

Synthesis of an Isoindoline-Annulated, Tricyclic Sultam Library via Microwave-Assisted, Continuous-Flow Organic Synthesis (MACOS)

Farman Ullah,^{a,c} Qin Zang,^{b,c} Salim Javed,^{b,c} Patrick Porubsky,^c Benjamin Neuenswander,^c Gerald H. Lushington,^{b,c} Paul R. Hanson,^{*b,c} Michael G. Organ^{*a,c}

^a Department of Chemistry, York University, 4700 Keele Street, Toronto, ON, M3J 1P3, Canada
Fax +1(416)7365936; E-mail: organ@yorku.ca

^b Department of Chemistry, University of Kansas, 1251 Wescoe Hall Drive, Lawrence, KS 66045-7582, USA

^c The University of Kansas Center for Chemical Methodologies and Library Development (KU-CMLD), Del Shankel Structural Biology Center, 2034 Becker Drive, Lawrence, KS 66047-3761, USA
Fax +1(785)8645396; E-mail: phanson@ku.edu

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Abstract: A microwave-assisted, continuous-flow organic synthesis (MACOS) protocol for the synthesis of an isoindoline-annulated, tricyclic sultam library, utilizing a Heck–aza-Michael (HaM) strategy, is reported. This sequence involves a Heck reaction on vinylsulfonamides with batch microwave heating followed by a one-pot, sequential intramolecular aza-Michael cyclization/Boc-deprotection using MACOS. Subsequent cyclization with either 1,1'-carbonyldiimidazole or chloromethyl pivalate using MACOS provided an array of tricyclic sultams. This efficient three-step protocol requires only a few hours to produce the target sultams starting from simple starting materials. Using this strategy, a 38-member library of isoindoline-annulated sultams was generated in good to excellent overall yields (53–87%).

Key words: MACOS, continuous flow, sultams, Heck reaction, aza-Michael addition, isoindolines

Microwave-assisted organic synthesis (MAOS) has had a significant impact on organic and medicinal chemistry by reducing reaction times dramatically, producing cleaner product mixtures, and making high-energy transformations routine that might otherwise be avoided.¹ Recently, microwave technology has also been applied to flowed reactions^{2,3} to gain the full advantage of working in flow; that is, reactions should proceed to a high degree of completion during the time that any plug of flowing reactants resides in the reaction tube. The merging of these two technologies, which is called microwave-assisted continuous-flow organic synthesis, or MACOS, offers many advantages in synthetic chemistry. Most prominently, successes in cross-coupling reactions,⁴ natural product synthesis,⁵ in situ generations of reactive intermediates,⁶ scale-out production, and library synthesis have elevated this powerful technology, aiding in early stage drug discovery.⁷

Sulfonamides, which have rich chemical and biological profiles, are of interest in drug discovery.⁸ In particular, attention has been directed toward cyclic sulfonamides, also known as sultams, that, while not found in nature, exhibit a wide spectrum of activity.⁹ The most well-known

examples of biologically active sultams include benzoxathiazepine 1,1-dioxides¹⁰ as glucokinase activators (type II diabetes), novel benzodithiazine dioxides¹¹ with both antiviral and anticancer activities, brinzolamide¹² for the treatment of glaucoma, the COX-2 inhibitors ampiroxicam¹³ and S-2474,¹⁴ selective inhibitors of calpain I,¹⁵ the antiepileptic agent sulthiame,¹⁶ and a number of benzodithiazine dioxides¹¹ displaying anti-HIV-1 activity. This heightened activity profile has guided the present study.

Diversity-oriented synthesis (DOS) has emerged as an effective strategy to synthesize large libraries of biologically relevant small heterocycles for high throughput screening.¹⁷ The need for new diverse heterocyclic probe collections has prompted the development of a variety of methodologies and protocols for the generation of diverse sultam collections. These efforts include recently reported protocols such as 'Click, Cyclize' to diversify benzoxathiazepine 1,1-dioxides,^{7c,f,18} 'Click, Click, Cyclize',^{7a,19} complementary amphiphile pairing (CAP),¹⁹ reagent-based DOS,²⁰ and 'Click, Click, Cy-Click'.^{7b,21} The MACOS platform was utilized in these strategies for the multigram synthesis of building blocks that were further diversified by alkylation and substitution reactions to generate skeletal and stereochemically diversified sultam libraries (Scheme 1).⁷ Building on these reports, we herein report the utilization of a MACOS platform for development of a Heck–aza-Michael (HaM) strategy for the efficient synthesis of a 38-member isoindoline sultam library.

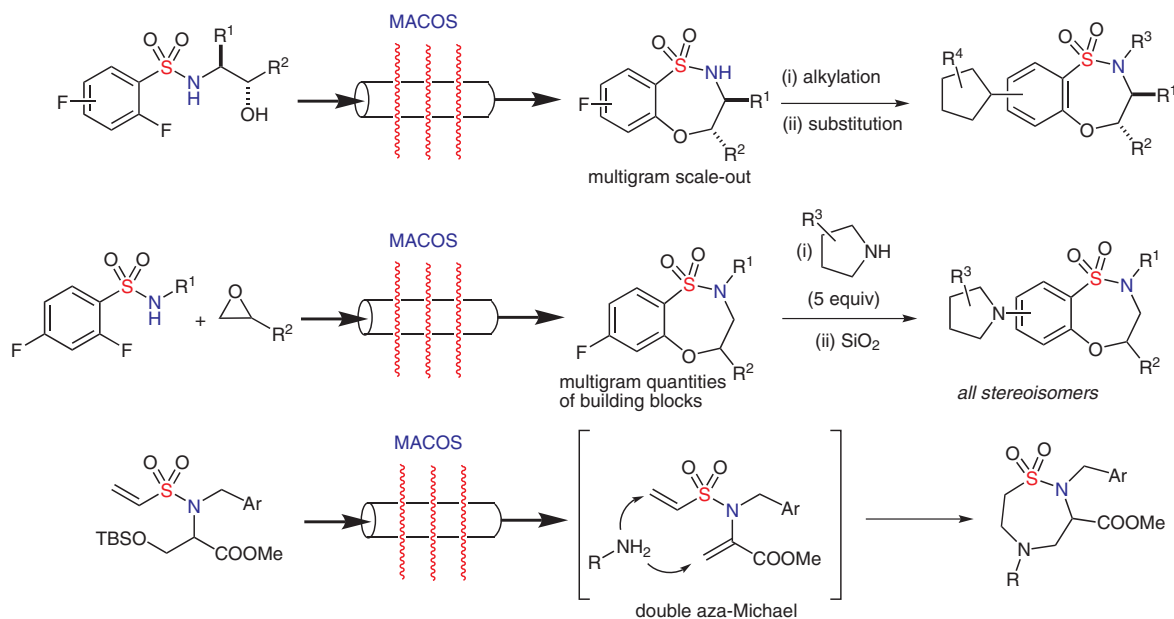
The batch HaM strategy developed previously to prepare the target scaffold required several days to carry out.²¹ To further optimize this method, we combined microwave heating and flow. Initial investigation focused on the development and optimization of the corresponding Heck and aza-Michael elements of this strategy. The electrophiles **1** for the Heck coupling were prepared readily from commercially available 2-chloroethanesulfonyl chloride with a variety of alkyl and aryl amines.²¹ Similarly, the nucleophilic partners **2** were generated from commercially available (2-bromophenyl)methanamine derivatives or by reduction of the corresponding cyanides.²² The prima-

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Scheme 1 Scale-out production of sultams via MACOS

ry amine was protected with Boc anhydride²³ to avoid polymerization with the vinylsulfonamide during Heck coupling of **1** with **2** in the next step (see Tables 1 and 2).

Initially, we intended to telescope the synthesis of **6** and **7** by combining all steps together and avoiding the isolation of intermediates. For this, we used the batch microwave to determine the optimal concentration, temperature, and reaction time. With some optimization, it was determined that secondary sulfonamide **3a** could be generated in 72% yield (100% conversion based on **1a**) utilizing 10 mol% Pd(OAc)₂ with triphenylphosphane as a catalyst, using 3 equivalents of triethylamine at 180 °C for 5 minutes, and employing a minimum concentration of 0.5 M (Table 1, entry 10). Utilizing this optimized protocol we synthesized an array of secondary sulfonamides **3a–w** in 54–79% yield (Table 2).

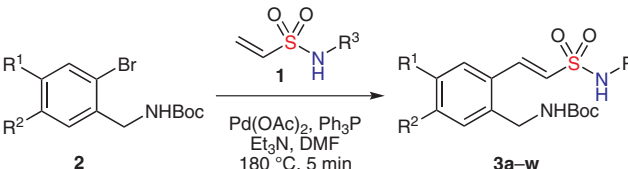
After preparing secondary sulfonamides **3a–w** (Table 2) by Heck coupling, we focused on screening different reaction conditions (Table 3) for the aza-Michael cyclization and Boc-deprotection to occur in one pot in order to find reaction conditions suitable for the MACOS platform. Many attempts were made to deprotect the Boc group by using a variety of bases reported in the literature²⁴ in order to facilitate the cascade reaction to get the isoindoline product **5** in a single step without additional reagents; however, all attempts led to aza-Michael cyclization product **4** containing the Boc-protected tertiary amine. Surprisingly, the use of DBU as base in tetrahydrofuran at room temperature for 24 hours gave no reaction and only starting material **3a** was observed (Table 3, entry 9). The same reaction mixture was further heated at 70 °C for 7 hours, yet still no progress was observed (Table 3, entry 10). Further studies revealed that DBU in *N,N*-dimethylformamide gave the desired product in excellent yield (Table 3, entry 8).

Table 1 Optimization of the Microwave-Assisted, Heck Reaction Conditions

Entry	Catalyst (mol%)	Temp (°C)	Time (min)	Concn (M)	Conv. (%)
1	A (20)	125	20	0.1	15
2	A (20)	150	10	0.1	60
3	A (20)	180	5	0.1	84
4	A (20)	180	10	0.1	86
5	A (20)	200	5	0.1	60
6	A (20)	180	5	0.25	93
7	A (20)	180	5	0.4	97
8	A (20)	180	5	0.5	100
9	A (10)	180	5	0.5	100
10	B (10)	180	5	0.5	100 (72 ^a)

^a Isolated yield after flash chromatography on silica gel.

With the optimized aza-Michael reaction conditions in hand, we next turned to the Boc-deprotection step. Use of trifluoroacetic acid, the most commonly used reagent for Boc-deprotection,²⁵ in *N,N*-dimethylformamide at 180 °C for 1 minute, yielded only starting material (Table 3, entry 11). Attempted deprotection with hydrochloric acid (1.0

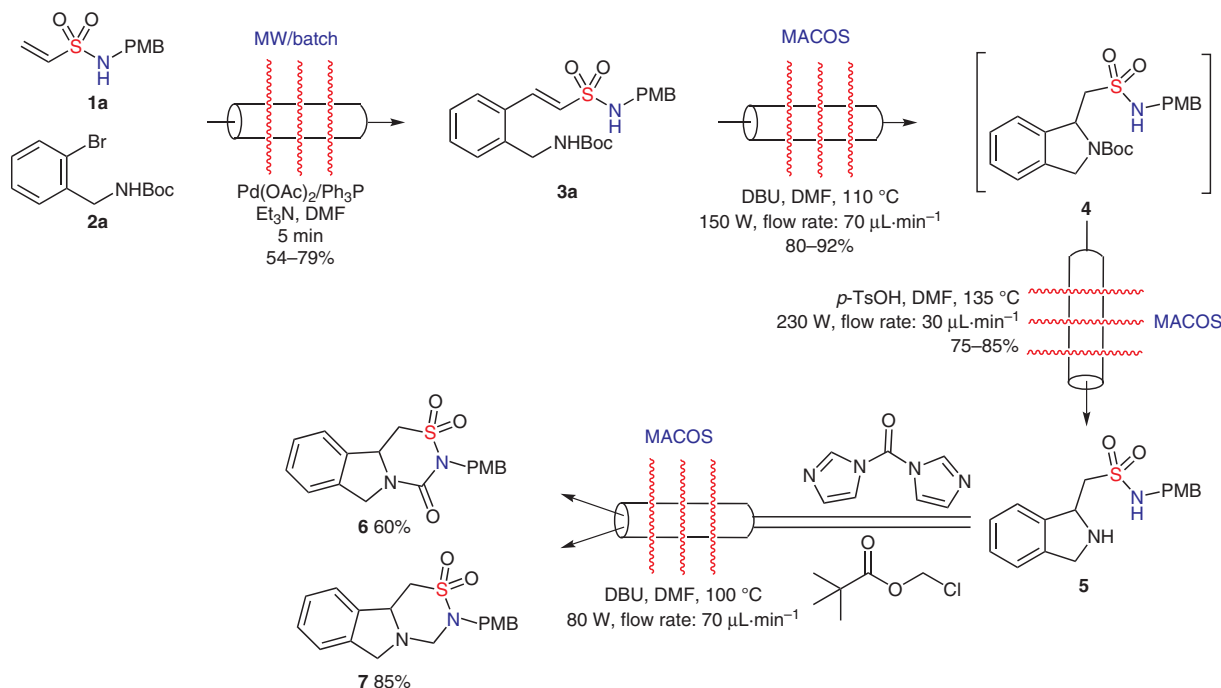
Table 2 Preparation of Sulfonamides **3** by the Heck Reaction^a


Product	R ¹ and R ²	R ³	Yield (%)	Product	R ¹ and R ²	R ³	Yield (%)
3a	R ¹ = R ² = H	PMB	72	3l	R ¹ = Me, R ² = H	CH(Me)Ph	60
3b	R ¹ = R ² = H	PCB	62	3m	R ¹ = H, R ² = F	PCB	54
3c	R ¹ = R ² = H	Cy	76	3n	R ¹ = H, R ² = F	Cy	69
3d	R ¹ = R ² = H	CH ₂ Cy	67	3o	R ¹ = H, R ² = F	CH ₂ Cy	67
3e	R ¹ = R ² = H	<i>n</i> -C ₁₀ H ₂₁	65	3p	R ¹ = H, R ² = F	<i>n</i> -C ₁₀ H ₂₁	59
3f	R ¹ = R ² = H	3,4-(MeO) ₂ C ₆ H ₃ CH ₂ CH ₂	78	3q	R ¹ = H, R ² = F	3,4-(MeO) ₂ C ₆ H ₃ CH ₂ CH ₂	65
3g	R ¹ = R ² = H	CH(Me)Ph	65	3r	R ¹ = H, R ² = F	CH(Me)Ph	57
3h	R ¹ = Me, R ² = H	PCB	55	3t	R ¹ -R ² = OCH ₂ O	<i>n</i> -C ₁₀ H ₂₁	65
3i	R ¹ = Me, R ² = H	Cy	56	3u	R ¹ -R ² = OCH ₂ O	Cy	54
3j	R ¹ = Me, R ² = H	<i>n</i> -C ₁₀ H ₂₁	62	3w	R ¹ -R ² = OCH ₂ O	3,4-(MeO) ₂ C ₆ H ₃ CH ₂ CH ₂	70
3k	R ¹ = Me, R ² = H	3,4-(MeO) ₂ C ₆ H ₃ CH ₂ CH ₂	79				

^a Reaction conditions: **1** (1.0 equiv), **2** (1.2 equiv), Pd(OAc)₂ (10 mol%), Ph₃P (20 mol%), Et₃N (3 equiv), DMF (0.5 M), 180 °C, 5 min, microwave heating.

M) led to a complicated mixture (Table 3, entry 12). The desired target **5** was produced in 72% conversion when 1.0 equivalent of *p*-toluenesulfonic acid (*p*-TsOH) was

employed at 140 °C (Table 3, entry 13) and full conversion was achieved when the temperature was increased to 180 °C (Table 3, entry 15). When the reaction was carried

**Scheme 2** Synthesis of the tricyclic isoindoline sultam library via MACOS

out with 3.0 equivalents of *p*-TsOH at 140 °C, there was full conversion with 83% isolated yield (Table 3, entry 17).

Upon successful optimization of the first two steps in this sequence, we worked to combine them into a one-pot, sequential reaction pathway. This sequence was carried out using 1 equivalent of DBU, with heating at 120 °C for 1 minute, and subsequent addition of 3 equivalents of *p*-TsOH, with heating at 140 °C for 1 minute, to provide **5** with favorable yield and efficiency (Table 3, entry 17). It should be noted that product **5** produced by this method could be used in further steps without additional purification. The cyclization step using 1,1'-carbonyldiimidazole (CDI) or chloromethyl pivalate worked smoothly affording **6** and **7**, respectively, in good yields (Scheme 2).

A variety of reactor parameters were next investigated taking the aforementioned preliminary conditions developed on the batch microwave into the MACOS platform (e.g., flow rate, temperature, and power) in order to find a suitable flow protocol (Scheme 2).

Initially, both reactions (aza-Michael cyclization and Boc-deprotection) were run using a single capillary flow reactor in sequential one pot under the same reaction conditions (50 µL/min, 120 °C, 160 W), but mixtures of compounds **4** and **5** were always observed. In order to circumvent this issue, reinvestigation of the individual steps was carried out to deduce which reaction needed a longer residence time, which could be simply accomplished by lowering the flow rate. During these attempts, it was observed that the first aza-Michael-cyclization step can be processed successfully with a flow rate of 70 µL/min at 110 °C using 150 watts of power. In addition, the concentration was found to be less important in this step as this reaction can be run successfully with any concentration from 0.1 M to 1.0 M, with the entire range of conditions providing a similar isolated yield. However, the Boc-deprotection step was found to be the slower step in the sequential one-pot synthesis, and thus required a slower flow rate (30 µL/min) and slightly higher temperature (135 °C) in order to achieve full conversion of **4** into **5**. With this optimization in hand, the reaction sequence

Table 3 Optimization of the Microwave-Assisted, Intramolecular Aza-Michael Cyclization and Boc-Deprotection Reaction Conditions

Entry	Reaction conditions	Conversion (%)	
		4	5
1	TBAF, DMF, 180 °C, 1 min	100	—
2	K ₂ PO ₄ , MeOH, 120 °C, 2 min	—	—
3	Cs ₂ CO ₃ (10 mol%), DMF–MeOH (5:1), 180 °C, 2 min	100	—
4	DMF, 180 °C, 1 min	—	—
5	Na ₂ CO ₃ , DMF, H ₂ O, 180 °C, 1 min	100	—
6	DBU, DMF, 180 °C, 1 min	100	—
7	DBU, DMF, 140 °C, 1 min	100	—
8	DBU, DMF, 120 °C, 1 min	100 (92 ^a)	—
9	DBU, THF, r.t., 24 h	—	—
10	DBU, THF, 70 °C, 7 h	—	—
11	TFA, DMF, 180 °C, 1 min	—	—
12	1 M HCl, DMF, 180 °C, 1 min	—	mixture
13	<i>p</i> -TsOH (1 equiv), DMF, 140 °C, 1 min	—	72
14	<i>p</i> -TsOH (1 equiv), DMF, 160 °C, 1 min	—	90
15	<i>p</i> -TsOH (1 equiv), DMF, 180 °C, 1 min	—	100
16	<i>p</i> -TsOH (3 equiv), DMF, r.t., 72 h	—	—
17	<i>p</i> -TsOH (3 equiv), DMF, 140 °C, 1 min	—	100 (83 ^a)

^a Isolated yield after flash chromatography on silica gel.

was carried out in a one-pot, sequential synthesis. After running the aza-Michael reaction at 110 °C with a flow rate of 70 $\mu\text{L}/\text{min}$, 3 equivalents of *p*-TsOH were added, and the conditions were switched for the Boc-deprotection (30 $\mu\text{L}/\text{min}$, 135 °C, 230 W), which provided compound **5** in good yield compatible with the results obtained on the bench. The product **5** was isolated as a brown solid, pure enough to be used in next step after workup with aqueous sodium bicarbonate solution.

After successful runs using a single capillary in the flow reactor, it was equipped with two capillaries in order to double throughput. Using this double-capillary flow reactor, we moved on to the cyclization step by reaction of isoindoline **5** with 1,1'-carbonyldiimidazole or chloromethyl pivalate using a flow rate of 70 $\mu\text{L}/\text{min}$ at 100 °C. These two reactions were run in parallel under the same reaction conditions, which provided the desired sultams **6**

and **7** in good yield. Overall, the three-step protocol, including the Heck coupling, was run successfully in a few hours. With these conditions in hand, we produced a 38-member library of tricyclic isoindoline sultams in yields ranging from 53% to 87% (Figure 1).

In conclusion, we have developed a one-pot, sequential HaM strategy in flow for a small library of isoindoline-annulated, tricyclic sultams using a multi-capillary flow reactor that significantly reduces the reaction time, is step-efficient, and minimizes chromatography. Overall this three-step protocol, one on the bench and two using MACOS, efficiently generates the tricyclic sultams **6** and **7** in a few hours. These compounds will be evaluated by our collaborators for biological activity in a variety of biological screens, the results of which will be reported in due course.

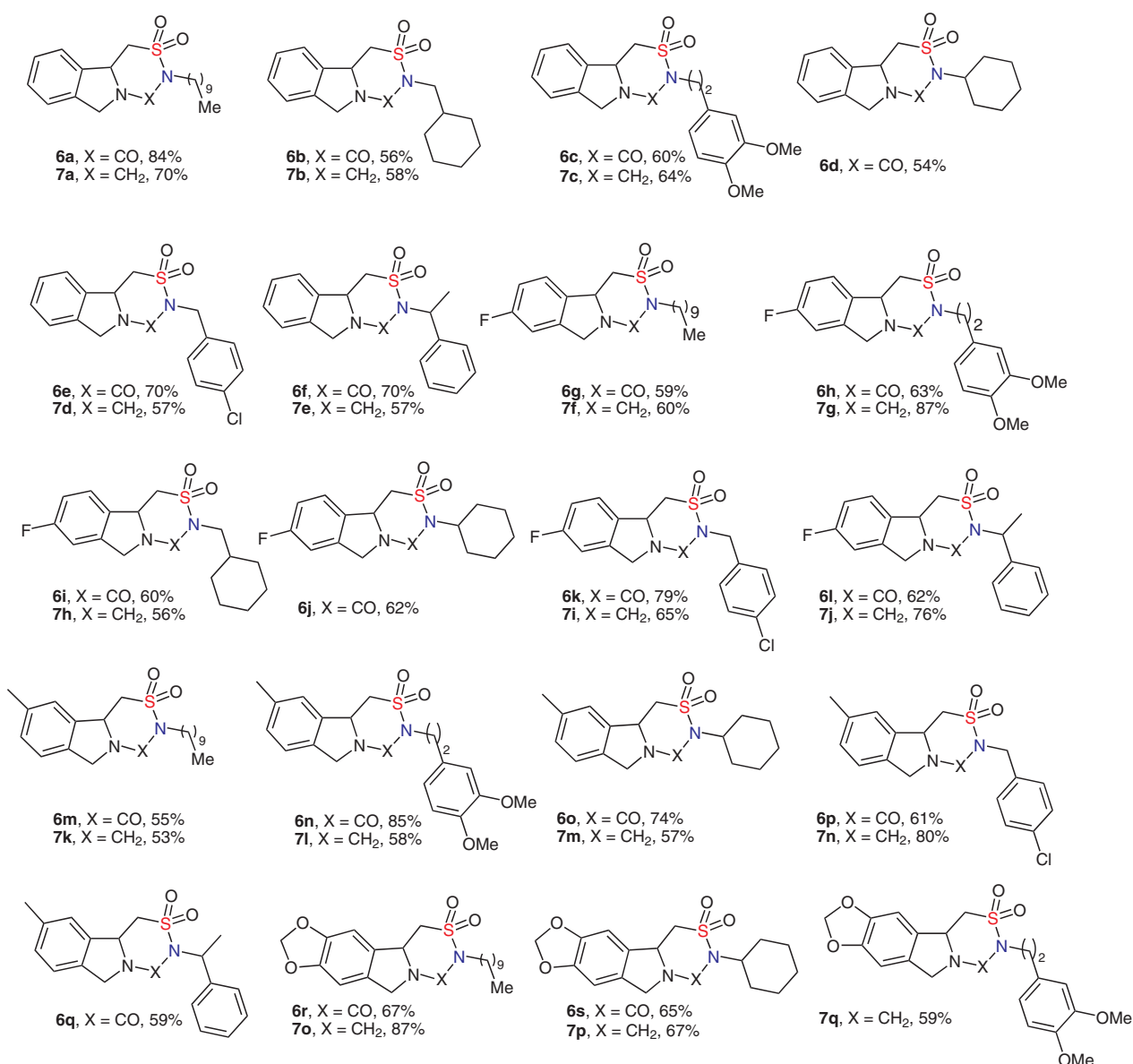


Figure 1 Tricyclic isoindoline scaffolds (the reported yields are isolated yields after flash column chromatography on silica gel)

All microwave irradiation (MACOS) experiments were performed in 1700 μm (i.d.) borosilicate capillaries, using a single-mode Biotage Initiator unit operating at a frequency of 2.45 GHz with irradiation power from 0 to 350 W. The capillary was fed reactants from Hamilton gastight syringes attached to a Harvard 22 syringe pump preset to the desired flow rate. The system was connected to a sealed collection vial, where a pressurized airline (75 psi) was attached to create backpressure. The temperatures reported were measured off the surface of the capillaries by an IR sensor built into the microwave chamber. All reagents and solvents were purchased from commercial sources and used without additional purification. Column chromatographic purifications were carried out using the flash technique on silica gel 60 (200–400 mesh). ^1H and ^{13}C NMR spectroscopy was run using a Bruker Avance 300 (300 MHz and 75 MHz, respectively) spectrometer. All ^1H NMR spectra were calibrated to the signal from the residual proton of the CDCl_3 solvent (7.26 ppm) while ^{13}C NMR spectra were calibrated to the middle carbon signal of the triplet for CDCl_3 (77.00 ppm). All compounds in this study have been isolated by silica gel or aluminum oxide chromatography for the purpose of spectroscopic identification.

Sulfonamides **3** by the Microwave-Assisted Heck Coupling of Vinylsulfonamides **1** with *tert*-Butyl 2-Bromobenzylcarbamates **2**; General Procedure

Into a 10-mL standard microwave vial (Biotage) was added the *tert*-butyl 2-bromobenzylcarbamate **2** (1.2 equiv), the vinylsulfonamide **1** (1.0 equiv, 0.3–0.8 mmol), anhyd DMF (0.5 M), $\text{Pd}(\text{OAc})_2$ (10 mol%), Ph_3P (20 mol%), and Et_3N (3 equiv). No special precautions to exclude atmospheric oxygen were taken. The reaction vessel was capped, and heated at 180 $^\circ\text{C}$ for 5 min using a single-mode Biotage Initiator Synthesizer with an irradiation power up to 350 W. The reaction mixture was cooled to r.t., diluted with EtOAc (150 mL), and washed with H_2O (50 mL). The layers were separated and the organic layer was concentrated under reduced pressure. The resulting crude product was purified by flash chromatography (EtOAc–*n*-pentane, 3:7) to afford the sulfonamide **3a–w** in 54–79% yield.

Isoindolines **5** by Aza-Michael Cyclization and Boc Deprotection Using MACOS; General Procedure

A stock solution containing a sulfonamide **3** (1.0 equiv, 0.3–0.8 mmol) and DBU (1.0 equiv) in DMF (0.1–0.2 M) was prepared and loaded into a Hamilton gastight syringe (10 mL). The tubing was primed with DMF and the syringe was connected to the reactor system with the aid of MicrotightTM fittings. The system was connected to a sealed collection vial, where a pressurized airline (75 psi) was attached to create backpressure. The syringe was placed in a Harvard 22 syringe pump that was set to deliver 70 $\mu\text{L}/\text{min}$. The single-mode microwave was programmed to heat constantly; the power level was controlled manually so as to keep the temperature constant at the specified levels (see Scheme 2). The effluent from the reactor was collected into a sealed vial. After completion of the reaction, the internal pressure of the system was released by piercing the septum with the needle, and the septum was removed and the product was analyzed directly by ^1H NMR spectroscopy. For the Boc-deprotection step, *p*-TsOH (3 equiv) was added to the crude reaction mixture and it was again loaded into a Hamilton gastight syringe (10 mL). The syringe pump was set to deliver 30 $\mu\text{L}/\text{min}$ (see Scheme 2 for specific conditions). After collection of the product mixture from the reactor, it was diluted with EtOAc (150 mL) and basified with sat. NaHCO_3 soln until it reached pH 8–9. The solution was extracted with EtOAc (150 mL), and the organic layer was washed with brine (100 mL), and dried (Na_2SO_4). The mixture was filtered through a small pad of silica gel and the solvent was removed under reduced pressure. The crude, pink-colored product **5** was purified by flash column chromatography (EtOAc–*n*-pentane, 9:1). Alternatively, the crude product was clean enough to be used in the next step without any further purification.

Isoindoline-Annulated Sultams **6** and **7** Using MACOS; General Procedure

A stock solution containing an isoindoline **5** (1.0 equiv, 0.3–0.8 mmol), CDI (2.0 equiv) or chloromethyl pivalate (2.0 equiv), and DBU (2.0 equiv) in DMF (0.1–0.2 M) was prepared and loaded into a Hamilton gastight syringe (10 mL). One syringe was loaded with the reagents containing isoindoline **5**, DBU, and CDI, and the second was loaded with the reagents containing isoindoline **5**, DBU, and chloromethyl pivalate, to deliver 70 $\mu\text{L}/\text{min}$. These reaction mixtures were irradiated parallel under the same reaction conditions (flow rate, power, temperature) and collected in separate sealed vials. After completion of the reaction, the internal pressure of the system was released by piercing the septum with the needle, and the septum was removed and the product was analyzed directly by ^1H NMR spectroscopy. The product was extracted with EtOAc (150 mL), and the organic layer was washed with brine (100 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude products were purified by flash column chromatography (EtOAc–*n*-pentane, 2:8) to afford products **6** and **7** in 53–87% yield.

Characterization Data for Representative Compounds **6** and **7**

3-Decyl-6,10b-dihydro-1*H*-[1,2,4]thiadiazino[5,4-*a*]isoindol-4(3*H*)-one 2,2-Dioxide (**6a**)

Yield: 170 mg (84%); colorless crystalline solid; mp 65 $^\circ\text{C}$.

FTIR (thin film): 2923, 2856, 1672, 1405, 1316, 1152, 747 cm^{-1} .

^1H NMR (300 MHz, CDCl_3): δ = 7.39–7.36 (m, 3 H), 7.26 (d, J = 6.9 Hz, 1 H), 5.44 (d, J = 12.3 Hz, 1 H), 5.02 (d, J = 15.0 Hz, 1 H), 4.73 (d, J = 15.0 Hz, 1 H), 3.99 (dd, J = 12.9, 3.0 Hz, 1 H), 3.90–3.83 (m, 1 H), 3.80–3.66 (m, 1 H), 3.24 (t, J = 12.8 Hz, 1 H), 1.74 (t, J = 7.2 Hz, 2 H), 1.26 (s, 14 H), 0.90 (t, J = 6.5 Hz, 3 H).

^{13}C NMR (75 MHz, CDCl_3): δ = 149.7, 135.9, 135.8, 129.2, 128.2, 123.3, 121.8, 56.4, 52.7, 51.8, 41.5, 31.8, 29.6, 29.5, 29.2, 29.1, 26.7, 22.6, 14.1.

HRMS (ESI): m/z calcd for $\text{C}_{20}\text{H}_{30}\text{N}_2\text{O}_3\text{S}$: 378.1977; found: 378.19776.

3-(4-Chlorobenzyl)-6,10b-dihydro-1*H*-[1,2,4]thiadiazino[5,4-*a*]isoindol-4(3*H*)-one 2,2-Dioxide (**6e**)

Yield: 113 mg (70%); colorless solid; mp 158 $^\circ\text{C}$.

FTIR (thin film): 2932, 1681, 1432, 1396, 1321, 1158, 1085, 729 cm^{-1} .

^1H NMR (300 MHz, CDCl_3): δ = 7.47–7.37 (m, 5 H), 7.32–7.23 (m, 3 H), 5.47 (d, J = 12.3 Hz, 1 H), 5.08–4.83 (m, 3 H), 4.75 (d, J = 15.0 Hz, 1 H), 4.03 (dd, J = 13.2, 2.7 Hz, 1 H), 3.36 (t, J = 12.9 Hz, 1 H).

^{13}C NMR (75 MHz, CDCl_3): δ = 149.6, 135.8, 135.4, 135.2, 133.6, 130.2, 129.4, 128.6, 128.3, 123.4, 121.7, 56.5, 52.7, 51.9, 43.5.

HRMS (ESI): m/z $[\text{M} - \text{H}]^+$ calcd for $\text{C}_{17}\text{H}_{14}\text{ClN}_2\text{O}_3\text{S}$: 361.0414; found: 361.0426.

3-Cyclohexyl-8-fluoro-6,10b-dihydro-1*H*-[1,2,4]thiadiazino[5,4-*a*]isoindol-4(3*H*)-one 2,2-Dioxide (**6j**)

Yield: 90 mg (62%); colorless crystalline solid; mp 219 $^\circ\text{C}$.

FTIR (thin film): 2923, 2851, 1654, 1490, 1445, 1392, 1241, 1169, 1134, 987, 738 cm^{-1} .

^1H NMR (300 MHz, CDCl_3): δ = 7.28–7.18 (m, 1 H), 7.11–7.06 (m, 2 H), 5.41 (d, J = 12.3 Hz, 1 H), 5.01 (d, J = 15.6 Hz, 1 H), 4.71 (d, J = 15.6 Hz, 1 H), 4.29–4.21 (m, 1 H), 3.89 (dd, J = 12.9, 3.0 Hz, 1 H), 3.35 (t, J = 12.6 Hz, 1 H), 2.34–2.22 (m, 2 H), 2.00 (d, J = 12.0 Hz, 1 H), 1.88 (d, J = 9.3 Hz, 3 H), 1.67 (d, J = 12.3 Hz, 1 H), 1.41–1.18 (m, 3 H).

^{13}C NMR (75 MHz, CDCl_3): δ = 165.1 (d, $J_{\text{C-F}}$ = 246.8 Hz), 149.5, 138.2 (d, $J_{\text{C-F}}$ = 9.0 Hz), 131.4 (d, $J_{\text{C-F}}$ = 3.0 Hz), 123.4 (d, $J_{\text{C-F}}$ = 9.0 Hz), 115.8 (d, $J_{\text{C-F}}$ = 22.5 Hz), 110.9 (d, $J_{\text{C-F}}$ = 24.0 Hz), 56.6, 55.8, 52.9, 52.5, 31.1, 30.7, 26.7, 26.5, 25.1.

HRMS (ESI): m/z calcd for $C_{16}H_{19}FN_2O_3S$: 338.1100; found: 338.1107.

3-Cyclohexyl-9-methyl-6,10b-dihydro-1H-[1,2,4]thiadiazino[5,4-*a*]isoindol-4(3H)-one 2,2-Dioxide (6o)

Yield: 176 mg (74%); greenish crystalline solid; mp 192 °C.

FTIR (thin film): 2927, 2847, 1677, 1383, 1316, 1160, 1138, 987, 729 cm^{-1} .

1H NMR (300 MHz, $CDCl_3$): δ = 7.25–7.18 (dd, J = 7.8, 7.8 Hz, 2 H), 7.02 (s, 1 H), 5.38 (d, J = 12.3 Hz, 1 H), 4.95 (d, J = 14.7 Hz, 1 H), 4.67 (d, J = 14.7 Hz, 1 H), 4.27–4.19 (m, 1 H), 3.90 (dd, J = 12.9, 3.0 Hz, 1 H), 3.31 (t, J = 12.9 Hz, 1 H), 2.39 (s, 3 H), 2.34–2.21 (m, 2 H), 1.99 (d, J = 12.0 Hz, 1 H), 1.84 (br d, J = 10.8 Hz, 3 H), 1.65 (d, J = 12.3 Hz, 1 H), 1.38–1.35 (m, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 149.6, 138.2, 135.9, 132.8, 130.1, 123.0, 122.3, 56.4, 56.1, 52.9, 52.5, 31.2, 30.7, 26.8, 26.5, 25.1, 21.3.

HRMS (ESI): m/z calcd for $C_{17}H_{22}N_2O_3S$: 334.1351; found: 334.1382.

3-(3,4-Dimethoxyphenethyl)-3,4,6,10b-tetrahydro-1H-[1,2,4]thiadiazino[5,4-*a*]isoindole 2,2-Dioxide (7c)

Yield: 182 mg (64%); brown solid; mp 90 °C.

FTIR (thin film): 2923, 2820, 1512, 1456, 1341, 1226, 1153, 1023, 755 cm^{-1} .

1H NMR (300 MHz, $CDCl_3$): δ = 7.27 (m, 3 H), 7.15 (m, 1 H), 6.83–6.78 (m, 3 H), 4.64 (d, J = 12.9 Hz, 1 H), 4.58 (d, J = 10.8 Hz, 1 H), 4.19 (d, J = 12.3 Hz, 1 H), 4.05 (d, J = 12.3 Hz, 1 H), 3.92 (d, J = 12.9 Hz, 1 H), 3.87 (s, 3 H), 3.86 (s, 3 H), 3.60–3.39 (m, 3 H), 2.95 (m, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 148.9, 147.6, 140.1, 139.0, 131.0, 128.0, 127.3, 122.9, 120.9, 120.8, 112.1, 111.3, 66.8, 63.2, 55.9, 53.7, 51.1, 50.0, 35.9.

HRMS (ESI): m/z calcd for $C_{20}H_{24}N_2O_4S$: 388.1457; found: 388.1448.

3-(Cyclohexylmethyl)-8-fluoro-3,4,6,10b-tetrahydro-1H-[1,2,4]thiadiazino[5,4-*a*]isoindole 2,2-Dioxide (7h)

Yield: 140 mg (56%); colorless solid; mp 105 °C.

FTIR (thin film): 2927, 2847, 1485, 1338, 1143, 1098, 738 cm^{-1} .

1H NMR (300 MHz, $CDCl_3$): δ = 7.13–7.09 (m, 1 H), 7.01–6.93 (m, 2 H), 4.69 (d, J = 12.9 Hz, 1 H), 4.56 (d, J = 11.1 Hz, 1 H), 4.27 (d, J = 12.6 Hz, 1 H), 4.15 (d, J = 12.9 Hz, 1 H), 4.00 (d, J = 12.3 Hz, 1 H), 3.44 (dd, J = 12.9, 3.0 Hz, 1 H), 3.08 (d, J = 7.2 Hz, 2 H), 2.93 (t, J = 12.0 Hz, 1 H), 1.86–1.55 (m, 6 H), 1.28–1.18 (m, 3 H), 0.99–0.72 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.3 (d, J_{C-F} = 243.8 Hz), 141.3 (d, J_{C-F} = 9.0 Hz), 136.5 (d, J_{C-F} = 1.5 Hz), 122.1 (d, J_{C-F} = 9.0 Hz), 114.4 (d, J_{C-F} = 22.5 Hz), 110.7 (d, J_{C-F} = 23.3 Hz), 66.8, 62.7, 54.3, 53.7, 50.9, 37.5, 30.7, 30.6, 26.4, 25.8, 25.7.

HRMS (ESI): m/z calcd for $C_{17}H_{23}FN_2O_2S$: 338.1464; found: 338.1453.

3-Cyclohexyl-9-methyl-3,4,6,10b-tetrahydro-1H-[1,2,4]thiadiazino[5,4-*a*]isoindole 2,2-Dioxide (7m)

Yield: 165 mg (57%); brownish viscous oil.

FTIR (thin film): 2923, 2851, 1450, 1330, 1307, 1147, 1085, 951, 813 cm^{-1} .

1H NMR (300 MHz, $CDCl_3$): δ = 7.17 (d, J = 7.8 Hz, 1 H), 7.08 (d, J = 7.5 Hz, 1 H), 6.96 (s, 1 H), 4.75 (d, J = 1.8 Hz, 1 H), 4.70 (d, J = 13.5 Hz, 1 H), 4.30 (d, J = 13.2 Hz, 1 H), 4.26 (d, J = 13.8 Hz, 1 H), 3.96 (br d, J = 12.2 Hz, 2 H), 3.27–3.22 (dd, J = 12.6, 3.6 Hz, 1 H), 2.94–2.77 (m, 2 H), 2.34 (s, 3 H), 1.92–1.62 (m, 4 H), 1.52–1.33 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.6, 137.0, 136.1, 128.6, 122.8, 121.8, 62.8, 60.8, 54.1, 53.7, 52.3, 32.1, 31.6, 26.0, 25.8, 25.3, 21.3.

HRMS (ESI): m/z calcd for $C_{17}H_{24}N_2O_2S$: 320.1558; found: 320.1552.

7-(3,4-Dimethoxyphenethyl)-4b,7,8,10-tetrahydro-5H-[1,3]dioxolo[4,5-*f*][1,2,4]thiadiazino[5,4-*a*]isoindole 6,6-Dioxide (7q)

Yield: 182 mg (59%); colorless solid; mp 155 °C.

FTIR (thin film): 2927, 1512, 1467, 1245, 1227, 1160, 1022, 916, 733 cm^{-1} .

1H NMR (300 MHz, $CDCl_3$): δ = 6.79 (m, 3 H), 6.70 (s, 1 H), 6.59 (s, 1 H), 5.94 (s, 2 H), 4.61 (d, J = 12.9 Hz, 1 H), 4.50 (d, J = 9.9 Hz, 1 H), 4.12 (d, J = 11.4 Hz, 1 H), 3.99 (d, J = 12.9 Hz, 1 H), 3.87 (s, 3 H), 3.85 (s, 3 H), 3.81 (s, 1 H), 3.54 (m, 2 H), 3.34 (dd, J = 12.9, 3.0 Hz, 1 H), 2.91–2.81 (m, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 148.9, 147.7, 147.6, 147.1, 133.6, 131.9, 131.0, 120.7, 112.0, 111.3, 103.9, 102.0, 101.4, 66.8, 63.1, 55.9, 53.6, 51.2, 49.9, 35.9.

HRMS (ESI): m/z calcd for $C_{21}H_{24}N_2O_6S$: 432.1355; found: 432.1354.

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