of the BRCT–BACH1 protein–protein interaction.

Table 1. Synthesis of 10,10-dioxo-3-piperidin-1-yl/piperizin-1-yl-thioxanthen-9-ones[a,b]



7 1a-1jj

	Yield (%)[b]		Yield (%)[b]		Yield (%)[b]
	**1a** 68		**1m** 98		**1y** 45[d]
	**1b** 99		**1n** 94		**1z** 49[d]
	**1c** 83		**1o** 80		**1aa** 45[d]
	**1d** 99		**1p** 82		**1bb** 57[d]
	**1e** 100		**1q** 70		**1cc** 82[d]
	**1f** 98		**1r** 88		**1dd** 18[d]
	**1g** 99		**1s** 98		**1ee** 40[d]
	**1h** 99		**1t** 98		**1ff** 6[d]
	**1i** 91		**1u** 87		**1gg** 40[d]
	**1j** 93		**1v** 47[d]		**1hh** 76[d]
	**1k** 72[c]		**1w** 25[d]		**1ii** 12[d]
	**1l** 73		**1x** 30[d]		**1jj** 74[d]

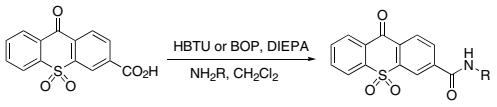
[a] Reactions were run using chloro-sulfone **7**, 1.2 equiv of amine and 1.2 equiv of K_2CO_3 and 6.0 mL of solvent in a CEM Discovery microwave system. A microwave irradiation power of 300 W, ramp time of 2.0 min. with a run time of 30 min at 155 °C and simultaneous cooling (powermax mode) was used.

[b] Unless noted isolated crude yields are reported.

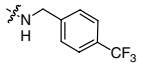
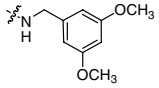
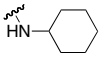
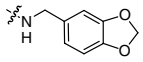
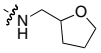
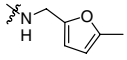
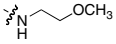
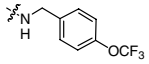
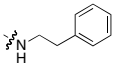
[c] 2.2 equiv of K_2CO_3 were used for the synthesis of this product.

[d] Isolated yields after column chromatography.

Table 2. Synthesis of 10,10-dioxo-3-carboxamides-thioxanthen-9-ones[a]



8 9a-9k

R	Product	Yield (%)[b]	R	Product	Yield (%) [b]
	**9a**	36		**9g**	29
	**9b**	46		**9h**	67
	**9c**	24		**9i**	57
	**9d**	30		**9j**	56
	**9e**	31		**9k**	71
	**9f**	66			

[a] Reactions were run using carboxylic acid-sulfone **8**, 1.1 equiv of amine, 1.1 equiv of HBTU or BOP and 5.0 equiv of DIPEA (Diisopropylethyl amine) in 5.0 mL of solvent (CH_2Cl_2) at rt.
[b] Isolated crude yields are reported.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2007.07.103.

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